
LCA Breast Cancer Clinical Guidelines

October 2013



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Introduction

The London Cancer Alliance (LCA) Breast Cancer Clinical Guidelines provide a practical multidisciplinary guide for the diagnosis, treatment and holistic care and support of breast cancer patients across the LCA.

These guidelines have been developed by the LCA Breast Pathway Group to ensure that care throughout the LCA conforms to national and international best practice. They draw on the expertise of a range of clinicians from across the LCA's provider organisations, and subsequently reflect the wider breast cancer pathway. They provide evidence-based clinical information and protocols on all aspects of the breast cancer pathway, while allowing sufficient flexibility to reflect good local practice and should therefore be used by clinicians to inform the treatment and care they provide. These guidelines supersede the guidance produced by the former cancer networks in north west, south west and south east London.

The LCA guidelines are designed to be used by all healthcare professionals in trusts within the LCA who are involved in the care of the breast cancer patient. They have been developed to take into account the wide range of clinical experience of the user and the different clinical settings in which they work. The guidelines are intended to assist in the initial assessment, investigation and management of patients. Adoption of the LCA guidelines will allow widespread implementation of up-to-date and evidence-based management of breast cancer patients, and will assist in the provision of a consistently high standard of care across the LCA.

All trusts are expected to be able to provide the standard of care detailed in these guidelines.

The LCA Breast Pathway Group meets regularly, and the guidelines will be reviewed annually to ensure they are updated with emerging evidence and changes in practice.

We would like to thank the following people for their contribution to the development of these guidelines: Dr LS Wilkinson, consultant radiologist and Director of Screening, South West London Breast Screening Service (imaging); Sarah E Pinder, Professor of Breast Pathology and honorary consultant breast pathologist, King's College London (pathology); Dr Susan Cleator, breast clinical and medical oncologist, Imperial College Healthcare (radiotherapy); Dr Mark Harries, consultant medical oncologist, Guy's and St Thomas' NHS Foundation Trust (systemic therapy); Nicola Glover, LCA Survivorship and Mental Health & Psychology project manager and AHP lead (survivorship); and Dr Anjana Kulkarni, consultant in clinical and cancer genetics, Guy's and St Thomas' NHS Foundation Trust (family history). We would also like to thank Mairead McKenzie and Breast Cancer Care for providing a patient perspective.

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Executive Summary

The London Cancer Alliance (LCA) Breast Cancer Clinical Guidelines combine the best features of earlier network protocols, and have been developed in agreement with clinicians across the LCA. The guidance combines evidence-based and best practice recommendations with the aim of ensuring that there are equitable high quality services across the LCA. The guidelines are multidisciplinary and cover imaging, pathology, surgery, radiotherapy, systemic therapy, survivorship and the management of women at high risk of breast cancer.

The imaging section ([Chapter 2](#)) outlines optimal imaging strategies for the diagnosis of breast cancer; it is based on referenced published national guidance. Strategies for screening women at high risk of breast cancer are referenced in this section as well as in the family history section ([Chapter 8](#)).

The breast pathology guidance ([Chapter 3](#)) is more detailed than previous documents and is in line with the latest NHS Breast Screening Programme Pathology Guidelines, which are currently in preparation.

The surgical section ([Chapter 4](#)) is based on the Association of Breast Surgery's *Surgical Guidelines for the Management of Breast Cancer* and *Oncoplastic Breast Reconstruction: Guidelines for Best Practice*. Equitable access to immediate breast reconstruction and the 23-hour model of care for non-breast reconstructive surgery are priority areas for the LCA and were highlighted in the model of care recommendations.

The radiotherapy section ([Chapter 5](#)) provides detailed guidance on the selective use of advanced radiotherapy techniques, including intensity modulated and image guided radiotherapy, which will be offered in accordance with emerging evidence of benefit. Heart-sparing techniques for women treated for left-sided cancers will be introduced across the LCA within the context of the FAST Forward trial. Partial breast radiotherapy by either external beam or brachytherapy, including TARGIT, is not recommended as routine treatment outside a trial on the basis of current evidence, but guidance will be regularly updated.

The systemic therapy section ([Chapter 6](#)) provides guidance on the systemic therapy management of early and advanced breast cancer. It incorporates NICE guidance and lists evidence-based regimens and schedules that are currently in use throughout the LCA. The guidelines will be updated regularly to reflect the rapid pace of change in this area.

The survivorship section ([Chapter 7](#)) lays out the principles of good survivorship care as guidelines and recommendations are made to all cancer services within the LCA. The chapter draws on the best available evidence and current national policy, and is written in response to work such as the national Cancer Patient Experience Survey. The chapter is shaped around the '10 Top Tips' guidance document for patients that was developed by the Consequences of Cancer and its Treatment (CCaT) collaborative group. These cover the key components of good survivorship care that LCA services are expected to address.

Recommendations for referral to clinical genetics services are outlined in detail in the family history section ([Chapter 8](#)) but, in summary, women with breast cancer who are presenting with a second breast primary, have a personal history of ovarian cancer, Jewish ancestry or a significant family history of breast or ovarian cancer, and those diagnosed under 50 years with bilateral or hormone receptor-negative disease should be referred to clinical genetics services for consideration for genetic testing.

Key priorities will be identified across sub-specialties with a view to auditing compliance. Alongside this there should be a continued emphasis on national clinical trial leadership, proven to improve the standard of care for all patients.

1 Patient-centred Care and the Multidisciplinary Team

1.1 Minimising delays

1.1.1 Waiting time targets

Current NHS waiting time targets for time from referral to first outpatient appointment and first treatment (Cancer Reform Strategy, 2007¹):

- 14 days from referral by GP to first outpatient appointment for all patients with a symptomatic breast problem regardless of urgency (does not apply to referral for asymptomatic issues or assessment of family history risk)
- 31 days from diagnosis/decision to treat to first treatment
- 62 days from referral from GP to first treatment.

Current guidance on waiting time for assessment of women referred from the NHS Breast Screening Programme (NHSBSP):²

- 90% of women should be seen for surgical assessment within 1 week of decision to refer
- 90% of women should receive first treatment within 62 days of decision to recall for assessment.

1.2 Referrals between multidisciplinary teams

1.2.1 Principles of referrals

Patients may be referred between multidisciplinary teams (MDTs) for clinical reasons or because of patient choice.

1.2.2 Screening patients being referred for treatment

After assessment, patients will be referred to their local MDT. Patients should be offered information and choice regarding the treating hospital.

When a patient is to be referred to a surgeon for treatment, the referring consultant from the screening assessment unit should use safe haven fax or secure electronic messaging to send a letter within 24 hours following the discussion with the patient.

The referring consultant should ensure that all relevant information is provided to allow clinicians to meet this target.

1.2.3 Referring patients to oncologists

All patients with newly diagnosed, recurrent or metastatic breast cancer will be discussed at a full MDT meeting. This will usually include the core oncology MDT members, who will action the referral from the meeting.

Patients who are being referred for neo-adjuvant treatment must begin their treatment within 31 days of their diagnosis, or 62 days of the date of referral for suspected cancer by their GP.

1.2.4 Referring patients for reconstruction or other complex treatment

If a patient is to be referred to a surgeon from another MDT to discuss options for primary surgical treatment, the referring consultant should use safe haven fax or secure electronic messaging to send a letter providing all the necessary clinical information within 24 hours following the discussion with the patient. The 31- and 62-day targets will still need to be met.

Rapid access pathways must be in place between breast cancer units and specialist centres for provision of complex surgery such as free flap breast reconstruction or chest wall resection. The unit must have a designated surgeon or team to whom the patient is referred

1.3 Communication

The principle aims of the consultation are to offer the patient information and recommendations in conditions allowing privacy, dignity and respect. The patient should be dressed and seated during conversations with the doctor, not lying down, especially when bad news is broken. The doctor should also be seated during these discussions. Women should be offered as much information as they find helpful when describing the different treatment options available to them. All patients should be offered comprehensive written information about breast cancer tailored wherever possible to their individual circumstances. An information prescription should be offered to the patient on or around the time of diagnosis, in whatever format the patient prefers.

The communication of a diagnosis of breast cancer to the patient's GP should be completed within 24 hours either by safe haven fax or secure electronic messaging or by telephone and this should be recorded for audit purposes in the patient record.

Although not formal national guidance, it is considered to be good practice to have a breast care nurse present when breaking bad news, and this person should take on the role of key worker or nominate another health professional for this role. Information and support are available from the key worker throughout the patient pathway and thereafter. Breast care nurses should have access to a dedicated private room for discussion and support at all times.

Information on all aspects of living with and beyond cancer can be discussed at any stage of the patient pathway and is not just limited to the end of treatment.

1.4 The breast care team

For minimum standards, members and the role of the breast MDT, see: Association of Breast Surgery (2005). [Guidelines for the management of symptomatic breast disease. *European Journal of Surgical Oncology* 31: S1–S21.](#)

The breast MDT must be compliant with peer review standards laid out by the National Cancer Action Team (2010). [National Cancer Peer Review Programme, Evidence Guide for: Breast MDT.](#)

1.4.1 Breast care nursing

Within the London Cancer Alliance (LCA), breast care nurses are available to give information and psychological support to patients and their families at all stages of the pathway from diagnosis, during treatment and follow-up, and through to palliative care. There is now strong evidence demonstrating the value of breast care nurses (NICE 2002).

The minimum standard is that all breast cancer patients should leave the hospital following diagnosis with the telephone contact details of the key worker, who is usually the breast care nurse. The breast care nurse will be the main point of contact between the patient and the team, and act as advocate for the patient.

Some of the breast care nurses/advanced nurse practitioners within the LCA provide diagnostic expertise, carry out follow-up clinics and family history clinics for women who are at increased risk of developing breast cancer. Some nurses will provide breast prosthetic fitting, lymphoedema management and seroma drainage, and run support groups; others will refer on for these services. There are also breast care nurses who possess specialist knowledge and skills relevant to the physical and psychological needs of patients with metastatic breast cancer.

The breast care nurses aim to:

- clarify the patient's understanding of their condition, its treatment and side effects by ensuring that each patient has access to information as and when they require it and delivered in an easily understandable format
- enhance involvement in decision making by providing the patient with the opportunity to discuss treatment options in order to make an informed choice
- provide appropriate support and advice in order to facilitate the patient's adjustment to the changes caused by treatment and to maximise confidence and self-esteem, thereby reducing anxiety and depression
- improve general health and reduce somatic symptoms for the patient; this is achieved by working in close liaison with other members of the MDT and referring to, for example, psychological medicine, palliative care and lymphoedema services as and when necessary.

Referral

Services are available to all inpatients and outpatients at various stages of treatment modalities. Referrals will be accepted from all members of the MDT.

Research and education

In addition to clinical responsibilities, the breast care nurses are active in educational and research initiatives. These include training colleagues and contributing to national study days and conferences, thus influencing the development of breast care nursing practice locally and across the country.

For further information on the role of the breast care nurse, please see the NICE clinical guidelines (2004).

1.4.2 The extended breast care team

The team as a whole should be responsible for planning care in a seamless way so that each patient receives prompt and appropriate care throughout the process of diagnosis and treatment, up to and including the period when palliation may be needed. The team must maintain close contact with all other professionals who are actively involved in supporting the patient or in carrying out the treatment strategy decided by the core team.

These include the following:

- breast radiographers
- clinical geneticists/genetics counsellors
- dieticians
- GPs/primary care teams
- lymphoedema services
- occupational therapists
- palliative care specialists/team
- physiotherapists
- plastic surgeons
- prosthesis services
- psychiatrists/clinical psychologists
- research nurses
- social workers.

Teams based in cancer units must maintain close liaison with the associated cancer centre.

Patients should be given information about the members of the team involved in their care and management and their roles.

Within the breast unit, rehabilitation services are provided by numerous practitioners, all of whom encourage a multidisciplinary approach. They offer care relating to physical and psychosocial functioning for both acute and metastatic breast patients undergoing any form of treatment. This section details the range of rehabilitation services available.

1.4.3 Physiotherapy

All Trusts provide physiotherapy services for both inpatients and outpatients which aim to restore or optimise functional independence and physiological and psychological wellbeing across the cancer pathway. Physiotherapists play an important role in the rehabilitation of patients, and it is imperative that physiotherapy starts as early as possible and is carried out under the supervision of an experienced specialist physiotherapist who is familiar with the surgical techniques and possible complications (Royal College of Surgeons, 2012).

Referral

Referrals are normally accepted from all members of the MDT and patients may be able to self-refer.

Criteria for referral include:

- patients with a cancer diagnosis requiring rehabilitation
- any surgical patient following breast or axillary surgery, experiencing physical side effects of treatment (e.g. cording, decreased range of movement at the glenohumeral joint, or shoulder pain unrelieved by analgesia)
- early/late cancer treatment-related symptoms that are influencing a patient's optimal function and require physiotherapy input (e.g. fatigue).

1.4.4 Lymphoedema

All Trusts in the LCA should be able to offer advice for patients at risk of developing lymphoedema and have pathways in place for referral of patients with the condition. Lymphoedema may cause physical, social and psychological problems that may in turn have a profound effect upon a patient's quality of life.

Management of the condition concentrates on conservative treatment measures. These encourage the patient to become actively involved in the care of their swollen limb in order to gain maximum benefit from treatment followed by long-term control of the swelling.

Referral

Patients with any limb swelling should initially be medically assessed within the hospital to establish the cause of swelling, to establish the disease status of the patient and to facilitate the correction of any factors such as low albumin, thrombosis or infection, before any residual swelling is treated.

All patients with lymphoedema, however mild, as a result of their cancer and/or its treatment, can then be referred to the lymphoedema service.

Treatment

Success in controlling lymphoedema depends upon:

- appropriate screening of patients at risk in order to provide education and advice
- early and prompt referral of patients with limb swelling
- follow-up at regular intervals to monitor progress.

Four principles of treatment are employed simultaneously in the management of lymphoedema:

- skin care and education to minimise the risks of infection and inflammation
- exercise to maintain good lymph flow
- massage to stimulate lymph drainage
- external support with compression to limit the accumulation of fluid in the limb.

Patients who present with cellulitis should be treated with antibiotics as per local guidelines, and referred to the appropriate lymphoedema service for support and advice

1.4.5 Occupational therapy

All Trusts in the LCA provide an occupational therapy service which aims to help patients achieve optimal functional independence. Based on a problem-solving approach, occupational therapy is problem-led, rather than diagnosis-led. The service provides assistance in the following areas:

- use of functional activities for the treatment of dysfunction
- retraining in the personal and domestic activities of daily living
- assessment and prescription of wheelchairs and pressure seating
- home assessments and referral for provision of equipment
- lifestyle management: investigating hobbies, work and leisure pursuits while adapting to the individual's needs and loss of function
- advice and education on relaxation techniques and energy conservation
- the use of splints to prevent deformities and to control painful joints.

Referral

The service is available to both inpatients and outpatients at any point in the disease trajectory. Referrals can be made by any healthcare professional, or by patients and their families. Patients may be referred with either physical or psychological dysfunction.

1.4.6 Nutrition and dietetics

Referral

At all Trusts within the LCA, any member of the MDT may refer a patient to the dietician for any of the following reasons:

- the patient requires advice on healthy eating
- the patient is experiencing eating difficulties or weight loss as a result of treatment or advanced disease
- the patient requests advice on complementary or alternative diets
- the patient requires a therapeutic diet.

1.4.7 Psychological support

Counsellors who are skilled and experienced in diagnosis and/or in the range of treatments available, and who are aware of the physical and psychological effects of both the disease and its treatment, should be available to support women with breast cancer as required.

Skilled and experienced rehabilitative therapy, psychological support, social work and chaplaincy services should all be available for patients.

Referral

Mechanisms will vary from Trust to Trust. Some Trusts also have access to psychiatric services. The (oncology) counsellor will accept referrals from healthcare professionals and directly from patients for an initial assessment.

1.4.8 Specialist palliative care team

Palliative care has been defined by the World Health Organization (WHO) as “the active total care of patients whose disease is not responsive to curative treatment”. In addition, WHO characterises the features of palliative care as follows. Palliative care:

- affirms life and regards dying as a normal process
- neither hastens nor postpones death
- provides a relief from pain and other distressing symptoms
- integrates the psychological and spiritual aspects of patient care
- offers a support system to help patients live as actively as possible until death
- offers a support system to help the family cope during the patient’s illness and with their own bereavement.

Many of the characteristics of palliative care are applicable to patients in whom a response to curative treatment is expected. Indeed, WHO has suggested that palliative care should have an increasing role from the diagnosis to the time of death, and should be seen as adjunct to anti-cancer treatment as opposed to an alternative to anti-cancer treatment.

Referral

The main indications for referral are:

- symptom control (pain and other symptoms)
- psychological support for patient
- psychological support for patient's relatives
- discharge planning (liaison with community palliative care services)
- wound management.

Referral can be made by an appropriate healthcare professional in contact with the patient.

1.4.9 Prosthetics service

After breast surgery, women are given access to a comprehensive and confidential breast prosthetic service according to their individual choice and need. Permanent prostheses are fitted by a breast care nurse or qualified appliance officer. In addition, all patients are given practical advice about swimming costumes and bras.

Referral

Referrals are accepted from all members of the MDT.

1.4.10 Spiritual care

The chaplaincy within each Trust is available to all patients at all stages of disease and treatment for the individual care of all spiritual needs. The chaplains are committed to helping patients regardless of individual religious beliefs.

1.4.11 Complementary therapies

There are different arrangements for complementary therapies at each of the Trusts. Information on these is routinely provided to patients.

1.4.12 Social services

Social workers are available to all patients at all stages of disease and treatment for a variety of social needs, such as finances, benefits, housing and community care assessments.

Referral

Referrals can be made by any healthcare professional.

¹ Department of Health, 2007. *Cancer Reform Strategy*.

www.mccn.nhs.uk/userfiles/documents/Cancer%20Reform%20Strategy.pdf

² NHS Cancer Screening Programmes, 2005. *NHSBSP 60 Consolidated guidance on standards for the NHS Breast Screening Programme*. www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp60.html

2 Imaging

Aim: To provide guidance on the optimal imaging strategies for the diagnosis and ongoing management of breast cancer for the multidisciplinary teams (MDTs) in the London Cancer Alliance (LCA).

The following guidance for investigation of possible breast cancer should be adopted:

- Assessment of patients referred from primary care:
 - Best practice diagnostic guidelines for patients presenting with breast symptoms, Willets, Michell, Lee, November 2010.
- Further investigation of lesions with uncertain malignant potential:
 - The London Region Quality Assurance Reference Centre Guidance on Management of Indeterminate Breast Lesions ([Appendix 1](#)).
- NICE clinical guidelines on early and advanced breast cancer.

2.1 Imaging standards for evaluation of malignancy

Mammography and ultrasound should be used as part of triple assessment where there are clinically suspicious or discrete findings present. Mammography is not routinely indicated in generalised lumpiness, pain or tenderness, or long-standing nipple retraction but may be worthwhile in women >40 years old with persisting non-suspicious breast symptoms.

2.1.1 Mammography

- Full field digital mammography with optimal image display on a mammography workstation should be used.
- The quality of mammography should adhere to NHS Breast Screening Programme (NHSBSP) standards¹ with reference to training of staff, quality assurance and the Ionising Regulation (Medical Exposure) Regulations 2000 (IRMER).
- All diagnostic breast units should have access to digital stereotactic image guided biopsy and immediate specimen radiography on site.
- All breast units should be able to perform intra-operative specimen radiography.

2.1.2 Ultrasound

- Ultrasound is the imaging modality of choice for women under the age of 40.
- Ultrasound should also be performed when mammography is discordant with clinical findings and if there is a palpable lesion.
- High resolution ultrasound machines with pre-sets modified for breast imaging should be used.
- Ultrasound scanners should meet NHSBSP standards.²

2.1.3 Magnetic resonance imaging

For indications, see [Appendix 2](#).

- MRI scanners should meet NHSBSP standards (NHSBSP, March 2012).
- MRI should be reported by clinicians with a specialist interest in breast MRI using the LCA reporting standards (2.2).

2.1.4 PET-CT

All breast units should have access to PET-CT and specialist reporting for selected cases as agreed within the MDT.

The current Royal College of Radiologists guidance for PET-CT in the evaluation of breast cancer is:

- assessment of multifocal disease or suspected recurrence in patients with dense breasts
- differentiation of treatment-induced brachial plexopathy from tumour infiltration in symptomatic patients with an equivocal or normal MRI
- assessment of extent of disease in selected patients with disseminated breast cancer before therapy
- assessment of response to chemotherapy in patients whose disease is not well demonstrated using other techniques (e.g. bone metastases).

Evidence Based Guidance for the Use of PET-CT in the United Kingdom 2012. A document prepared for the Intercollegiate Standing Committee on Nuclear Medicine, by members of the Royal College of Physicians and the Royal College of Radiologists, Sally Barington, Andrew Scarsbrook.

[www.rcr.ac.uk/docs/radiology/pdf/BFCR\(12\)3_PETCT.pdf](http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(12)3_PETCT.pdf)

2.2 Documentation and reporting standards

Imaging should be reported by clinicians with a specialist interest in breast imaging and experience in specific modality interpretation. Where relevant, reports should include information on:

- breast density
- imaging features of lesion
- size of lesion (longest dimension at least)
- site of lesion (quadrant and distance from the nipple)
- multifocality/multicentricity (including distance between foci, and whole size)
- assessment of the axilla
- change from previous images (e.g. in monitoring tumour response to treatment) – comparable measurement should be stated on consecutive images
- level of suspicion with reference to the UK 5-point scoring system (with category 6 for biopsy proven lesions)³
- the reporting clinician(s).

2.3 Imaging strategy for cancer by type

2.3.1 In situ cancer: ductal carcinoma in situ (DCIS) and pleomorphic lobular carcinoma in situ (LCIS)

- 2-view mammography of both breast +/- additional views to show extent
- 14-gauge or vacuum-assisted core biopsy of index site and other areas of suspicion to assess for multifocal/multicentric lesions
- ultrasound to demonstrate and to guide biopsy of soft tissue change, particularly if microcalcification lies in an area of dense breast tissue.

2.3.2 Invasive cancer

- 2-view mammography – further views as needed to demonstrate mammographic features
- ultrasound of ipsilateral breast and axilla
- MRI for lobular, mammographic and ultrasound indistinct cancer and significant discrepancy between clinical and imaging findings (to assess the extent and focality of ipsilateral disease)
- 14-gauge core biopsy of index site and other areas of suspicion to assess for multifocal/multicentric lesions
- core biopsy or fine needle aspiration (FNA) of axillary adenopathy suspicious of metastatic spread.

2.3.3 Pre-operative localisation

Optimal surgical excision should be supported by pre-operative localisation in all cases when conservative treatment is planned and the cancer is not clearly palpable. Ultrasound is the imaging method of choice with stereotactic localisation for lesions seen only on mammography. The wire tip should transfix the lesion (minimum standard: should lie within 1cm of the lesion), and a skin marker should be placed over the lesion. A skin marker alone is helpful when the cancer is palpable. Images and a report should be available to the surgeon prior to the operation.

2.3.4 Staging

TNM staging (UICC TNM 7) should be recorded for all stages of disease.

Pre-operative staging with CT and bone scan should be considered for:

- large volume node positive cancer (four or more nodes)
- symptoms suggesting metastases
- T3 or T4 cancer
- recurrent cancer in the ipsilateral breast.

It may be appropriate to consider staging for a lesser extent of disease if the cancer is triple negative on core biopsy.⁴

2.4 Surveillance of cancer patients and women at increased risk of cancer

2.4.1 Surveillance strategies⁵

- Annual mammography for all patients with early breast cancer, including DCIS, until they enter the NHSBSP. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for at least 5 years.⁶
- Mammography should be delayed for 6 weeks after cessation of lactation because of the reduced sensitivity of the denser breast. The NHSBSP recommends that ultrasound may be used as an alternative screening modality while women are breast feeding.
- Consider annual MRI for women under the age of 40.
- Patients at underlying increased risk should follow the appropriate NHSBSP guidance if it offers more intensive screening during or after the initial surveillance period.
- Routine surveillance imaging of the post-mastectomy reconstructed breast is not indicated.

2.4.2 High-risk surveillance

(see [Appendix 3](#); also see [Chapter 8](#), NHSBSP 74⁷)

2.4.3 Moderate increased risk surveillance⁸

- Women at moderately increased risk should be offered annual mammography between the ages of 40 and 50.
- Any other surveillance strategy should only be part of an approved trial (e.g. FH02).

2.5 Reporting interval cancers⁹

- All cases of newly diagnosed breast cancer in women of screening age should be reported to the responsible screening service.
- If a woman asks to discuss her screening mammogram, she should be informed that all cases of breast cancer identified after a normal outcome to screening are formally reviewed by the screening service. The director of screening should be made aware of the woman's wishes and will arrange a consultation.

2.6 Mismatch/discordance of screening pre-operative diagnosis and surgery

- All cases where a mismatch between the pre-operative diagnosis at screening and the post-surgical diagnosis is suspected should be promptly reported to the responsible NHSBSP director of screening and the screening pathologists.
- All cases should be investigated according to the guidance in [Appendix 4](#) and raised as an incident with the local screening service if appropriate. The final outcome should be documented through the MDT in the local and NHSBSP records.

¹ NHSBSP, 2006. *NHSBSP 63 Quality assurance guidelines for mammography: Including radiographic quality control*. www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp63.html

² NHSBSP, 2011. *NHSBSP 70 Guidance notes for the acquisition and testing of ultrasound scanners for use in the NHS Breast Screening Programme*. www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp70.html

³ A.J. Maxwell, N.T. Ridley, G. Rubin, M.G. Wallis, F.J. Gilbert, M.J. Michell, on behalf of the Royal College of Radiologists Breast Group. *Clinical Radiology*. 2009; 64:624-627.

⁴ [S. Aebi](#), [T. Davidson](#), [G. Gruber](#), [F. Cardoso](#) on behalf of the ESMO Guidelines Working Group. *Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. [Annals of Oncology](#); [Volume 22, Issue suppl 6](#): vi12-vi24

⁵ NICE, 2009. *Breast cancer (early & locally advanced): diagnosis and treatment (CG80)*. www.nice.org.uk/guidance/index.jsp?action=byID&o=12132

⁶ Health Technology Assessment 2011, Vol 15: No.34 ISSN 1366-5278.

⁷ NHSBSP, 2013. *NHSBSP 74 Protocols for the surveillance of women at higher risk of developing breast cancer*. www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.pdf

⁸ NICE, 2006. *Familial breast cancer (CG41)*. <http://publications.nice.org.uk/familial-breast-cancer-cg41>

⁹ NHSBSP, 2006. *Cancer Screening Series No. 3 – Disclosure of audit results in cancer screening.*
www.cancerscreening.nhs.uk/publications/cs3.html

3 Breast Pathology Protocols and Guidelines

3.1 Pre-operative assessment

3.1.1 Core biopsy (e.g. 14 gauge) and vacuum-assisted core biopsy (e.g. 8 or 11 gauge)

Clinical details and handling

Once sampled, the cores should be placed directly into formalin.

The request form should include:

- patient information (including details of previous clinical management), clinical and imaging (e.g. U1 to 5 and M1 to 5) details
- site of the lesion
- if the specimen is urgent, or required for a specific date/time
- if the core biopsy is taken for microcalcification, the result of specimen X-ray
- information on whether research cores have also been taken.

It is helpful if cores containing microcalcification are separately identified, e.g. in a separate cell safe capsule. Core biopsies of two lesions or lesions in different breasts should be sent in separate packets with individual forms.

Pathology handling

Specimens should be sent to the pathology department as promptly as possible in order to be processed overnight on the same day. They can then be embedded, cut and stained and reported, ideally by the end of the following working day. All cases for microcalcifications should have at least three levels examined, as per the NHS Breast Screening Programme (NHSBSP) guidelines. Cases needing further serial sections or special stains will take up to 36 hours longer.

Microscopy

The report will comment on the following in the **microscopy section**:

- presence of specialised breast tissue
- epithelial hyperplasia (usual and atypical)
- calcification (presence and relationship to benign or malignant lesions)
- type and provisional (core) grade of invasive cancer and provisional grade and type of in situ carcinoma, where possible (it should be noted that invasive carcinoma grade in core has approximately 75% accuracy)
- lympho-vascular invasion is rarely identified in core biopsies and its absence need not be commented upon; if present this should, conversely, be stated
- ER and HER2 status should be assessed on all invasive carcinoma in cores.

The summary/conclusion of the histology report should include, as per the UK NHSBSP guidelines for all **diagnostic** samples, the 'B' category of the core or vacuum-assisted core biopsy, and the diagnosis. This is not, however, required if the specimen is a vacuum-assisted **excision** specimen.

The B categories are as follows:

B1 – normal

B2 – benign

B3 – uncertain malignant potential

B4 – suspicious

B5 – malignant.

For B5, it should be noted whether this is B5a, ductal carcinoma in situ (DCIS), or B5b, invasive carcinoma, or other malignancy.

3.1.2 Fine needle aspiration cytology specimens

Fine needle aspiration cytology (FNAC) samples from breast lesions should be handled and reported as per the NHSBSP guidelines, and each report should include the categorical result (C1 (inadequate/insufficient) through to C5 (malignant)) as well as indication of the populations of cells identified.

FNAC from lymph nodes under ultrasound guidance is increasingly received for pre-operative assessment of nodes with suspicious features, although some centres will perform core biopsy for such samples in some circumstances. These should be also be handled and reported as per NHSBSP guidance.

3.2 Surgical specimens

3.2.1 General clinical details and handling

Specimens from which tissue is not to be biobanked can be placed immediately in sufficient buffered formalin (ideally 10 times the specimen size) or sent immediately fresh to the laboratory, according to local protocol. In some rare circumstances, with collaboration and education, the surgeon may be advised to slice from the posterior aspect of a large excision specimen/mastectomy in order to optimise fixation; this should not, however, be performed without prior agreement with the consultant breast pathologist. Specimens which are pushed into small containers without adequate surrounding formalin will be adversely affected, and clinically important pathological information (particularly ER status, HER2 status, histological grade, presence or absence of lympho-vascular invasion) may not be accurately assessable.

3.2.2 Wide local excision

Clinical details and handling

Specimens should be orientated with marker sutures and/or clips (e.g. 1 = anterior; 2 = superior; and 3 = nipple margin, as per local protocol) and should ideally be sent unfixed to the pathology department (or biobank) with all relevant information on the request form.

If pathology staff will not be available to handle fresh specimens, the specimens should be placed immediately in sufficient buffered formalin and sent to the laboratory as soon as possible.

It is essential that relevant clinical information be provided. For example, if the disease is multifocal or there are synchronous lesions, omission of this information will lead to delay in issuing the final histology report. Details of any neo-adjuvant therapy should be provided.

Pathology handling (in fresh or fixed state)

The specimen should be immediately dealt with as follows:

- weighed, measured and palpated
- resection margins marked according to local protocol (e.g. anterior = red; posterior = black; medial = green; lateral = orange; inferior = yellow; superior = blue)
- the tumour should be incised (if this is performed on the fresh specimen, tissue for the biobank, where appropriate, should be taken at this stage)
- if the specimen is received fresh, buffered formalin is now added; orientation of the specimen should be maintained so that appropriate blocks can be taken the following day
- blocking should include tumour blocks and blocks of **all** radial margins to allow accurate measurement of tumour size and distance to resection margins.

There are a variety of acceptable methods for handling of wide local excisions (WLEs)

(see Pathology Reporting Guidelines publication no. 50, 2005.

www.cancerscreening.nhs.uk/breastscreen/publications/pathology.html#p-pr)

Different methods may be more appropriate for different lesions and according to the pathologist's preference (see the diagrams below).

Figure 3.1: 'Bread-slicing' for mass lesion

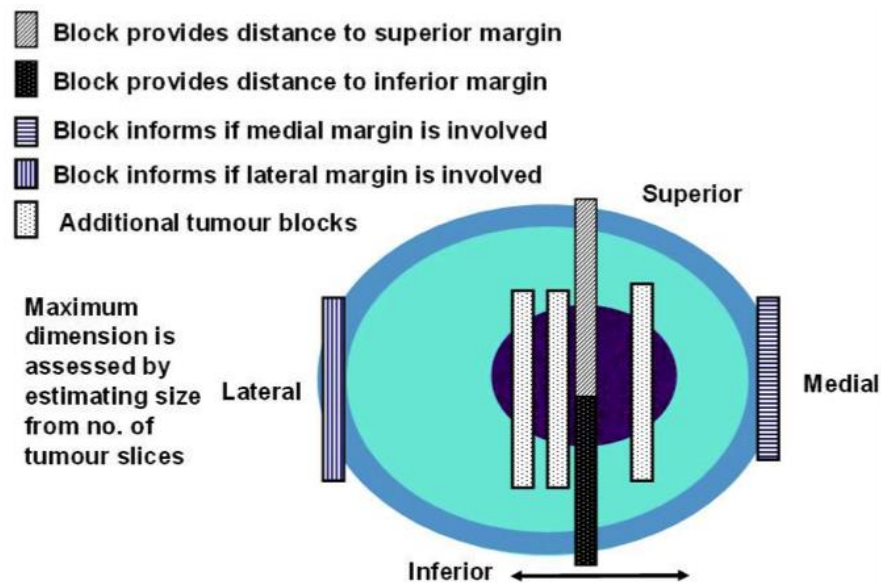
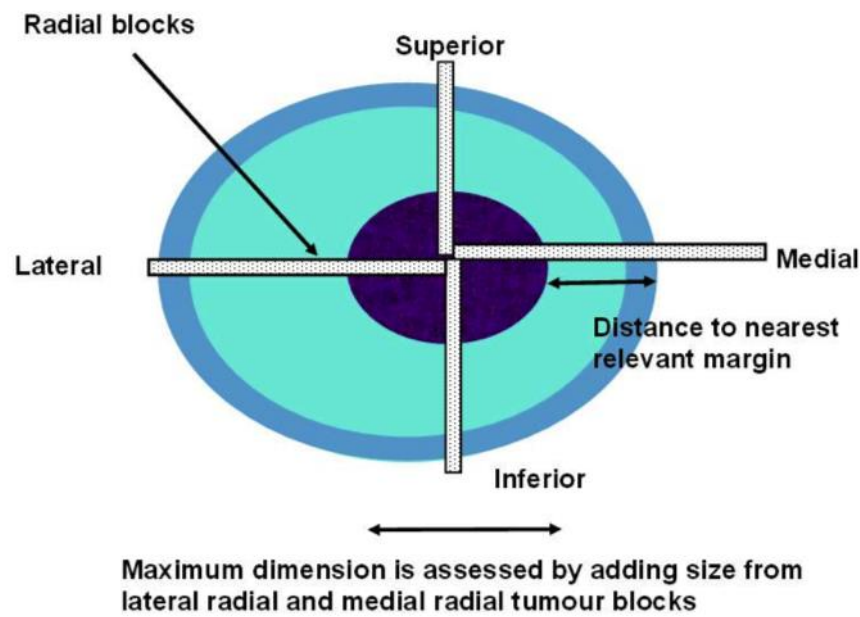


Figure 3.2: Radial blocking technique

Most reports from breast surgical specimens should therefore be available within 5 working days after receipt of the specimen, unless further sections are taken or special or immunohistochemical (IHC) stains are needed for diagnosis.

3.2.3 Therapeutic needle localisation specimens

Clinical details and handling

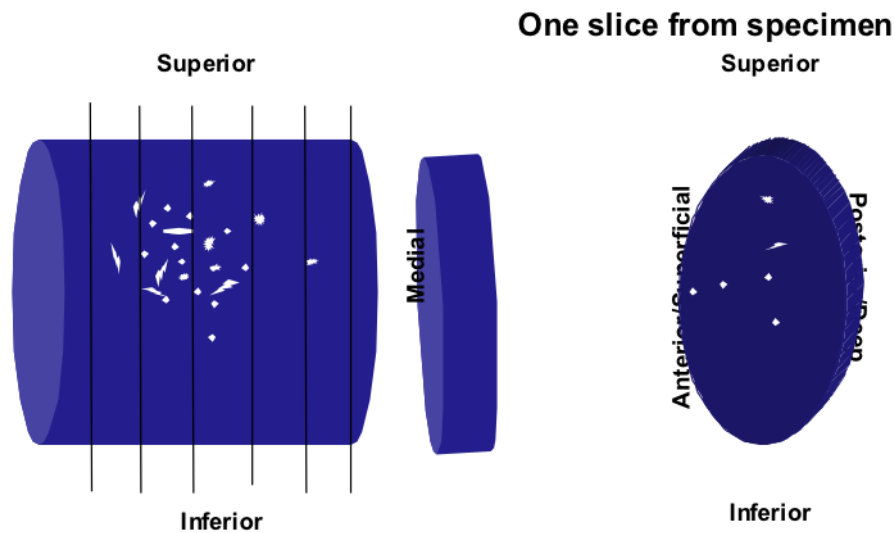
After specimen X-ray, the sample is sent to the pathology department and should ideally be accompanied by a copy of the specimen X-ray (or available on the Picture Archiving and Communications System (PACS)) with an appropriately completed request form.

The specimen should be orientated as per local protocol (e.g. with up to three sutures (e.g. 1 = anterior; 2 = superior; 3 = nipple margin) and ideally also with clips (1 = anterior; 2 = superior; 3 = nipple margin)).

Pathology handling

The specimen should be dealt with as described for WLE; but if no definite macroscopic lesion is identified then either the whole specimen should be processed or an X-ray of specimen slices carried out (depending on the size of the specimen) to enable selection of blocks to include, for example, the calcified areas plus adjacent tissue.

X-ray of residual tissue or tissue cassettes may be needed to locate calcification if none is found on the preliminary sampling. Reporting time on specimens is similar to that for WLEs in straightforward cases but will take longer when there are problems locating calcification.

Figure 3.3: 'Bread-slicing' for microcalcification

3.2.4 Diagnostic localisation biopsies (microductectomies)

Clinical details and handling

Diagnostic localisation specimens are typically those of a lesion for which either pre-operative diagnosis has proven unsuccessful or where core biopsy has shown a B3 lesion such as a radial scar, papilloma or atypical epithelial proliferation. Fresh sampling of these is therefore, in general, not appropriate and these typically require immediate fixation in an adequate amount of formalin, unless requested for a specific study.

Microductectomies (microdocheotomies) are samples from the sub-areolar ducts, usually in patients who have a single-duct or blood-stained nipple discharge.

Pathology handling

- The specimen should be weighed and measured, and inked if orientation markers have been positioned by the surgeon, and then serially sliced at intervals of approximately 3–5mm. For microductectomies this is best done from anterior or posterior aspects (there is usually a suture on the anterior aspect of the specimen).
- Small samples (e.g. those 30mm in size or less) should be embedded in their entirety. This is particularly important if no macroscopic lesion is visible.
- Microductectomies may bear a small papillary lesion that is often not visible to the naked eye and embedding the whole tissue (as these are not large, but if resources permit) will avoid return to take further blocks.
- Larger diagnostic localisation biopsies will often benefit from specimen slice X-ray examination, particularly those with an impalpable lesion such as microcalcification.
- The sampling technique and the number of blocks taken are dependent on the size of both the specimen and the abnormality; for larger specimens, sampling should be adequate to determine accurately the size of the lesion.
- Sampling should include the extremes of the abnormality and adjacent tissue in order to avoid underestimation of size. This is particularly important with cases of DCIS, as it is recognised that size of microcalcification may be an underestimate of true tumour size.

3.2.5 Shave biopsies/cavity shavings

Clinical details and handling

These are very variable specimens, ranging from small portions submitted as ‘bed biopsies’ (which can be embedded whole) to larger re-excisions of a specific margin. Cavity shave specimens/re-excisions of a specified margin, either received at the same time or subsequent to a therapeutic excision, should be received with orientation sutures. If the re-excision is of the entire margin, it may be orientated with sutures/clips as per a WLE. If a single margin has been excised, typically a single suture can be placed on the ‘cavity side’.

Pathology handling

- Once fixed these should be weighed and measured.
- Paint according to standard protocol if the whole cavity is present, or on the cavity side and opposite (new margin) side if the specimen is derived from a single aspect (e.g. medial cavity shaving).
- If small, the specimen should be sliced transversely and all the tissue embedded.
- If larger, sliced and random (e.g. alternate) slices can be embedded (e.g. typically approximately two to three per 10mm of maximum dimension cavity shaving).

3.2.6 Mastectomy specimens

Clinical details and handling

The specimen should ideally be sent unfixed with an appropriately completed request form as speedily as possible to the laboratory or biobank, as appropriate. These specimens are most likely to be affected by poor fixation if not sliced prior to submersion in formalin and are those which, with collaboration, may be sliced by the surgeon prior to fixation after discussion with the pathologist (e.g. if performed out-of-hours).

The request form must include details of number, site and extent of lesion(s) and of any prior chemotherapy, as well as any other relevant information.

If the axilla has not been dissected in continuity with the breast, an orientation suture should be placed (e.g. superiorly) to highlight the axillary fat.

Pathology handling

The specimen should be handled as follows:

- described, weighed, orientated and palpated
- either (a) sliced in the sagittal plane at 10mm intervals from the deep surface to the skin throughout; (b) sliced in a cruciate-fashion through the tumour (as for WLEs) and then the remainder of the breast parenchyma sliced at 10mm intervals; or (c) sliced from posterior to anterior aspect
- all macroscopic abnormalities should be described
- fresh tissue for the biobank may be taken at this stage
- formalin should then be added
- in cases of extensive DCIS only, or extensive DCIS with a small invasive lesion, slice X-rays may be invaluable, once the slices are adequately fixed, if no visible lesion is identified.

Blocks should include several slices of the full face of the tumour and all the peripheral aspects of the lesion to gauge the size of the disease (although it should be noted that the cruciate approach provides a more accurate assessment of lesion size). Any other macroscopic abnormality should also be sampled. The distance of tumour from deep margin can be assessed macroscopically and sampled. It is not possible to provide unequivocal advice regarding the number of blocks of tumour that should be taken; in general five to six blocks of a 2cm tumour is considered appropriate.

It is important to note that the tumour blocks are more important than blocks of the deep margin and 'normal' tissue from quadrants in mastectomy specimens. However, random blocks can be taken from all four quadrants as well as from the nipple if resources permit; these are less important than blocking the tumour sufficiently.

The axillary tail of all mastectomy specimens should be sliced and lymph nodes sought. All lymph nodes should be identified and processed according to the NHSBSP guidelines. Ideally, this approach includes multiple slices from each lymph node per cassette.

Reporting time for mastectomy specimens is similar to that for WLEs; however, cases of pure DCIS will take longer because of the need to X-ray slices before taking blocks.

3.2.7 Sentinel lymph node biopsy specimens

Clinical details and handling

These should be placed in sufficient formalin and sent to the pathology laboratory.

Pathology handling

The NHSBSP guidelines and the medical literature to date indicate that the most important step in the examination of sentinel lymph nodes is thin slicing of the sample.

- All nodes measuring 5mm or less in maximum diameter should be sliced, if possible, and processed (usually in two portions/halves) for histological examination.
- Nodes that are greater than 5mm in maximum diameter should be sliced thinly at 2mm intervals and all will be processed for histological examination.
- There is no requirement to place only one or two slices in each cassette; if all slices fit into a single cassette then the workload, both for laboratory and microscopy, is reduced.
- There is little evidence on the **clinical** value of additional levels for the detection of small deposits of nodal metastasis. However, it is clear that additional H&E levels increase the likelihood of detection of these small metastatic foci and can be considered; these are not mandatory.
- Routine IHC assessment of sentinel lymph nodes is not recommended by UK guidelines, even if of lobular sub-type. However, if suspicion is high (e.g. if suspicious cells are identified on H&E stained sections), then AE1/AE3 antibody staining should be undertaken (this has been shown to be the most effective cytokeratin for assessment of metastasis in sentinel lymph nodes).

Criteria for reporting nodes

The following must be reported:

- macrometastases, i.e. 2mm or more in size
- micrometastases up to 2mm in size, or deposits within the parenchyma (as per the European Guidelines; Cserni. Cancer 2005)
- isolated tumour cell clusters (these are regarded as node negative).

There is increasing evidence that the tumour volume in the sentinel lymph node is predictive of metastatic disease in additional axillary lymph nodes. It is recommended that the size of the largest metastatic deposit should be recorded in the histology report.

3.2.8 Axillary clearances

Clinical details and handling

These may be excised either in continuity with a mastectomy specimen or as a completion axillary dissection in a patient with a previously positive sentinel lymph node. The latter specimens should be placed in a separate pot of sufficient formalin.

Pathology handling

- Identify all nodes by palpation and blunt dissection.
- Those <5mm can be embedded whole and put with similar-sized nodes into one cassette.
- Those lymph nodes >5mm in diameter should be sliced across the shortest diameter of the node and the slices embedded into one or more cassettes.
- As a minimum, at least one slice should be examined for each 5mm of overall node size; thus, at least four slices of a 2cm node should be examined histologically.
- Ideally (as per the UK NHSBSP Pathology Guidelines, 2005), the whole of each node should be embedded and examined; if slicing is required, each should be placed in a separate cassette.
- The exception is obviously involved nodes, which need only have one slice examined for confirmation.
- A suture may be used to mark the apical lymph node, or this may be submitted separately. In either situation the presence or absence of metastatic disease in the 'highest' node or the apical lymph node should be noted.

3.2.9 Breast reduction specimens

Clinical details and handling

These should be placed in sufficient formalin and sent to the pathology department.

Pathology handling

- These should be weighed and the size of the fibro-fatty specimen and any attached skin should be recorded.
- If there is no macroscopic abnormality, two cassettes of each specimen are usually sufficient.
- If the patient has had contra-lateral breast carcinoma, more blocks should be taken (e.g. 4–6).

3.2.10 Prophylactic mastectomies

Clinical details and handling

These should be placed in sufficient formalin and sent to the pathology department.

Pathology handling

- These should be weighed and measured, as for excisions for known carcinoma.
- As the patient is known to have an increased risk of breast carcinoma, more blocks should be taken from these samples than from similar breast reductions.
- It is recommended that two random blocks from each quadrant should be sampled as well as a nipple block and any other suspicious areas.

3.2.11 Therapeutic excision and mastectomy specimens for invasive carcinoma following neo-adjuvant chemotherapy: macroscopic handling

Clinical details and handling

Some patients with high grade, large, locally advanced or inflammatory breast cancers may receive chemotherapy prior to surgery. This permits an assessment of tumour responsiveness to the chemotherapy and may result in tumour downstaging, i.e. a reduction in tumour size and/or nodal involvement.

- The macroscopic handling of breast excision specimens following neo-adjuvant (primary) therapies can be difficult, particularly if there has been a good, or complete, response to the systemic treatment. This is especially the case for the post-neo-adjuvant chemotherapy specimen, when the situation is more common than following primary endocrine therapy.
- The proper pathological approach to such specimens is therefore crucially dependent on knowledge of the previous clinical, imaging and pathological findings, including tumour type and grade and the location of the tumour within the breast. The difficulties in identification of the tumour bed are exacerbated if limited clinical information is provided, for example if mastectomy is performed and details of the original location of the lesion are not provided on the request form by the surgeon. Multiple invasive foci may similarly be missed if inadequate information is included in the information given to the pathologist.
- The initial laboratory handling of post-chemotherapy specimens should be undertaken in a similar manner to wide local excision or mastectomy specimens from patients not receiving such treatment.
- Specimens from post neoadjuvant chemotherapy cases should be orientated as described above for other specimens and as per local protocol and sent to the laboratory.

Pathology handling

- Adequate and prompt fixation is as important here as in any other breast specimen.
- A marker may be inserted into the tumour prior to starting treatment and its localization within the excised breast tissue can help determine the site of tumour. In order to ensure that this tumour site is completely removed, some units mark the skin to delineate the tumour size prior to treatment, which can be helpful. In essence, for these specimens close working with the other members of the multidisciplinary team is vital.
- On palpation and slicing, a mass lesion may be obvious if there has been little response to neo-adjuvant therapy and the specimen can be handled as for any other primary resection specimen. If there has been a significant tumour response, the lesion may be difficult to identify, both with the naked eye and by palpation; a pale, ill-defined, soft, oedematous area of fibrosis may be all that can be detected. With a good or complete pathological response there may only be a vague impression that the tissue architecture is abnormal (pathologically and radiologically). In such cases the marker, or residual microcalcification, can be seen in specimen X-ray and will direct the attention of the pathologist to the appropriate area. Often the marker can be detected macroscopically on thin slicing of the specimen.

- The tumour bed (as identified by the location of the radiological marker, in conjunction with clinically described site and macroscopic recognition of corresponding mass or area of fibrosis) should be thoroughly sampled in order to detect residual disease and allow for assessment of the tumour bed in three dimensions.
- A tumour that has responded to chemotherapy may regress focally and appear as multiple, apparently separate foci. Blocks should therefore be taken to include the entire tumour bed, as residual tumour foci may be scattered throughout it.
- For large tumours where cruciate blocks cannot easily be taken, assessment of the tumour bed can be achieved by estimation of slice thickness and the number of consecutive blocks involved, along with the two dimensions seen histologically.
- Overall, the extent of sampling will depend on the size of the tumour and tumour bed and is often necessarily more extensive than for a tumour not previously treated by chemotherapy. The extent of block sampling should be sufficient to assess the maximum extent and cellularity of any residual tumour.
- Large blocks, if available, are very useful in preserving the tissue architecture. They can facilitate the assessment of multiple foci of invasive carcinoma and the assessment of the amount of residual tumour in relation to the tumour bed, thus aiding an assessment of tumour response.

Lymph nodes should be blocked as per the guidelines for those patients who have not received neo-adjuvant therapy, depending on the surgical procedure (i.e. sentinel lymph node or axillary clearance). As with the lesion in the breast, lymph nodes may also be more difficult to identify macroscopically after neo-adjuvant treatment; some patients may have had a pre-treatment sentinel lymph node biopsy and others may be known to have metastatic disease (confirmed by pre-operative, pre-therapy ultrasound guided FNAC or core biopsy). In both such situations macroscopic assessment of the lymph nodes may be difficult. There is also some evidence that there is a decreased yield of nodes in patients who have received neo-adjuvant chemotherapy.

3.3 Histopathology reports

All specimens are reported by a consultant breast pathologist, or a pathology trainee closely supervised and reviewed by a consultant breast pathologist. All consultants who report breast pathology must participate in the National Breast Screening Programme External Quality Assessment scheme and regularly attend a Breast Pathology Update Course.

See sample breast proforma ([Appendix 5](#)) for reporting. Reports will include all the information listed in the Royal College of Pathologists' publication 'Minimum dataset for breast cancer histopathology reports', as well as additional pathological information.

In situ carcinoma:

- presence and grade and architectural growth pattern of in situ carcinoma
- presence of comedo-type necrosis (optional)
- pure DCIS size
- presence of foci of definite microinvasion (<1mm)
- completeness of excision; any radial resection margins <5mm distant should be listed and the measurement provided (unless <1mm, when this should be stated).

Invasive carcinoma:

- grade of invasive carcinoma and grade components (TPM scores, in that order, e.g. 121, 332)
- histological sub-type of invasive carcinoma
- maximum dimension of invasive carcinoma
- whole tumour (invasive + DCIS) size (lobular carcinoma in situ, unless pleomorphic is not included)
- presence or absence of lympho-vascular invasion (categories: absent, possible or definite)
- ER and HER2 status (see below)
- completeness of excision; any margin <5mm distant should be specifically listed and the distance to that margin given, or stated to be <1mm (as per the UK NHSBSP guidelines and data form); margins >5mm distant may be listed as such and precise distance need not be provided
- total number of lymph nodes identified and number involved by metastatic tumour
- number of nodes bearing (a) micrometastasis and (b) macrometastasis and (c) ITCs should be identified
- size of largest nodal metastatic deposit
- TN(M) stage ([Appendix 6](#)).

Additional information will be provided as applicable:

- presence of extracapsular spread in lymph nodes
- response of carcinoma to prior neo-adjuvant therapy.

The information above should be provided using a synoptic report/proforma as per UK NHSBSP recommendations.

It is helpful, for block selection for clinical trials and for further research, if the specific paraffin wax blocks containing tumour (and potentially those with metastasis in lymph node) are identified in the histology reports as this obviates the need for retrieval and re-review of all of the H&E sections subsequently.

3.4 Biomarkers

- ER and HER2 should be assessed on all patients with invasive breast cancer (see Appendices [7](#) and [8](#)).
- This should be performed on the core biopsy so that patients can be included in appropriate neo-adjuvant studies and to ensure that results are available for MDM post-excision, as per the updated UK HER2 guidelines¹ and NICE quality standards.
- The ER and HER2 status from the core biopsy will be noted in the subsequent excision specimen for completeness (with core biopsy reference number) but will not be repeated on the surgical sample, with exceptions as follows.

ER and HER2 should be reassessed on the surgical excision specimen if:

- biomarker status is not known (e.g. core biopsy performed elsewhere and not sent for review)
- there was insufficient invasive tumour in the core biopsy for accurate assessment
- invasive carcinoma is identified in an excision, where previously only in situ disease was seen
- there is significant heterogeneity of a tumour on excision (e.g. a mixed lesion) or if multiple lesions with different morphology are seen at excision; biomarkers will not be repeated if multiple foci are seen which are clearly of similar appearance/tumour type and grade

- the core biopsy result was 2+ with IHC and the fluorescence in situ hybridisation (FISH) score on core biopsy was in the borderline range (1.8–2.2)
- patients have a subsequent biopsy from recurrent disease (either local or disseminated) but not necessarily on the primary tumour after receipt of primary (neo-adjuvant) chemotherapy at this time.

Of note, HER2 IHC (and potentially ER) can be problematic on bone marrow trephines and bone samples which have been decalcified by some methods – false negatives may result. As a rule of thumb, both HER2 IHC and HER2 FISH should be requested on such specimens as there is evidence that the in situ hybridisation is more robust in decalcified material.

It is therefore prudent to include comment that reporting of biomarkers on these specimens may potentially result in false negative results for ER and HER2 on decalcified tissue.

3.5 Neo-adjuvant therapy

Patients who have had neo-adjuvant therapy should have a semi-quantitative assessment of the degree of response recorded. There is no universally agreed method or system for this and it is recognised that additional research is required.

One option is to report the Residual Cancer Burden²

www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Nevertheless, the size of the residual invasive carcinoma and the percentage cellularity of this should be documented in histopathology reports from such samples.

¹ Nunes, C.B., et al., False positivity in HER2 testing of breast cancer: novel paths for approaching an old dilemma. *J Clin Pathol*, 2008. **61**: p. 818-24.

² Symmans, W.F., et al., Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*, 2007. **25**: p. 4414-22.

4 Surgical Management of Breast Cancer

4.1 General principles

- Where surgery is the first treatment, this should take place within 31 days of the diagnosis being made.
- In medically fit patients, non-reconstructive breast cases should be done as day-case/23-hour surgery.
- Patients should have all surgical options (breast conservation, mastectomy with or without reconstruction and, if appropriate, oncoplastic conservation procedures) discussed with them in the presence of their key worker/clinical nurse specialist (CNS).
- The patient's choice must always be respected.
- The National Mastectomy Audit reported unacceptable levels of pain in women having mastectomy alone or mastectomy plus reconstruction. Protocols should exist to manage and assess post-operative pain in these patients.
- Young women, who are likely to have chemotherapy and wish to preserve their fertility, should be referred to an assisted conception service to discuss their options as early as possible.

4.2 Choice of breast operation

Surgery may be the initial treatment or it may be undertaken after primary chemotherapy or endocrine therapy. The same principles will apply in either case. The majority of cases will be suitable for breast conservation. However, it is important to ensure that conservation surgery will leave the patient with an aesthetically acceptable breast (preserved breast shape and well placed scars).

Indications for mastectomy:

- Unfavourable tumour: breast volume ratio (i.e. a large tumour in a small breast). In these circumstances, consideration should be given to oncoplastic resections (therapeutic mammoplasty, Grissoti flap or round block resections). If these techniques are not available locally, patients should be given the option of referral to an oncoplastic surgeon. Also consider downsizing the tumour with primary medical treatment.
- Where there is a recurrent tumour in a breast that has previously been irradiated with whole breast radiotherapy.
- Where radiotherapy may be contraindicated – excessive photosensitivity, vasculitis, severe pulmonary fibrosis, scleroderma, previous mantle radiotherapy.
- Where there is extensive ductal carcinoma in situ (DCIS) of high or intermediate grade. If there is extensive low grade DCIS, the patient should be informed of the uncertainty over the natural history of low grade DCIS. Observation may be considered within the context of a clinical trial. Consideration should also be given to biopsy of more than one focus of microcalcification prior to proceeding with mastectomy. A second biopsy should ideally be taken from the edge of suspected extent.
- Where there are multifocal/multicentric tumours, whether invasive or non-invasive. In some circumstances, oncoplastic techniques may obviate the need for mastectomy and can be considered

4.3 Breast reconstruction

All patients for whom mastectomy is a treatment option should have the opportunity to receive advice on breast reconstructive surgery. Not all patients will be physically fit for or wish to consider reconstruction. The reason a patient declines or is advised against immediate breast reconstruction (IBR) should be recorded. IBR rates will be compared across Trusts and should not be lower than national average.

For patients who express an interest in breast reconstruction, discussions should take place on the ideal timing of the reconstruction. This should include the risks and benefits of immediate versus delayed breast reconstruction techniques. The timing of breast reconstruction should take into account the need for post-mastectomy radiotherapy (PMRT) and be discussed with the reconstructive surgeon. The multidisciplinary team (MDT) should identify patients in whom a delayed reconstruction would be a better option.

Contraindications to IBR include:

- inflammatory breast cancer/T4 tumours
- multiple co-morbidities.

Relative contraindications include:

- need for adjuvant chest wall radiotherapy
- metastatic disease that is not stable.

The full range of suitable reconstructive techniques should be discussed with the patient. These should include tissue expansion/implant reconstruction with or without acellular dermal matrix reinforcement, latissimus dorsi flap reconstruction (autologous or with implant), and free flap reconstruction (muscle-sparing TRAM, DIEP, TMG, SGAP or IGAP).

All patients should have access to specialist plastic surgical advice if requested or required and treatment in a timely fashion, so as to allow for treatment within guideline times. Neo-adjuvant chemotherapy can be used to give time for consideration of reconstruction. All units should have a clear documented pathway for referral.

If PMRT is likely, full information regarding the potentially unfavourable longer term impact of radiotherapy on both implants and autologous tissue needs to be discussed and considered.

- Upfront sentinel lymph node biopsy (SLNB) may help to guide choices with regards to IBR or DBR as well as techniques.
- A 'delayed-immediate' or staged reconstruction may be appropriate.
- If an expander is used as a 'skin-banking' device, then expanders with integrated ports should be avoided to facilitate the PMRT.

For more specific guidance please refer to:

www.associationofbreastsurgery.org.uk/media/23851/final_oncoplastic_guidelines_for_use.pdf

4.4 Surgical management of the axilla

4.4.1 Invasive breast cancer: axillary staging is mandatory

- Pre-operative staging of the axilla should be undertaken in all invasive cancers using ultrasound and, if indicated, guided fine needle aspiration cytology or core biopsy.
- If pre-operative staging of the axilla reveals metastases (C5 or B5), a Level II/III axillary lymph node dissection (ALND) should be recommended.
- If pre-operative staging of the axilla is normal both clinically and on imaging, the axilla should be further staged by SLNB.
- SLN localisation technique must include radio-isotope as a minimum. If Trusts do not have nuclear medicine on site, they should collaborate with neighbouring Trusts so that patients can receive isotope injection in one Trust and have surgery in another. Lymphoscintigraphy is a matter of choice. Where for technical reasons radio-isotope localisation is not possible, it is acceptable to carry out Patent Blue V guided 4 node sampling of the axilla.
- Following a positive SLNB, the need for further axillary treatment for low volume disease is unclear. All SLN positive cases should be discussed at the MDT meeting and risks and benefits discussed with the patient. In general:
 - Macrometastases: further axillary treatment is recommended, usually as completion ALND.
 - Micrometastases: further axillary treatment is generally not required. Completion ALND may be useful if further staging information is likely to influence adjuvant treatment outcome.
 - Isolated tumour cells (ITC) should be regarded as a negative axilla and further axillary treatment is not recommended.
- The use of intra-operative assessment of the sentinel node will reduce the need for re-admission for completion surgery.
- All patients undergoing surgery on their axilla, whether sentinel node or clearance, should be given information on risk-reduction strategies for lymphoedema.
- Inflammatory breast cancer: the accuracy of SNB is unknown.
- Primary medical therapy (PMT)
 - ALND should be offered to all node positive patients irrespective of response to primary systemic therapy.
 - SLNB can be offered prior to or after PMT in conjunction with surgery to the breast.

4.4.2 Ductal carcinoma in situ

- Axillary staging should be SLNB only.
- Axillary staging should not be offered unless there is considered to be a high risk of invasive disease (mass or extensive microcalcification, size >40mm, microinvasion).
- SLNB should be offered if the patient is having a mastectomy.

4.5 Surgical margins and cavity markings for breast conservation

- Radial margins must comply with the local MDT standard. There are no data to support a specific margin of excision but it should be at least > or equal to 1mm.
- Liga clips should be applied to the surgical cavity to allow intensity-modulated radiation therapy.
- All specimens should be orientated.
- Specimen X-rays may be required in breast conserving surgery but are essential for impalpable lesions.

4.6 Axillary presentation of breast cancer

Patients may present, symptomatically or via screening, with axillary nodes containing adenocarcinoma cells. Two-thirds of such patients prove to have an occult breast cancer that can usually be demonstrated by mammography or magnetic resonance imaging. These patients should be treated as for breast cancer with palpable nodal metastases. The remaining third should be assumed to have a truly occult breast cancer and should be managed as follows:

- Level II/III axillary clearance
- adjuvant systemic therapy as per protocol
- radical ipsilateral breast radiotherapy (plus supraclavicular fossa radiotherapy if >4 positive nodes).

Alternative options include mastectomy or no local breast treatment.

4.7 Ductal carcinoma in situ

4.7.1 Surgery

The aim of surgery is to achieve complete excision of the in situ tumour and to minimise local recurrence. This may involve mastectomy. The same principals apply as for invasive disease.

Lymph node staging is not normally required for patients with DCIS treated by breast conserving surgery, unless microinvasion, extensive high or intermediate grade DCIS (>4cm) or frank invasion is suspected on the pre-operative biopsies. In such cases, SNLB may be considered. Women having a mastectomy +/- immediate reconstruction for an extensive area of microcalcification with a pre-operative diagnosis of DCIS alone may, however, be considered for SLNB. Axillary clearance is contraindicated in the treatment of patients with a pre-operative diagnosis of DCIS alone.

4.7.2 Radiotherapy

See [Chapter 5.1.2](#)

4.7.3 Systemic treatment

See also [Chapter 5.1.3](#)

In general, adjuvant endocrine therapy is not recommended for patients with DCIS.¹ However, in patients with ER positive DCIS treated with breast conserving surgery, tamoxifen may be considered for those with a strong family history or for patients regarded as having a high risk of recurrence when a recommendation of mastectomy is not acceptable to the patient (see NSABP B-24² and UK DCIS trials³).

4.8 Lobular carcinoma in situ

Lobular carcinoma in situ (LCIS) is generally considered to be a risk factor for subsequent invasive breast disease rather than representing pre-invasive breast cancer, with the exception of pleomorphic LCIS. In some cases LCIS co-exists with invasive carcinoma. Generally it is an incidental finding and some form of open surgical or vacuum-assisted wide biopsy should be performed. Pleomorphic LCIS should be regarded more as pre-invasive disease and excised as for DCIS.

Patients with LCIS should be under annual mammographic follow-up for a minimum of 5 years and then can be discharged to the NHS Breast Screening Programme (NHSBSP). Patients still under the age of 50 should

continue with annual screening until eligible for NHSBSP. In the context of a strong family history, the presence of extensive LCIS and/or other histological risk factors such as atypical ductal hyperplasia, as well as certain imaging characteristics, may constitute a reasonable indication for mastectomy. Such cases should involve discussion with the multidisciplinary team and, if appropriate, the genetics unit prior to making any decision to have a mastectomy. If these women opt not to have a mastectomy, screening protocol may extend to 60 as for high-risk women.

4.9 Special subgroups of breast cancer

4.9.1 Breast cancer in men

Men with breast cancer (usually ER positive) are staged and treated along the lines of post-menopausal breast cancer in women. Tamoxifen is, however, the hormone therapy of first choice, since aromatase inhibitors do not suppress testicular production of oestrogens and therefore are of uncertain benefit as single agents (may be used as second-line therapy, in combination with an LHRH analogue).

4.9.2 Favourable histologies

Patients with pure tubular, colloid or adenoid cystic (despite being ER negative) breast cancer have a better prognosis; the absolute benefit from adjuvant treatments may be smaller compared with similar patients with ductal or lobular histology.

4.9.3 Encapsulated papillary carcinoma

Although some recent studies have suggested that these may represent circumscribed nodules of low grade invasive carcinomas, the current advice is to manage them as in situ lesions until further evidence is available.⁴

4.9.4 Phyllodes tumours

These should be classified as benign, borderline or malignant. Treatment of phyllodes tumours is surgical resection with wide margins. After resection of a local recurrence, radiotherapy to the breast or chest wall may be considered. Similarly, post-operative radiotherapy may be considered for malignant lesions. There is no indication for axillary dissection. Staging with computed tomography (CT) may be considered before resection of lesions that are large or have unfavourable histology as the lungs are (rarely) a site of metastatic spread. Systemic disease should be treated along the lines of soft tissue sarcomas. It may be appropriate to liaise with the local sarcoma unit in cases of malignant phyllodes.

4.9.5 Paget's disease of the nipple

The majority of patients with Paget's disease of the nipple have an associated in situ or invasive cancer elsewhere in the breast. Surgical treatment may consist of a mastectomy or breast conserving procedure (resection of nipple–areola complex and cancer with negative margins) with appropriate axillary procedure. Breast conserving surgery must be followed by radiotherapy. Systemic adjuvant therapy depends on the characteristics of the invasive component.

4.9.6 Sarcoma of the breast

These tumours, including radiation-induced angiosarcoma, are rare. Liaison with the sarcoma MDT is recommended.

4.10 Locally recurrent disease

A biopsy should always be obtained to confirm diagnosis and receptor status. Staging: a CT scan of the neck, thorax, abdomen and pelvis, a bone scan and routine blood tests should be considered. If restaging is negative, the patient can be treated with curative intent:

- mastectomy if prior breast conserving surgery and external beam radiotherapy; if previous breast conserving surgery and no radiotherapy, conservation surgery can again be considered as long as adjuvant radiotherapy also given
- surgical resection (if feasible) plus radiotherapy if prior mastectomy and no prior radiotherapy
- sentinel lymph node with a scintigram should be considered since there are numerous reports of new sentinel lymph nodes in unusual positions
- radiotherapy if surgery is not feasible.

All suitable patients being considered for mastectomy should be offered reconstruction.

For uncontrolled local disease, further lines of endocrine and/or chemotherapy should be considered. Also consider miltefosine topical solution 6mg/ml (6%); 10ml to treat cutaneous/inflammatory breast cancer metastases; to be applied to chest wall breast cancer nodules less than 2cm that are refractory or resistant to standard or experimental intravenous chemotherapies.

4.11 Post-operative care and information

- Patients will require information on post-operative care and support, management of any drains and dressings. They should also be given information about the likelihood of seroma formation so that they know how to recognise it and seek advice and management.
- Patients should be provided with their outpatient appointment prior to discharge.
- Patients who have had a mastectomy without reconstruction will be provided with a temporary prosthesis prior to discharge from hospital. They will be supported by the breast care nurses and provided with adequate written information about bras and swimwear to enable them to regain body confidence quickly. All patients should be provided with a permanent prosthesis as soon as they have healed following surgery. Patients who have a noticeable breast defect following surgery should be offered a partial prosthesis to correct this in the bra.
- Patients will be given written advice about shoulder exercises either pre-operatively or prior to discharge. Patients undergoing breast reconstruction may need to be given additional exercises or information regarding return to function relevant to their surgery. The National Cancer Action Team (NCAT) rehabilitation pathways advocate that all breast surgery patients should be seen by a physiotherapist for shoulder exercises and advice. The gold standard is that all breast patients will be assessed pre and/or post-operatively by a specialist physiotherapist. Where there is currently no immediate access to specialist breast physiotherapy, an LCA wide risk-stratification tool must be used to ensure appropriate onward referral ([Appendix 9](#)). In either case each Trust must ensure that there are pathways for rapid access to a named physiotherapist.
- Consider referral to physiotherapy for patients with additional symptoms of ongoing fatigue, pain and functional impairments secondary to cancer diagnosis and treatment.
- Patients who have had lymph node removal will be given information about lymphoedema risk and how to help lower this risk.
- An assessment of the patient will be carried out and referrals to physiotherapists, social workers and other key contacts will be made as necessary. This is usually provided by the CNS.

- Following discharge, patients should have telephone access to support and advice via their breast care nurse.
- Post-surgical complication rates for all surgery should be clearly documented and data collected for audit purposes.

4.12 Risk-reducing surgery

Information on bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk. The aim of risk-reducing mastectomy is to reduce the incidence of breast cancer in high-risk women and to relieve anxiety. These advantages need to be balanced against the cosmetic outcome and subsequent quality of life issues for the woman. If a woman wishes to consider risk-reducing mastectomy she should be fully assessed by members of the MDT as follows:

- if available, by specialist multidisciplinary clinics where all specialists listed below are available
- by the genetics unit for formal risk assessment, family history verification and genetic testing if appropriate
- by a psychologist or counsellor to discuss the psychosocial/sexual consequences of surgery
- by a CNS and support groups or women who have undergone the procedure
- by a specialist oncoplastic surgical team to discuss reconstructive options
- by pre-operative mammograms plus magnetic resonance imaging (MRI), if appropriate.

4.12.1 Evidence

- Risk-reducing mastectomy reduces the risk of breast cancer by 90%.
- There is limited evidence to guide on the type of mastectomy but there is some non-statistical evidence to suggest that subcutaneous mastectomy (nipple–areolar sparing) may be less effective than total mastectomy.
- Overall, risk-reducing surgery is associated with high levels of satisfaction and reduced anxiety and psychological morbidity provided there is pre-surgical multidisciplinary support as outlined above.
- A minority of women may express regret and dissatisfaction.

¹ NICE, 2009. *Breast cancer (early & locally advanced): diagnosis and treatment (CG80)*.
www.nice.org.uk/guidance/index.jsp?action=byID&o=12132

² National Cancer Institute. *Clinical Trial, NSABP-B-24*.
www.cancer.gov/clinicaltrials/search/view?cdrid=76907&version=HealthProfessional

³ Cuzick J et al, 2011. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol*. 12(1): 21–9.

⁴ Collis L et al, 2008.

5 Radiotherapy

5.1 Pure ductal carcinoma in situ

The risk of local or systemic recurrence after pure ductal carcinoma in situ (DCIS) treated with mastectomy is 1% at most and therefore mastectomy need not be followed by adjunctive therapy.¹ No reliable data are available to guide decision making when the deep margins of the mastectomy specimen are shown to be close to or involved by DCIS.

5.1.1 Local relapse risk after local excision without radiotherapy

In all four randomised trials testing breast radiotherapy (RT) after complete local excision of pure DCIS, the total ipsilateral tumour relapse risk after surgery alone was 20–33% at 10 years, of which roughly one-half relapsed as invasive tumours (Level Ib^{2–5}). The risk of relapse after local excision of symptomatic DCIS is reported by Silverstein to be closely related to tumour size, nuclear grade, patient age and margins of excision, and his analysis forms the basis of the Van Nuys Index (VNI), see Table 5.1 (Level II⁶).

Table 5.1: The Van Nuys Index

Score	1	2	3
Size (mm)	<15	16–40	>41
Margin width (mm)	>10	1–9	<1
Pathologic classification	Non-high grade without necrosis	Non-high grade with necrosis	High grade with or without necrosis
Age (years)	>60	40–60	<40
One to three points are awarded for each of four different predictors of local breast recurrence (size, margin width, pathologic classification and age). Scores for each of the predictors are totalled to yield a Van Nuys Prognostic Index (VNPI) score ranging from a low of 4 to a high of 12.			

Reported risks of ipsilateral recurrence at 12 years after local excision alone are as follows: score 4–6 = <5%; score 7–9 = 20%; score 10–12 = 80%.^{7,8} It should be noted that the numbers in each of the three risk categories were limited: 161 patients excision alone VNPI 4–6, 42 patients excision alone VNPI 10–12). The current index incorporates age <40 years as a powerful independent risk factor for local recurrence. The VNI has not been independently validated as a guide to therapy. None of the trials testing the effects of RT after tumour excision planned a prospective evaluation of prognostic indices. Retrospective evaluations of trial data by the National Surgical Adjuvant Breast Project (NSABP) and European Organisation for Research and Treatment of Cancer (EORTC) do not confirm the reliability of the VNI, although their ability to test the index properly can be questioned.^{3,9} Indeed, subgroup analysis of the randomised trials have not revealed a group at <10% risk of recurrence. It should be noted that in a prospective study of 157 women with low risk lesions (small (<2.5cm), widely excised (>1cm), low nuclear grade DCIS lesions with no necrosis), treated with wide excision alone, the risk of recurrence at 5 years was 2.4% per year.¹⁰ This is considerably higher than predicted by the VNI and other retrospective analyses. Furthermore, in the Eastern Cooperative Oncology Group (ECOG) study of excision alone for DCIS, in 565 patients with low/intermediate grade DCIS, excision margin ≥ 3 mm, and size ≤ 2.5 cm, ipsilateral breast cancer events were 6.1% at 5 years and 10.5% at 7 years.¹¹

5.1.2 Effects of radiotherapy for pure DCIS

Whole breast radiotherapy (RT) reduces the risk of ipsilateral breast relapse after complete excision of pure DCIS. The NSABP B-17, EORTC, the UK Coordinating Committee on Cancer (UKCCCR) and SweDCIS trials report that the risks of recurrent DCIS and invasive tumours are each reduced to a similar degree, corresponding to an odds ratio ≤ 0.5 , the lowest odds ratio of 0.33 (95% CI 0.24–0.47) being reported by the SweDCIS trial (Level Ib²⁻⁵). The dose prescription in all trials was 50Gy in 25 fractions (or similar) to the whole breast without a planned boost dose to the tumour bed.

In a retrospective study of outcome after surgical excision of DCIS in 373 young women (<45 years) by the Rare Cancer Network, a non-randomised boost dose (median dose 10Gy) after whole breast radiotherapy (median dose 50Gy) halved the ipsilateral relapse risk at 10 years, with an odds ratio 0.45 (95% CI 0.23–0.90).¹² Without boost, the relapse rate was 28%, consistent with the importance attached to young age in the VNI. The large boost effect is consistent with that reported for invasive disease by the EORTC boost trial (Level Ib¹³). If 50Gy halves local relapse risk, and a 16Gy boost halves this risk again in pure DCIS, an overall 75% reduction in ipsilateral relapse risk still does not match that achieved by mastectomy in a young woman.

Consider entry into BIG 3-07 (TROG 07.01) – A randomised phase III study of radiation doses and fractionation schedules for DCIS.

Table 5.2: Eligibility criteria for BIG 3-07

Main inclusion criteria	Main exclusion criteria
<ul style="list-style-type: none"> • women >18 years with histologically proven DCIS without an invasive component • clinically node negative who have undergone breast conserving surgery (BCS) or re-excision with clear radial margins of at least 1mm • assessed as suitable for BCS and post-operative RT • able to tolerate protocol treatment • ECOG performance status 0–2 • life expectancy >5 years • available for long-term follow-up and with written informed consent. 	<ul style="list-style-type: none"> • multicentric disease or extensive microcalcifications not excisable • pathologically node positive, locally recurrent breast cancer, previous DCIS or invasive breast cancer of opposite breast • other concurrent or previous malignancy other than non-melanomatous skin cancer and invasive cancer of the cervix, endometrium, colon or thyroid and melanoma treated 5 or more years previously • serious non-malignant disease which precludes surgical or radiation treatment • EGOG \neq / > 3 • pregnant or lactating women

Recommendations for radiotherapy in pure DCIS treated with breast conserving surgery

DCIS lesions with a Van Nuys score of 10-12 are at high risk of local recurrence despite additional radiotherapy and should be considered for re-excision or mastectomy. For other cases, following BCS, RT should be considered as a means of reducing risk of local recurrence as there is no reliable means of identifying a group that derives no or minimal benefit. The VNPI can help define risk, but results should be interpreted with caution. A whole breast RT (50Gy in 25 fractions) is recommended. A boost dose (16Gy in 8 fractions, or similar, including alternative fractionation assuming an alpha/beta ratio of 3Gy) should be considered in patients <50 years (Grade B).

A whole breast dose of 40.05Gy is acceptable for those centres happy to extrapolate evidence on dose from the invasive setting.

5.1.3 DCIS and tamoxifen

In the NSABP B-24 trial, women who were treated with BCS plus RT were randomly assigned to receive tamoxifen (20mg OD) or placebo for 5 years. Women with incompletely excised DCIS were allowed to enter this study. Tamoxifen reduced the risk of both ipsilateral and contra-lateral breast cancer. At 5 years the cumulative risk of breast cancer events was 13.4% and 8.2% ($p = 0.0009$) among patients receiving placebo and tamoxifen respectively. The risk of an invasive event was reduced from 7.2% to 4.1% ($p = 0.004$) and the risk of an in-situ event was reduced from 6.2% to 4.2% ($p = 0.08$).¹² The proportional reduction of breast cancer events was 38%; however, the absolute number of women who benefited in terms of avoiding an ipsilateral breast cancer recurrence was small – 3% at 5 years. A recent unpublished analysis of the ER status in this study has indicated a greater benefit within the ER positive subgroup with no benefit in the ER negative subgroup.¹⁴

The UKCCCR DCIS trial did not find a significant reduction in risk of invasive breast cancer with the use of tamoxifen in those patients who received RT (Cuzick J et al, Lancet Oncol, 2011). Unlike NSABP B-24 only a small proportion of the trial subjects were randomised to receive tamoxifen in addition to RT. There was also a higher proportion of women over 50 years and clear margins of excision were mandated.

Tamoxifen is also associated with a small risk of potentially life-threatening complications, and often has an impact on quality of life. A clear recommendation that all women with unilateral DCIS should receive tamoxifen cannot be made at this time. The potential benefits and risks of tamoxifen should be discussed with patients with ER positive DCIS. Tamoxifen may be a reasonable option for a woman motivated to do everything possible to avoid breast cancer recurrence but who declines mastectomy, especially if she has a higher risk of contra-lateral breast cancer and a lower than average risk of tamoxifen complications.

Recommendations for use of tamoxifen in women with pure DCIS

The role of tamoxifen in the management of patients with DCIS continues to evolve. For those at very low risk of recurrence with radiotherapy alone or for those with ER negative DCIS, the absolute benefits of tamoxifen are predicted to be very small. The potential benefits and risks should be discussed with patients.

5.2 Invasive breast cancer

5.2.1 Local relapse risk after breast conserving surgery without radiotherapy

There is, as yet, no reliably identified group of patients whose breast recurrence risk is <10% at 10 years after local excision alone (Level Ib^{15,16}). A summary of the current published evidence relating to the most favourable subgroups evaluated in randomised clinical trials is summarised in Table 5.3.

Table 5.3: Local relapse risk in women randomised to tamoxifen-only after complete tumour excision in five trials testing radiotherapy where ≥80% patients had pT1 ER positive pN negative breast cancer, age >50 years

Trial	Number	Breast relapse (%)	FU (years)
NSABP B-21	334	16.5	8
Canada ^{17,18}	383	12.2	8
CALGB ¹⁹	319	4.0	5
GBSG ²⁰	80	2.8	6
ABCSG-8A ²¹	416	3.2	4

In addition to these prospective data, a retrospective analysis of 8,724 women in the SEER database all age ≥70 years treated between 1992 and 1999 for pT1 ER positive/NK pN negative M0 invasive²² breast carcinoma by tumour excision plus endocrine therapy but without radiotherapy reported an actuarial rate of local relapse of 5% at 5 years and 8% at 8 years.²³

Previous breast irradiation (including mantle irradiation for Hodgkin's disease) is a contraindication to breast irradiation. In some instances, following discussion at the multidisciplinary team meeting, if a woman is particularly keen to avoid mastectomy, breast conservation and partial breast RT can be considered.

5.2.2 Local relapse risk post-mastectomy

After mastectomy, a review of 5,352 women entered in International Breast Cancer Study Group (IBCSG) trials between 1978 and 1993 generated a simple algorithm for estimating chest wall relapse risk without RT (see Table 5.4²⁴). Patients were given post-mastectomy adjuvant systemic therapy as follows: pN positive patients received 3–12 months of classical CMF ± low dose prednisolone and/or tamoxifen; two-thirds of pN negative patients received a single cycle of classical CMF. Overall, one-third received no adjuvant therapy.

Table 5.4: Chest wall recurrence risk 10 years after mastectomy and appropriate systemic therapy without radiotherapy²⁴

Age ≤50 years					Age >50 years				
pT	pN	VI	Grade	10-year risk	pT	pN	VI	Grade	10-year risk
1	-	-		<10%	1	1–3		1	10–15%
1	-	+		15%	>1	1–3		1	10–15%
>1	-	-		15%	1	1–3		2	10–15%
>1	-	+		15–20%	>1	1–3		2	15–20%
	1–3	-	1	10–15%	1	1–3		3	15–20%
	1–3	+	1	10–15%	>1	1–3		3	20–25%
	1–3	-	2	10–15%	1	4+		1	20–25%
	1–3	+	2	15–20%	>1	4+		1	20–25%
	1–3	-	3	10–15%	1	4+		2	20–25%
	1–3	+	3	25–30%	>1	4+		2	30–35%
	4+	-	1	15–20%	1	4+		3	30–35%
	4+	+	1	25–30%	>1	4+		3	30–35%
	4+	-	2	25–30%					
	4+	+	2	35%					
	4+	-	3	25–30%					
	4+	+	3	35%					

If 10% chest wall recurrence risk represents an appropriate threshold for considering chest wall radiotherapy (see [Effects of Radiotherapy 5.2.4](#)), it is not clear what combination of tumour and treatment characteristics identify this subgroup in the current era. This uncertainty is being addressed by the SUPREMO trial, which tests the benefits of chest wall RT after mastectomy and optimal axillary and systemic therapy in intermediate risk patients, most typically those with 1–3 positive axillary lymph nodes. The eligibility criteria are summarised in Table 5.8. It is not known how these risk estimates are influenced by neo-adjuvant systemic therapies, but a reliable assumption is that local recurrence risk is reduced to the same extent as after the same therapies in the adjuvant setting (Level Ib²⁵).

The presence of tumour extending to the deep fascia is not an absolute indication for post-mastectomy chest wall RT as long as the fascia has not been breached, although systematic review suggests that close margins may have an impact on local control.²⁶ There is also retrospective evidence that HER2) positivity (if non-trastuzumab treated) and ER negativity are also independent predictors of post-mastectomy local recurrence.^{27,28}

5.2.3 Regional relapse

After Level II or III dissection, isolated axillary recurrence rate is <1% in node negative patients, remains low in node positive patients but increases to ≤7% in the presence of extranodal extension.^{29–33} Risks of isolated supraclavicular relapse are very low (≤1%) in node negative patients or those with 1–3 positive nodes, but

are up to 12% in women with ≥ 4 involved axillary lymph nodes. Also, patients with 1–3 nodes positive and Grade 3 disease are at elevated risk of supraclavicular recurrence.³⁴ Roughly 30% of patients with positive axillary nodes have positive internal mammary chain (IMC) nodes.³⁵ Isolated recurrence in the parasternal region is rare, but pleural effusion secondary to involved nodes is common.

5.2.4 Effects of radiotherapy on ipsilateral local relapse and mortality

Fifteen-year follow-up confirmed that one breast cancer death is prevented per four local recurrences prevented.³⁶ This 2005 overview of the effect of adjuvant RT after BCS and mastectomy showed a statistically significant overall survival advantage of 3.1% at 15 years despite a large excess of non-breast cancer deaths, especially cardiovascular disease and second malignancies, in trials started before 1975. The greatest absolute gain from improved local/regional control was seen in axillary node positive patients, in whom the absolute reduction in breast cancer deaths is 7% after BCS and 5% after mastectomy.³⁶ The benefit is independent of the contribution of adjuvant systemic therapies to local/regional control and survival. The most recent overview of 15-year breast cancer specific survival and 10-year recurrence after RT following BCS confirmed a reduction in 10-year local/ regional or distant recurrence of 15.7% and a reduction in 15-year risk of breast cancer death of 3.8%.³⁷

Four trials testing hypofractionation (Canadian, RMH/Cheltenham and START), involving a total of 7,000 patients, have been published with broadly consistent results.^{29–32} The most recently published, the UK Standardisation of Breast Radiotherapy Trials (START trial A and START trial B) confirm non-inferiority in terms of late adverse effects and local/regional control for 40Gy in 15 fractions compared with 50Gy in 25 fractions.^{31,32}

Recommendations for radiotherapy in invasive disease following breast conservation

Whole breast RT is recommended as part of standard treatment in all patients after complete microscopic excision of invasive disease (Grade A), unless life expectancy is estimated to be ≤ 3 years due to co-morbidity (Grade C). The recommended dose prescription is 40Gy in 15 fractions to the 100% isodose. Partial breast RT by external beam, intra-operatively (TARGIT/intra-operative electron beam radiotherapy (IOERT), or by brachytherapy, e.g. mammosite), should be considered a non-standard technique until long-term efficacy and safety data are available to allow comparison with whole breast radiotherapy

The EORTC boost trial confirms the effects of 16Gy in 8 fractions after 50Gy in 25 fractions to whole breast, reducing local recurrence by about 40% (Level Ib¹³). The absolute benefit was greatest in women ≤ 40 years, whose local recurrence risk was reduced from 19.5% to 10.2% at 8 years (odds ratio = 0.59; 95% CI 0.43–0.81). Women over 50 years gained less in absolute terms, although the odds ratio was similar to that in younger women. It should be noted that in a subsequent study in patients of up to 50 years designed to assess the need for an elevation in boost dose from 16Gy to 26Gy ('Young Boost Trial', NCT00212121), after recruitment of 2,000 patients, local control at 4 years as reported in 2011 remains $< 2\%$, which is far less than that seen in this age group in the EORTC study.³⁸ This suggests that the need for a boost in invasive cancer and probably also DCIS is diminishing over time as RT techniques improve.

Absolute indications for a boost of 16Gy in 8 fractions (or similar dose, including alternative fractionation assuming an alpha/beta ratio of 3Gy) to the 100% isodose include *either* of the following:

- age < 40 (Grade B)
- disease at resection margins and patient unable to undergo further surgery (ignore deep margins if resection extends to deep fascia) (Grade B).

50Gy in 25 fractions may be used in place of 40Gy in 15 fractions at the discretion of the responsible clinician as both represent 'International Gold Standard' regimens. In particular, 50Gy in 25 fractions may be favoured in the following settings:

- connective tissue disease (as RT can be discontinued in the 5th week if patient develops a severe acute radiation reaction)
- very high risk of local recurrence – heavily node positive or inflammatory breast cancer (as 50Gy in 25 fractions is a slightly higher total dose compared with 40Gy/15 fractions – equivalent to 46–48Gy in 2Gy fractions)
- locally advanced breast cancer with no prior surgery.

Patients should be considered for entry into the UK FAST-Forward Trial, a randomised clinical trial testing a 1-week against a standard 3-week schedule of RT in terms of local cancer control and late adverse effects in women with early breast cancer. (Arms: Control: 40.05Gy in 15Fr of 2.67Gy; Test 1: 27.0Gy in 5Fr of 5.4Gy; Test 2: 26.0Gy in 5Fr of 5.2Gy.)

Table 5.5: Eligibility criteria for UK FAST-Forward Trial

Main inclusion criteria	Main exclusion criteria
<p>All the following must be met:</p> <ul style="list-style-type: none"> • age ≥ 18 years • female or male • invasive carcinoma of the breast • breast conservation surgery or mastectomy (reconstruction allowed but not with implant. Tissue expanders with distant metal ports are allowed) • axillary staging and/or dissection • complete microscopic excision of primary tumour • pT1-3 pN0-1 M0 disease • written informed consent • able to comply with follow up. <p>N.B. Concurrent trastuzumab and hormone therapy is allowed.</p>	<p>The patient is ineligible if any of the following are met:</p> <ul style="list-style-type: none"> • past history of malignancy except (i) basal cell skin cancer and CIN cervix uteri or (ii) non-breast malignancy allowed if treated with curative intent and at least 5 years disease free • contra-lateral breast cancer, including DCIS, irrespective of date of diagnosis • breast reconstruction using implants • concurrent cytotoxic chemotherapy (sequential neo-adjuvant or adjuvant cytotoxic therapy allowed) • RT to any regional lymph node areas (excepting lower axilla included in standard tangential fields to breast/chest wall).

Breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiation therapy is preceded by chemotherapy. However, there is no defined time following surgery after which RT can be said to be of no benefit.

5.2.5 Tumour bed boost recommendations

All women under the age of 40 or women of any age who have undergone resections with involved margins (no further surgery planned) should receive a boost. The standard dose is 16Gy in 8 fractions (or equivalent assuming an alpha/beta value of 3.0Gy). Units may also choose to boost all women under the age of 50.

A boost should be considered in women >age 51–60 with additional risk factor(s) for local recurrence: lympho-vascular invasion, Grade 3 disease, lack of recommended systemic therapy, ER negativity, HER2 positivity, ‘tight’ margins, tumours >3cm. It should be noted that the only factors shown to influence local recurrence in the context of completely excised invasive disease on multivariate analysis in a consistent manner are high grade and presence of lympho-vascular invasion.³⁹

Patients >age 60 should also be prescribed a boost if considered to be at particular risk of local recurrence. Women in this age group overall have a local recurrence rate at median follow-up of 10 years of 5.5% without boost.⁴⁰

Many centres in the UK have historically employed a boost dose of 10Gy in 5 fractions (as recorded within the START trial) with acceptable local control rates. This therefore represents an acceptable dose, particularly where cosmesis or other late tissue complications are a concern.

A higher boost dose (e.g. 21Gy in 7 fractions) may be given in the following situations:

- microscopic residual disease (e.g. positive margins) (Grade C)
- primary medical treatment with complete response without surgery, or macroscopic residual disease after surgery (Grade C).

Consideration should be given to the dose delivered to the heart during the boost, especially if delivered by electrons, as a treatment plan is rarely generated in this setting.

Patients receiving RT to the whole breast after breast conservation and for whom a boost is indicated may be eligible for the National Cancer Research Institute (NCRI) IMPORT HIGH trial, see Table 5.6.

Table 5.6: Eligibility criteria for NCRI IMPORT HIGH trials

Main inclusion criteria
<ul style="list-style-type: none"> • age ≥ 18 years • operable unilateral breast cancer (T1–3, N0–1, M0 at presentation) • breast conserving surgery • histological confirmation of invasive carcinoma • complete microscopic resection • RT prescription including whole breast radiotherapy plus boost dose.* <p>*Boost dose should be considered if at least one of the following applies: age 18–49 years; tumour size >2.0 cm after primary surgery (maximum microscopic diameter of invasive component); tumour of any size treated by primary medical therapy; Grade 3 disease; minimum microscopic margin of non-cancerous tissue <2mm (excluding deep margin if this is at deep fascia); lympho-vascular invasion; axillary node positive.</p>

Recommendations for chest wall radiotherapy after primary mastectomy +/- reconstruction

Chest wall RT recommendations following primary surgery are based on current American Society of Clinical Oncology (ASCO) guidelines, see Table 5.7.⁴¹ Chest wall RT is recommended in patients with *either* of the following:

- pT ≥ 50 mm (Grade A)
- ≥ 4 involved axillary lymph nodes (Grade A).

The recommended dose prescription without reconstruction is 40Gy in 15 fractions to the 100% isodose (Grade A) with bolus administered as per local policy (e.g. whole field for half the fractions) (Grade C). The option of 50Gy in 25 fractions for reconstructed breasts after mastectomy is retained. Bolus should be applied after reconstruction if the overlying skin is considered at risk.

Patients who satisfy the eligibility criteria for the NCRI SUPREMO trial (Table 5.8), most commonly those who are pN positive (1–3), should be asked to consider participation. Those who satisfy the eligibility criteria, but who are unsuitable or decline trial entry, may be considered for RT out of protocol (Grade B).

Note that the eligibility for the SUPREMO study has been extended to include pT3N0 cancers on the basis that reports suggest that the local recurrence in this group is modest with ‘modern surgery and systemic therapy’.⁴²

Recommendations for chest wall radiotherapy after primary medical therapy and mastectomy +/- reconstruction

Post-mastectomy chest wall RT is recommended when:

- any primary tumour with pathologically positive axillary nodes (ypN positive) after induction chemotherapy (Grade B)
- large primary tumour (≥ 5 cm) or ER negative PR negative HER2 negative disease plus cytologically positive axillary nodes and/or clinically suspicious enlargement at presentation, even though axillary nodes are pathologically negative (ypN negative) after induction chemotherapy (Grade C).

See also eligibility from SUPREMO protocol (Table 5.8) which has been extended to include patients in this setting.

Table 5.7: Summary of ASCO guidelines for radiotherapy after primary mastectomy – post-mastectomy radiotherapy⁴¹

1. Post-mastectomy radiotherapy (PMRT) is recommended for patients with four or more positive axillary lymph nodes.
2. There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT in patients with T1/2 tumours with one to three positive nodes.
3. PMRT is suggested for patients with T3 tumours with positive axillary nodes and patients with operable stage III tumours.
4. There is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with pre-operative systemic therapy should be given PMRT.
5. There is insufficient evidence to make recommendations or suggestions for modifying guidelines regarding the routine use of PMRT based on other tumour-related, patient-related, or treatment-related factors.
6. In patients given PMRT, we suggest that adequately treating the chest wall is mandatory.
7. There is insufficient evidence for the Panel to recommend or suggest such aspects of chest wall irradiation as total dose, fraction size, the use of bolus and the use of scar boosts.
8. We suggest that full axillary radiotherapy not be given routinely to patients undergoing complete or Level I/II axillary dissection. There is insufficient evidence to make suggestions or recommendations as to whether some patient subgroups might benefit from axillary irradiation.
9. The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest a supraclavicular field should be irradiated in all such patients.
10. There is insufficient evidence to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes.
11. There is insufficient evidence to make suggestions or recommendations on whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup.
12. There is insufficient evidence to recommend the optimal sequencing of chemotherapy, tamoxifen and PMRT. The Panel does suggest, based on the available evidence regarding toxicities, that doxorubicin not be administered concurrently with PMRT.
13. There is insufficient evidence to make recommendations or suggestions with regard to the integration of PMRT and reconstructive surgery.
14. The potential long-term risks of PMRT include lymphoedema, brachial plexopathy, radiation pneumonitis, rib fractures, cardiac toxicity and radiation-induced second neoplasms. Data would suggest that the incidence of many of these toxicities will be lower when modern radiotherapy techniques are used, although follow-up in patients treated with current radiotherapy is insufficient to rule out the possibility of very late cardiac toxicities. In reviewing the available evidence with its limitations, however, the Panel suggests that, in general, the risk of serious toxicity of PMRT (when performed using modern techniques) is low enough that such considerations of toxicity should not limit its use in most circumstances when otherwise indicated.
15. There is insufficient evidence to make recommendations or suggestions that PMRT should not be used for some subgroups of patients because of increased rates of toxicity (such as radiation carcinogenesis) compared with the rest of the population.

Table 5.8: Eligibility criteria for the SUPREMO trial of chest wall RT

Main inclusion criteria	Main exclusion criteria
<ul style="list-style-type: none"> • Stage II histologically confirmed unilateral breast cancer following mastectomy including the following pTNM stages: • pT1N1M0; pT2N1M0; pT2N0M0 • if grade 3 histology and/or lympho-vascular invasion. • pT3N0M0 • Stage II histologically confirmed unilateral breast cancer following neo-adjuvant systemic therapy and mastectomy, if the original clinical stage was cT1-2cN0-1M0 or cT1-2pN1(sn)M0 and with the following (ypTNM) stages after neo-adjuvant systemic therapy: • ypT1pN1M0; ypT2pN1M0; ypT2pN0M0 • if grade III histology and/or lympho-vascular invasion; • ypT0pN0 or ypT1pN0 or ypT0pN1 • ypT2N0 independent of grade or lympho-vascular invasion, if the original clinical stage was cT3N0. <p>Also:</p> <ul style="list-style-type: none"> • ypT3N0M0, if original clinical staging was cT1-3cN0 M0 or cT1-3pN0 (sn) M0. • Unilateral invasive breast cancer that conforms to the initial clinical staging of ‘adjuvant eligibility criteria’, but has been downstaged by neo-adjuvant systemic therapy to ypT0 pN0 or ypT1pN0 or ypT0pN1 (pathological complete remission, or near complete remission). If tumour stage cT3 or ypT3, then nodal status must be N0 both before and after neo-adjuvant systemic therapy. 	<ul style="list-style-type: none"> • Any pT0pN0-1 or pT1pN0 tumours after primary surgery. • Any pT3pN1 or pT4 tumours. Initial stage cT3cN1 or pN1(sn) or cT4 in patients receiving neo-adjuvant systemic therapy cannot be included, even if downstaging has occurred and the pathological ypT and N stage is lower. • Patients who have four or more pathologically involved axillary nodes. For the purpose of this study protocol, nodal scarring after neo-adjuvant systemic therapy will be considered as evidence of previous pathological nodal involvement and count towards the total number of involved axillary nodes. • Past history or concurrent diagnosis of ductal carcinoma in situ (DCIS) of the contra-lateral breast, unless treated by mastectomy. Previous DCIS of the ipsilateral breast if treated with radiotherapy (i.e. previous DCIS treated by conservation surgery not followed by radiotherapy would be considered eligible).

5.2.6 Axillary radiotherapy after primary surgery or primary medical therapy

Axillary RT is not recommended after complete microscopic clearance, even if nodes are positive or in the presence of extracapsular spread, due to an enhanced risk of treatment-related morbidity (Grade B^{30,32}).

If microscopic tumour extends to the margins of axillary resection, treatment may be considered to dose of 50Gy in 25 fractions or equivalent (recommendation to use the IMPORT HIGH trial field arrangement and dosimetry) (Grade C), ensuring that the brachial plexus dose is kept within safe limits.

If macroscopic disease extends to the margins of axillary resection, treatment is recommended to dose of $\geq 50\text{Gy}$ in 2.0Gy fractions or equivalent using shrinking field technique localised using surgical clips and/or MRI to image residual disease (Grade C).

If sentinel node biopsy (applies to primary surgery only) or level I axillary dissection is positive (pN1b), axillary RT generally is recommended if axillary dissection cannot be undertaken (Grade B). On the basis of the Z0011 study, older women with low risk disease and a macrometastasis in a sentinel node can be considered for no further surgery to the axilla provided they have had optimal systemic therapy and will be undergoing lower axillary RT. In discussing this approach, it should be emphasised that the Z0011 study was underpowered for overall survival and does not yet have long-term follow-up.⁴³ If the involvement is confined to a single micrometastasis $< 2\text{mm}$, axillary RT need not be given if Level I nodes are included in tangential fields to breast/chest wall (Grade C).

Axillary RT is recommended in all patients in the absence of axillary surgery, unless surgery has been withheld on the basis of very low risk of involvement (Grade A).

Centres may choose to employ a dose of 50Gy in 25 fractions in place of 40Gy in 15 fractions when treating nodal areas.

5.2.7 Supraclavicular fossa radiotherapy after primary surgery or primary medical therapy

After primary surgery

Supraclavicular fossa (SCF) RT is recommended following primary surgery in patients with ≥ 4 metastatic axillary lymph nodes (Grade B). One retrospective series showed a 44% risk of SCF relapse (median follow-up 8.1 years) if a single axillary lymph node was $\geq 2\text{cm}$.³³ On the basis of this, SCF RT may be considered in the setting of a single node $\geq 2\text{cm}$ in size. Furthermore, Yates et al. published a large retrospective series suggesting that three nodes positive and G3 disease should be indications for SCF RT.³⁴

After primary medical therapy

- If axillary nodes are cytologically negative at presentation and if ypN negative after primary medical therapy, no RT is given (Grade C).
- If axillary nodes are cytologically positive, and/or clinical/radiological suspicious enlargement at presentation and if ypN negative after primary medical therapy, there is no consensus with strong views for/against RT. Hence, SCF RT may be offered, but a policy of observation is acceptable (Grade C).
- If ypN positive, SCF RT is recommended (Grade B).

5.2.8 Supraclavicular fossa radiotherapy in setting of radical management of patient with SCF involvement

Such patients generally receive induction chemotherapy. In the setting of a good clinical and radiological response to treatment, radical RT to the SCF may be undertaken, including a high dose boost to a conformal planned volume to the area of persistent/original disease.

5.2.9 Adjuvant radiotherapy to the internal mammary chain

On the basis of current evidence, this should only be undertaken in exceptional circumstances (e.g. radiological or cytological/histological evidence of involvement). Even in this setting, the benefits are unclear. Intensity-modulated radiation therapy/arc/matched electron field technique/breath-hold techniques must be employed to minimise dose to myocardium. Three randomised trials awaiting reporting should shed some light on the benefit of adjuvant RT to the IMC:

- a French study included 1,281 patients who underwent modified radical mastectomy and were randomly assigned to RT or no RT to IMC44
- EORTC 22922/10925
- National Cancer Institute of Canada MA20 trials randomly assigned high-risk patients to adjuvant radiation therapy with or without inclusion of the IMN, supraclavicular nodes and axilla.

5.3 Adverse effects of radiotherapy

Patients should be told about the risks of treatment side effects, both verbally and in writing.

Information on early side effects should include:

- fatigue (30%)
- skin erythema +/- irritation (100%)
- moist desquamation in inframammary fold (especially large breast size), axilla or SCF (10% risk).

5.3.1 Skin care for acute radiotherapy reaction

- Aqueous cream or similar emollient should be used to moisturise the skin while skin is intact.
- If the skin becomes broken, the use of aqueous cream should be stopped and the appropriate dressing applied.
- Apart from recommended applications, patients should avoid all other products in the area (e.g. deodorants, perfumes, creams).
- A gentle shower is preferable to prolonged soaking.
- Patients should avoid causing friction to the skin (e.g. by using flannels); to dry the treatment area, patients should pat it with a soft towel, or fan dry with a cool hair dryer.
- Patients with mild to moderate erythema (RTOG 2a), with associated pruritus, may use hydrocortisone 1% cream with caution, to help relieve symptoms. The skin should be intact; if used when the skin is broken, there is a risk of developing secondary fungal infections. The cream should be applied sparingly, usually up to twice a day and for no longer than 7 days. If the skin should break prior to the end of the recommended period, application should stop
- Some patients elect to use aloe vera gel; there is little evidence to suggest it is of more benefit than simple emollients. If selected, it is recommended to use pure aloe vera 98%.
- Cooling hydrogel sheets can also offer some comfort when the skin is intact and there are no other associated complications.

Management of moist desquamation

- Aim to promote comfort and optimise the wound healing environment.
- Once moist desquamation develops, the patient should be assessed by the RT nurse for appropriate dressing(s). Any topical creams should be stopped, as these may promote bacteria growth and complicate eventual wound healing.
- Irrigate with warm normal saline 0.9% in a clinical setting, to remove superficial slough and visible debris. When cleaning the wound bed, gauze should be used.
- If the patient is self-caring at home, showering gently with warm water is permitted. Tap dry with sterile gauze or fan with cool air – this can be helpful for a tender skin surface and skin folds and help to preserve the skin layer.

Dressing management: low exudate wounds

- Consider the use of hydrogel sheets/gel to offer comfort and absorb exudate.
- For secondary dressing, use a simple non-adhesive dressing such as a soft silicone dressing. These dressings may require the additional use of simple dressing to cover.
- If there is associated trauma or bleeding, an alginate dressing may also be considered as a primary dressing +/- hydrogel.
- A Silicone Lite dressing +/- Mepitel border may be left in place for 2–3 days if clinically indicated; this is best considered at the end of treatment or when there may be a period of treatment rest days such as at a weekend.

Dressing management: heavy exudate wounds

- Foam or silicone dressings may be used, either single use or in combination with hydrogel preparations.
- Hydrocolloid dressings have the capacity to absorb exudate and de-slough wounds; if applied dry, they change from dry fibre dressings to gel as they absorb body fluids.
- Healthy tissue surrounding wounds with heavy exudate can be vulnerable to maceration; Cavilon lotion can be applied to healthy tissue to help maintain tissue integrity.
- Tapes to secure dressings should be avoided but if border dressings are used and the surrounding skin is vulnerable, Cavilon can be applied to healthy skin prior to dressing application.
- Flamazine Cream is beneficial for promoting wound healing, it contains silver which is anti-bacterial and promotes wound healing. It should only be used when RT is completed. It may be used for skin that is intact or broken with low to moderate exudate.

Antibiotics should be used if infection suspected.

5.3.2 Information on late side effects

Information on late side effects should include:

- breast shrinkage (30% mild/mod; ≤10% marked at 10 years)
- breast induration (30% mild/mod; ≤10% marked at 10 years)
- breast pain and tenderness (30% mild/mod; ≤10% marked at 10 years)
- capsule formation after reconstruction and fat necrosis after TRAM/DIEP (≤10% at 10 years)
- extremely high risk of capsule formation in patients with implant-based reconstructions
- rib fracture (<1% at 10 years)

- symptomatic cardiac damage – left breast RT only if any heart in treatment volume (1–2% at 20 years). Risk is eliminated if cardiac shielding introduced on both fields. Deep inspiratory treatment can also reduce risk. See [section 5.6](#)
- symptomatic lung fibrosis – only after lymphatic RT ($\leq 10\%$ at 10 years)
- arm lymphoedema – only after lymphatic RT (10% at 10 years)*
- shoulder stiffness – only after lymphatic RT (10% at 10 years)*
- stroke – only after lymphatic radiotherapy (<1% at 10 years)
- arm paralysis – only after lymphatic RT ($\ll 1\%$ at 10 years)*
- second malignancy, including contra-lateral primary breast cancer (1–2% at 20 years)
- connective tissue restriction/tightness in radiotherapy field
- ongoing fatigue.

* probably only axillary and not SCF radiotherapy

There should be onward referral for any side effects causing limitation of function or lifestyle.

5.4 Radiotherapy in patients with collagen disease

There is Level III evidence that active collagen disease, especially systemic sclerosis, is associated with an increase in the risk of late adverse effects. A recent systematic review of the literature emphasised the heterogeneity of published reports, all retrospective studies characterised by varying study designs, sample size and criteria for reporting late adverse effects.⁴⁵ However, the review concludes that a hazard ratio of 1.5 is the best estimate of effect for a history of collagen disease. If this is an accurate estimate (it may not be), a 50% increase in the risk of late adverse effects can be offset by a 10% reduction in total dose (e.g. a reduction from 50Gy to 46Gy in 2.0Gy fractions which is also achieved by a prescription of 40Gy in 15 fractions Grade B).⁴⁶ As an added precaution in patients who are keen to avoid mastectomy, it may be possible to exclude most, if not all, of the ribcage and intra-thoracic structures by reducing the target volume. In practice, this is done by adjusting the position of the medial and lateral field borders; possibly the superior and inferior borders too (Grade C).

5.5 Breast reconstruction and radiotherapy

Indications for RT after mastectomy are not formally influenced by breast reconstruction. However, patients must understand and accept the possibility of late changes, including induration (fibrosis) and skin atrophy, in exchange for protection against local tumour relapse. The cosmetic impact of radiation is particularly marked in the setting of implant-only reconstruction. A recent systematic overview concludes that cosmetic outcome is better when breast reconstruction follows RT, rather than precedes it (Level III).⁴⁷ Either way, there are no evidence-based guidelines that justify a change from standard therapy for post-mastectomy RT, either in terms of target volume, dose schedule or use of bolus. It is current practice to use 2.0Gy fractions to a total dose of 50Gy in preference to 2.67Gy fractions to a total dose of 40Gy, although the latter schedule is equivalent to 46Gy in 2.0Gy fraction in terms of its late adverse effects, assuming an α/β value of 3.0Gy.

5.6 Radiotherapy and the cardiovascular system

The systematic overview by the Early Breast Cancer Collaborative Group (EBCTCG) confirms an excess annual risk of cardiovascular mortality after RT that is higher in the second decade post-treatment than in the first.⁴⁸ Non-breast cancer deaths are mostly due to cardiac and cerebrovascular disease (SCF RT), corresponding to two or three excess deaths at 20 years per 100 women irradiated. The excess risk is not yet seen in randomised trials started since 1975.

Analysis of the different techniques used in the Scandinavian randomised trials of post-mastectomy radiation suggests that the risk of ischaemic heart disease is associated with radiation dose rather than volume.⁴⁹ Minimising dose is certainly worthwhile in our patients, but the implication is that reducing volume does not reduce risk until the heart is totally excluded. This may be because the anterior descending coronary (or possibly other key segments of the vasculature), which lies within the high dose volume whenever cardiac tissue is exposed, functions as a 'serial' structure (like spinal cord) in terms of atheroma risk. On the precautionary principle, and recognising the potential for enhancement by anthracyclines in chemotherapy patients, it is judged to be preferable to protect the myocardium if there is more than minimal inclusion of cardiac tissue in the treatment volume. This is fairly straightforward in patients treated by breast conservation, since most tumours are in the central or upper quadrants and >75% of tumour recurrence risk is concentrated in the index quadrant. In these patients, cardiac shielding either protects only non-target tissue or a small volume of peripheral breast tissue. It may be more difficult to apply after mastectomy, when cardiac protection may shield skin very close to, or including, the medial end of the scar. Deep inspiratory techniques may also be useful.

Recommendations for cardiac shielding

After breast conservation surgery for invasive disease or pure DCIS, cardiac shielding is recommended unless it also shields the tumour bed (Grade B).^{49–52} After mastectomy, electrons should be considered as an alternative to tangential photon fields if the heart encroaches on the treatment volume. Deep inspiratory breath-hold has also been shown to reduce cardiac dose.⁵³

5.7 Inflammatory carcinoma

This is a controversial area. Historically, the impact of RT on large inoperable primary tumours with extensive dermal lymphatic invasion was limited, with high rates of in-field and out-of-field recurrence. There is retrospective evidence from several series that women with operable primary disease treated with primary chemotherapy followed by radical surgery enjoy 5-year local control rates of >70% after high dose ($\geq 60\text{Gy}$) RT (reviewed in⁵⁴ Level II). Retrospective review of Royal Marsden Hospital data in women receiving neo-adjuvant chemotherapy and radiotherapy with (N = 17) or without (N = 35) surgery fails to confirm the benefits of surgery in this disease, although local recurrence rates were very high (42% and 34% respectively) regardless of whether surgery was given or not.⁵⁵ It is standard to treat these patients surgically if it is felt that negative margins can be attained due the impact of uncontrolled local disease even in the setting of metastatic disease.

Recommendations for radiotherapy in inflammatory carcinoma

Radiotherapy should be recommended regardless of the type of surgery (Grade B). Fields to the chest wall or intact breast need to take account of the characteristically widespread dermal lymphatic permeation. If wide tangential photon fields to the chest wall encompass excessive lung (>2cm), electrons should be considered as an alternative. After mastectomy, and if the planning target volume can be encompassed adequately, a prescribed dose of 60Gy in 2.0Gy equivalents should be considered on the advice of the consultant (Grade B). If a bulky tumour remains in situ despite systemic therapy and no surgery can be offered, or if fields cannot encompass areas of suspected disease after mastectomy, the chances of local tumour control are low, and it may not be sensible to prescribe high dose RT (Grade C). Radiotherapy to the lymphatic pathways needs to be considered separately, and care should be taken in selecting dose fractionation (see [5.2.6-5.2.19](#)).

5.8 Radiotherapy in inoperable locally advanced disease (non-inflammatory)

The standard clinical target volume comprises the whole breast (Grade A). It is sometimes appropriate to confine RT to the affected quadrant, most commonly in elderly (>75yr) and frail patients with a long history, sometimes spanning years, of a slowly growing cancer confined to the breast (Grade C).

Standard high dose palliative regimens deliver 40Gy in 2.67Gy fractions to the whole breast followed by a boost to the primary tumour of 12–21Gy in 3.0Gy fractions (Grade B). Low dose palliation (20Gy in 5 fractions or 40Gy in 15 fractions) is appropriate in poor prognosis patients in whom short-term relief (weeks rather than months/years) of symptoms (bleeding, pain) is required (Grade B). For treatments confined to the affected quadrant, a dose prescription of 30Gy in 5 fractions of 6.0Gy to the 100% isodose treating once per week can be considered as equivalent in terms of late adverse effects to a total dose of 52Gy in 2.0Gy fractions. Using a shrinking field technique, 1 or 2 additional fractions of 6.0Gy can be considered under consultant supervision (increasing the equivalent dose in 2.0Gy fractions from 50 to 60 and 70Gy, respectively). This hypofractionated approach is not appropriate for RT to the lymphatic pathways, nor for high dose RT delivered with locally curative intent as part of multimodality treatment.

5.9 Scheduling of radiotherapy

Concurrent chemo-radiotherapy should not be given, since there is no benefit in terms of anti-cancer effects and the incidence and severity of early and late adverse effects are enhanced, especially when anthracyclines are used.^{56–57} The available data on taxanes are less worrying, but there is seldom a reason to consider concurrent delivery of both modalities. There are no reports of enhanced adverse effects when trastuzumab and RT are given concurrently. There is (Level 2) evidence that concurrent tamoxifen and RT enhance radiation-induced lung fibrosis, although this does not appear to be a problem in non-lung tissues and does not prevent tamoxifen or aromatase inhibitors being given during RT unless axilla and SCF irradiation are prescribed (Grade B).⁵⁸

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6 Systemic Therapy for Breast Cancer

6.1 Endocrine therapy

All pre-menopausal and post-menopausal women with invasive ER positive and or PR positive tumours should be offered adjuvant endocrine therapy. The histopathology report of ER and PR status specifies the level of positivity typically on a 0–8 (Allred) scale. A score of 0 or 2 is considered negative. Patients with tumours which express any degree of ER positivity (scores of 3 or more) can be considered for endocrine treatment, but if the level of positivity is very low the risks and benefits should be discussed with the patient.

6.1.1 Timing of endocrine therapy

Current evidence suggests that the concurrent administration of chemotherapy and endocrine therapy is less effective than when they are given sequentially. In addition, there is evidence that concurrent administration (especially with tamoxifen) carries an increased risk of thromboembolism. For these reasons, if the patient is receiving adjuvant chemotherapy, the endocrine therapy should only be started 2–3 weeks after completion of chemotherapy. Otherwise it should be started as soon after surgery as convenient. Endocrine therapy can be given concurrently with radiotherapy.

6.1.2 Adjuvant aromatase inhibitors

Aromatase inhibitors (AI) should never be prescribed for pre-menopausal women with any ovarian function as they are not effective and may indeed cause ovarian hyperstimulation. The concurrent administration of hormone replacement therapy (HRT) may entirely negate the effects of an AI and is contraindicated.

NICE guidance was issued in November 2006 relating to adjuvant endocrine therapy for hormone receptor positive breast cancer in post-menopausal women. All women with an ER positive early breast cancer who are post-menopausal should be offered the option of tamoxifen and/or an AI. The decision about treatment choice should be made by the woman and the responsible clinician after appropriate discussion and consideration of breast cancer risk factors and the potential side effects. Tamoxifen alone should no longer be considered the standard of care for post-menopausal women. New guidelines¹ issued in February 2009 state that an AI (anastrozole or letrozole) should be offered as initial therapy for this group of patients if they are not considered to be at low risk (10 years predictive survival of 93% or above on Nottingham Prognostic Index or Adjuvant! Online). Tamoxifen should be offered if AI is not tolerated or contraindicated.

For the purpose of these recommendations, menopause is defined as age over 60 years or amenorrhoea for at least 12 months (in the absence of chemotherapy, tamoxifen or ovarian suppression).

6.1.3 Pre-menopausal women

The standard of care is for tamoxifen for an initial 5 years. If there is a contraindication to tamoxifen then an AI with an LHRH analogue or oophorectomy should be considered.

Patients who have completed endocrine therapy and who wish to become pregnant should be advised to discontinue tamoxifen for a minimum of 2 months before trying to become pregnant.

After 5 years of tamoxifen, see below for extended adjuvant endocrine therapy.

6.1.4 Peri-menopausal women

Peri-menopausal women – defined as women not clearly post-menopausal – should also receive 5 years of tamoxifen and be considered for extended adjuvant endocrine therapy at the completion of the 5-year period if appropriate.

6.1.5 Women with chemotherapy-induced amenorrhoea

These women should be managed as peri-menopausal women with five years of tamoxifen and then consideration of extended adjuvant endocrine therapy.

A switch to an AI could be considered after 2–3 years of tamoxifen in amenorrhoeic women over the age of 50 but this would require the biochemical proof of post-menopausal status after stopping tamoxifen for 3 months and repeat biochemical testing of oestrogen levels performed 3–6 months later to ensure that no further stimulated production of oestrogen occurs. Alternatively, the concurrent use of an LHRH analogue or oophorectomy to ensure that ovarian function does not return could be considered.

6.1.6 Endocrine therapy beyond five years in pre/peri-menopausal women

Pre-menopausal women with ER and/or PR positive breast cancer who become amenorrhoeic secondary to chemotherapy and who have completed 5 years of tamoxifen should be considered for extended adjuvant treatment with an AI. This group of patients should have serum levels of FSH/LH/oestradiol measured 3 months after discontinuing tamoxifen and, if proven to be post-menopausal, a further 5 years of letrozole should be offered and a baseline bone mineral density scan (DXA scan) should be performed within the first 3 months of commencing treatment.

Following the publication of the ATLAS trial in December 2102 a further five years of tamoxifen should be considered for women who are not postmenopausal or for whom an aromatase inhibitor is contraindicated.

6.1.7 Post-menopausal women

- At outset: all post-menopausal women with ER and/or PR positive who are not considered to be at very low risk should receive initial adjuvant endocrine therapy with either anastrozole or letrozole. Therapy should either be for 5 years or for 2 years followed by tamoxifen for 3 years.
- After 2–3 years of tamoxifen: women who have been started on tamoxifen should be considered for a switch to an AI (anastrozole, letrozole or exemestane) for the remainder of the 5-year period.
- After 5 years of tamoxifen: women who have completed 5 years of tamoxifen and originally had node positive breast cancer or who were otherwise considered to have not low risk breast cancer should be considered for receiving 5 years of letrozole.

Co-morbidity and potential side effects should be considered when discussing the above options with patients. For example, a post-menopausal woman with a history of thromboembolism should not be treated with tamoxifen.

6.1.8 Ovarian suppression

Adjuvant ovarian ablation reduces the risk of breast cancer recurrence in pre-menopausal patients. Suppression of ovarian function (GnRH analogues, e.g. goserelin) with or without tamoxifen for 2 years is at least as effective as CMF chemotherapy but the latter is rarely used now in pre-menopausal women with evidence of the superiority of anthracyclines.

Therefore it is unknown as to whether tamoxifen and ovarian suppression is as effective as anthracycline-based chemotherapy and also as to whether ovarian suppression in addition to anthracycline-based chemotherapy and tamoxifen confers further benefit. A number of international trials are addressing these issues.²

Meanwhile, such patients should have the current evidence discussed with them in clinic. If the patient wishes to have ovarian suppression then the following options are available. GnRH agonists have the advantage of being reversible, which is of benefit if the patient has intolerable menopausal symptoms or has a desire to become pregnant at a later date.

- GnRH analogue goserelin given 4-weekly. In the adjuvant setting, the recommendation is for 4-weekly injections for a period of 2 years. In the metastatic setting, patients can switch to 12-weekly injections after two courses of 4-weekly injections.
- Laparoscopic oophorectomy has the advantage of being a one-off procedure which avoids the need for regular medical treatments. There may be an additional benefit of this approach in confirmed or likely BRCA carriers at risk of ovarian carcinoma. In this later case bilateral salpingo-oophorectomy should be performed according to a BRCA protocol.

Goserelin in addition to tamoxifen can be discussed with women who maintain/regain menstruation within 6 months of completing chemotherapy in younger women who are perceived to be at high risk of recurrence.

Goserelin in addition to tamoxifen may also be offered to women who decline recommended chemotherapy or when there is a small benefit from chemotherapy.

6.1.9 Neo-adjuvant endocrine therapy

Post-menopausal women with large operable ER positive cancers are at moderate to high risk of systemic failure and, if fit, should be considered for both chemotherapy and endocrine therapy. Neo-adjuvant chemotherapy should be considered followed by loco-regional treatment and then adjuvant endocrine therapy.

Neo-adjuvant endocrine therapy is preferably given in the context of a trial. Outside trials, current evidence suggest that neo-adjuvant letrozole is more effective than tamoxifen in terms of both clinical response and avoidance of mastectomy in post-menopausal women with large ER positive tumours, otherwise requiring a mastectomy. Such patients should be offered a therapeutic trial of letrozole 2.5mg OD prior to surgery.

Normally, 4–6 months of neo-adjuvant endocrine therapy would be given providing the primary tumour is responding. Clinical response should be checked 2–4 weeks after starting therapy and then at 4-weekly intervals, preferably by the same clinician at each visit. These measurements should be recorded sequentially in the case notes. Response to endocrine therapy can be slow. Measurable disease progression (a 25% or greater increase in the product of the two longest perpendicular diameters of the tumour) is an indication to stop therapy and refer urgently to the surgical team.

Women with ER positive breast cancers who refuse surgery or who are unfit for surgery should also be offered letrozole as primary medical therapy. In exceptional circumstances it may be more appropriate to prescribe tamoxifen at the clinician's discretion.³

Neo-adjuvant endocrine therapy is considered in rare circumstances for pre-menopausal women with strongly ER positive cancers. However, this should only ever be a consultant/multidisciplinary team (MDT) decision.

6.1.10 Management of side effects of endocrine therapy

Hot flushes

According to NICE clinical guidelines, the selective serotonin re-uptake inhibitor antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not for those taking tamoxifen because of concerns that they may reduce the metabolism of tamoxifen. Venlafaxine, which does not interfere with tamoxifen metabolism, at an initial starting dose of 37.5mg OD increasing to 75mg OD can be helpful in some patients. Citalopram 10–20mg OD can also be considered.

Gabapentin and clonidine have also been shown to reduce the symptoms of hot flushes in some studies but should only be offered to women with breast cancer after they have been fully informed of the significant side effects.

The prescribing of treatments for unlicensed indications will require approval according to local Trust policies.

HRT (including oestrogen/progestogen combinations) should not be offered routinely to women with menopausal symptoms and a history of breast cancer. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed. It may be acceptable in combination with tamoxifen or in patients with ER negative tumours. As treatment is controversial, it should be a consultant decision.

Other approaches with only limited evidence of efficacy but which may be considered include acupuncture, oil of evening primrose and cognitive behavioural therapy (CBT).

Atrophic vaginitis

Vaginal dryness that fails to respond to non-hormonal topical therapies (Sylk, Replens, Astraglide, Yes etc) can be treated with topical oestrogen creams or pessaries. Systemic 'spillover' effect is likely to be low and will probably not affect the efficacy of tamoxifen. However, this is not the case with the AIs, where their use is relatively contraindicated.

Vaginal bleeding while on tamoxifen

Atypical vaginal bleeding while on tamoxifen needs to be evaluated urgently by a gynaecologist as this may be a symptom of endometrial hyperplasia or dysplasia. Assessment will usually include pelvic examination, transvaginal ultrasound and often hysteroscopy. The decision to continue tamoxifen after such an evaluation needs to be made in conjunction with the gynaecologist and is a consultant decision.

6.2 Chemotherapy

Summary of accepted regimens for patients not involved in clinical trials

Neo-adjuvant setting:

EC x 4-docetaxel x 4
 Docetaxel x 4-EC x 4
 FEC 75

Adjuvant schedules listed below can also be considered in the neo-adjuvant setting.

Adjuvant setting:

FEC 75
 FEC 60
 FEC-T
 EC x 4
 AC x 4
 EC x 4-paclitaxel x 4 (3-weekly or accelerated)
 TC (docetaxel, cyclophosphamide)
 CMF
 TCH (docetaxel, carboplatin, trastuzumab)
 Weekly paclitaxel x 12
 Paclitaxel x 4
 Docetaxel x 4

Patients with HER2 positive tumours should receive trastuzumab concomitantly with taxanes in the neo-adjuvant and adjuvant settings or after completion of anthracycline-only chemotherapy.

The overview of randomised trials of polychemotherapy for early breast cancer shows an absolute 10-year survival benefit in women under 50 years old with node positive disease of around 11% and node negative disease 7%. The absolute survival benefit falls with age but statistically significant survival is still seen up to but not beyond the age of 70. A survival benefit for chemotherapy over and above that achieved with endocrine therapy alone is seen in patients whose tumours are ER positive.

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials.⁴

The decision to offer chemotherapy is based on many factors including age, general clinical condition, prognostic factors for outcome and the patient's own wishes following informed discussion.

6.2.1 Low risk

In this category, the absolute survival benefit for adjuvant chemotherapy is either unproven or so small as to be not clinically recommended.

- Patients aged 70 or over: chemotherapy may need to be discussed with some patients aged over 70 with multiple poor risk factors but deemed fit for chemotherapy. This is always an MDT/consultant decision.

- Patients with all of the following:
 - tumour ≤ 2 cm in diameter
 - ER positive
 - Grade 1 histology
 - no lympho-vascular invasion
 - negative lymph nodes
 - HER2 negative.

6.2.2 Moderate to high risk

Patients with any of the following are at sufficient risk to offer adjuvant chemotherapy on the basis of established survival benefits. For each patient, the pros and cons of the treatment need to be discussed. As a general guideline, the greater the number of factors involved, the greater the risk and the stronger the recommendation for chemotherapy:

- node positive disease
- ER negative
- lympho-vascular invasion present
- Grade 2 and 3 histology
- tumour ≥ 2 cm in diameter
- patients ≤ 35 years
- HER2 positive.

There has been increasing evidence regarding the use of taxanes as part of adjuvant treatment for women with high risk of relapse. NICE guidance from September 2006 and updated in 2009 stated that women with node positive breast cancer should be offered the option of being treated with a regimen containing taxane. The registration regimen for docetaxel in the adjuvant setting was TAC (concurrent docetaxel, adriamycin and cyclophosphamide), but this is associated with considerable toxicity and has similar efficacy to a regimen of 3 cycles FEC 100 (epirubicin 100mg/m²) and 3 cycles of docetaxel (100mg/m²). Many UK cancer networks have accepted 3 cycles FEC 100 followed by 3 cycles of docetaxel as their standard of care for women with node positive breast cancer.

Our general recommendation is for node negative patients to be treated with anthracycline-containing regimens (e.g. FEC 75) and all node positive patients to be considered for anthracycline- taxanes (e.g. FEC 100/docetaxel or dose dense EC-paclitaxel). However, there are circumstances where this advice might be modified. For example:

- Patient has otherwise good prognostic factors/older-age group/significant co-morbidities, therefore FEC 75 can be considered.
- Adjuvant taxane is unlikely to add significant extra benefit (e.g. for a one node positive patient with strongly ER positive low grade invasive carcinoma).
- Adjuvant taxane is likely to add extra benefit for a node negative patient (e.g. with ER negative, Grade 3 invasive carcinoma).
- Adjuvant taxanes should also be considered for all HER2 positive cancers.

Other regimens that are used in the adjuvant setting include FEC 60 and AC x 4 or EC x 4 in the elderly or frail; CMF in patients not willing to experience alopecia and TC x 4 (docetaxel and cyclophosphamide) in patients requiring adjuvant chemotherapy in whom anthracyclines are contraindicated or inappropriate.

For patients with HER2 positive disease, see section on trastuzumab (6.3).

www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf

6.2.3 Molecular profiling of tumours to determine risk and prediction of chemotherapy benefit

There is much interest in individual profiling of tumours for prognostic and predictive information, for example Oncotype DX and immunohistochemical (IHC) 4 scores. NICE has now assessed the MammaPrint, Oncotype DX, IHC4 and Mammostrat. Oncotype DX is recommended as an option for guiding adjuvant chemotherapy for people with oestrogen receptor positive (ER+), lymph node negative (LN-) and human epidermal growth factor receptor 2 negative (HER2-) early breast cancer if the person is assessed as being at intermediate risk and information on the biological features of the cancer provided by Oncotype DX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy. MammaPrint, IHC4 and Mammostrat are currently only recommended for use in research in ER+, LN- and HER2- early breast cancer.⁵

6.2.4 Timing of adjuvant chemotherapy

Adjuvant chemotherapy is given before adjuvant radiotherapy and endocrine therapy. There is evidence of an increased risk of thromboembolism if chemotherapy is given concurrently with tamoxifen. Also, there is pre-clinical and clinical evidence of sequential chemotherapy and endocrine therapy being more effective than concurrent.

6.2.5 Standard chemotherapy regimens

The policy is to offer patients entry into adjuvant chemotherapy clinical trials wherever possible. Standard chemotherapy should be considered for those who do not wish to take part in a trial or who are ineligible for trial entry.

FEC 75

5 FU 600mg/m² IV day 1

Eirubicin 75mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

21-day cycle for 6 cycles

FEC 60

5 FU 600mg/m² IV day 1

Epirubicin 60mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

21-day cycle for 6 cycles

FEC 100-T

5 FU 500mg/m² IV day 1

Epirubicin 100mg/m² IV day 1

Cyclophosphamide 500mg/m² IV day 1

21-day cycle for 3 cycles followed by:

Docetaxel 100mg/m² IV day 1

21-day cycle for 3 cycles

Consider primary prophylaxis with GCSF (e.g. pegfilgrastim, filgrastim or equivalent)

EC

Epirubicin 90mg/m² IV day 1

Cyclophosphamide 600mg/m² IV day 1

21-day cycle for 4–6 cycles

or 14-day cycle with GCSF in accelerated schedule

CMF

Cyclophosphamide 100mg/m² PO days 1–14

or 600mg/m² IV days 1 and 8

Methotrexate 40mg/m² IV days 1 and 8

5 FU 600mg/m² IV days 1 and 8

Folinic acid rescue 15mg 6-hourly x 6 doses PO days 2 and 9 (start 24 hours post- MXT)

CMF alone is rarely used because of the compelling evidence suggesting the superiority of anthracycline-based regimens. It can be used if a patient does not wish to lose their hair, is frail or has significantly impaired cardiac function (LVEF ≤ 45%).

Docetaxel

Docetaxel 100mg/m² IV day 1

21-day cycle for 4 cycles

Consider primary prophylaxis with GCSF, with docetaxel 100mg/m² (e.g. pegfilgrastim, filgrastim or equivalent)

Paclitaxel

80mg/m² IV day 1

Weekly for 12 weeks

Paclitaxel can be used as an alternative to docetaxel, typically for patients who are allergic to docetaxel or when there is contraindication for high dose of steroids.

Paclitaxel

175mg/m² IV day 1

21-day cycle for 4 cycles

or 14-day cycle +/- GCSF

TC (cyclophosphamide)

Docetaxel 75mg/m²

Cyclophosphamide 600mg/m²

21-day cycle for 4 cycles

For a small subgroup of patients with a low left ventricular ejection fraction (LVEF) measurement on an echocardiography/radionucleotide multiple-gated acquisition (MUGA) scan or where there is concern about the use of an anthracycline, the TC regimen could be considered.

TC (carboplatin) H

Docetaxel 75mg/m² IV day 1

Carboplatin AUC 6 IV

Trastuzumab 8mg/kg IV loading then 6mg/kg thereafter

Every 21 days for 6 cycles then single agent trastuzumab for 12 further cycles

For the up-to-date list of many of the agreed chemotherapy regimens and the individual protocol details see www.londoncanceralliance.nhs.uk. Each protocol describes the drugs and doses, the schedule of treatment, administration guidelines, extravasation and emetogenic potential, regular investigations required, common toxicities, drug interactions and guidance for management of common toxicities.

6.2.6 Primary or neo-adjuvant chemotherapy

Primary or neo-adjuvant chemotherapy should be considered for patients with:

- large tumours (≥3cm) that would require a mastectomy
- a central primary tumour less than 2cm from the centre of the nipple
- locally advanced breast cancer
- tumours of >2cm in a small volume breast where the multidisciplinary team considers the tumour to be inoperable and operability may be achieved and/or the chance of breast conservation with optimum cosmesis can be significantly improved
- all women <50 years of age who have ER/PgR/HER2 negative tumours, regardless of tumour size. Systemic chemotherapy is offered as part of the overall management and neo-adjuvant therapy allows additional scope for not only potential downstaging of the tumour but allows women to consider BRCA testing and decision regarding optimal surgery if found to be a mutation carrier. Referral to the genetics service should be made at the start of neo-adjuvant chemotherapy
- trials in neo-adjuvant chemotherapy may be available.

A relative contraindication to neo-adjuvant chemotherapy being given to avoid mastectomy is the presence of extensive microcalcification at baseline which may prevent conservation after chemotherapy. A coil marker to define the tumour bed is recommended in patients who are triple negative or HER2 positive, or a good response is seen early in treatment.

The standard neo-adjuvant regimens are as above.

All patients receiving primary or neo-adjuvant chemotherapy should have assessments with breast ultrasound scan before starting chemotherapy (baseline), mid-treatment and following completion of chemotherapy (end of treatment). Mid-treatment scans should be reviewed and chemotherapy may be switched if there is no clinical and/or radiological response to the initial regimen. Chemotherapy may also be discontinued earlier and surgery brought forward if there is no clinical and/or radiological response. Some units may use MRI as part of the imaging protocols.

HER2 positive patients should have cardiac assessment as per the UK National Cancer Research Institute (NCRI) recommendations (see below) and trastuzumab should be added to taxanes prior to surgery and continued to complete a total of 17–18 cycles (standard regimen) or as appropriate if the patient is participating in a clinical trial.

In brief, HER2 positive patients should have echocardiograms performed prior to commencing chemotherapy, following treatment with anthracyclines and at 4 and 8 months of trastuzumab treatment. End of treatment echocardiogram (12 months) should only be performed if a cardiac intervention was required during treatment. Patients receiving adjuvant trastuzumab only (following completion of chemotherapy) should have clinical reviews with blood tests and echocardiogram result on 4-monthly basis and a pro-active approach with ACE inhibitors should be adopted as per the UK NCRI recommendations (see below).

6.2.7 General procedure for prescription and administration of adjuvant/neo-adjuvant chemotherapy

- Obtain written informed consent from the patient. It is essential to discuss the need for contraception and conversely the risk of infertility/early menopause with all pre-menopausal patients (see later section on fertility).
- Check and record in the notes whether there is a history of, or strong risk factors for, cardiac disease. If present then consider electrocardiogram (ECG) and echocardiography/MUGA assessment prior to administration of an anthracycline-containing regimen.
- All patients should have a full blood count (FBC), urea and electrolytes (U&E) and liver function (LFT) tests prior to each cycle of chemotherapy.
- Blood results and toxicity should be recorded.
- A bone scan, CT scan (or liver ultrasound and CXR if CT scan is not readily available) should be considered in all women at significant risk of metastatic disease and routinely performed for women with four or more positive nodes (stage IIIa or above) prior to adjuvant chemotherapy. These tests should also be organised for patients due to receive neo-adjuvant chemotherapy if they have palpable or radiologically involved ipsilateral axillary lymph nodes or locally advanced disease in the breast (see imaging guidelines, section 2.3.4)
- The prescription of any chemotherapy must be protocol based and consultant led. If the consultant is temporarily unavailable then chemotherapy can be initiated by a specialist registrar (SpR) providing this

is protocol based and it is recorded in the notes that the consultant has been informed. Follow-up courses of chemotherapy initiated by a consultant can be prescribed by the SpR or clinical fellow.

- Wig referral and a discussion of scalp cooling should be part of the pre- chemotherapy work-up of all patients who are receiving treatment where alopecia is likely (e.g. all standard adjuvant and neo-adjuvant regimens).
- Prior to completion of chemotherapy, the patient should be reviewed to check, if appropriate, that a start date for radiotherapy is scheduled and, if appropriate, that a plan to commence endocrine therapy post-chemotherapy has been finalised.

6.2.8 Managing common chemotherapy-related toxicity

Toxicity after each cycle should be recorded and ideally graded using the CTC grading system.

Leucopenia/neutropenia

G-CSF should not be routinely prescribed as primary prophylaxis except for regimens with the highest risks of neutropenia (e.g. docetaxel 100mg/m²).

Maintaining dose intensity is an important aim for early breast cancer chemotherapy.

On day 1 of each new cycle, treatment should be given if neutrophil count is $\geq 1.0 \times 10^9/l$ providing the patient is clinically well. If the neutrophil count is $< 1.0 \times 10^9/l$, delay chemotherapy and repeat FBC on subsequent days. GCSF support (e.g. pegfilgrastim, lenograstim, filgrastim or bioequivalent) should be considered for subsequent cycles.

If there is persistent neutropenia despite the use of GCSF, then a dose reduction may be necessary. This should be a consultant decision.

Refer to individual treatment protocols for further recommendations (neutropenic sepsis is a medical emergency and should be managed according to LCA Acute Oncology Clinical Guidelines).

Anaemia/thrombocytopenia

Anaemia can occur, particularly after several cycles of treatment. Mild anaemia can be treated with ferrous sulphate (if due to iron deficiency). If the Hb falls below 8–10g/dl consider blood transfusion after discussion with the patient.

Thrombocytopenia is rare. If the platelet count on day 1 is below $100 \times 10^9/L$ discuss with consultant before proceeding with chemotherapy

Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of anthracycline regimens and these patients routinely receive dexamethasone and 5HT₃ receptor antagonist prophylaxis at the time of administration and for 3 days afterwards. If the patient experiences protracted CINV despite this, then the addition of domperidone for a longer period of time may be helpful.

Domperidone can be administered PO or PR. In extreme cases it may be necessary to admit a patient to hospital for subcutaneous anti-emetic infusions at the same time as chemotherapy. Lorazepam should be considered for anticipatory nausea. Aprepitant may also be useful for CINV refractory to standard emetic regimens (refer to LCA Acute Oncology Clinical Guidelines on CINV).

Alopecia

Scalp cooling may be effective in reducing hair loss with some chemotherapy schedules. If hair loss is occurring, ensure that a wig referral has been made and advise the patient about minimal hair washing and avoidance of heat/chemical treatments to limit hair damage.

Stomatitis

Grade 1 or 2 stomatitis should be treated with prophylactic mouth care for subsequent cycles. This consists of chlorhexidine and nystatin mouthwashes after each meal. In addition, sucralfate can also be used. Grade 3 or 4 stomatitis may require hospital admission for intravenous fluids, antimicrobials and analgesics. Subsequently, prophylactic mouth care should be given and a dose reduction discussed with the consultant.

Disturbance of bowel function

Diarrhoea can be treated with loperamide or codeine phosphate, although infective causes should also be considered. Constipation can also occur, most probably due to the use of anti-emetics such as 5-hydroxytryptamine 3 (5HT₃) receptor antagonists (e.g. granisetron). Laxatives are commonly required.

Fatigue

Patients need to be given general advice about managing their fatigue and, where appropriate, referred for specialist rehabilitation particularly in relation to exercise and relaxation (Cramp and Daniel, 2008, NCAT rehabilitation pathway on fatigue).

Peripheral neuropathy

This is a specific taxane side effect and patients should be asked about symptoms after each taxane treatment. It tends to be accumulative. If a patient has persistent sensory symptoms in the hands or feet and/or is developing difficulty with tasks such as doing up buttons, then the case needs to be discussed with the consultant concerned before any further taxane is given. If patients are having problems with functional activities as a result of peripheral neuropathy, consider referral to occupational therapy.

Myalgia/arthralgia

These symptoms often occur with taxane-based chemotherapy, typically 2–3 days after docetaxel treatment. It is self-limiting, but the patient can take analgesia as necessary and this should also be recommended for subsequent cycles. Docetaxel is reported to be more likely to cause these symptoms than paclitaxel, and in patients with severe myalgia/arthralgia a change to paclitaxel (especially weekly) can be considered.

Fertility, pregnancy and treatment

Women of child-bearing age who are advised to have chemotherapy may be particularly concerned about the potential side effects of ovarian suppression and subsequent infertility. This risk is very much age-related. The risk is low (<10%) in women under 30 years and rises steadily to >50% in patients aged 40 or over. The risk also relates to the duration of chemotherapy.

Patients for whom fertility is an issue should have access to a rapid consultation with a fertility specialist, although they should be aware that any treatment may delay the start of chemotherapy and there is a

theoretical risk concerning the use of ovulatory-stimulating agents in patients with ER positive breast cancer.

Conversely, all patients of child-bearing age who start chemotherapy should be strongly advised to use contraception (non-hormonal) during chemotherapy and for at least 6 months afterwards. Contraceptive advice thereafter will depend on the individual circumstance and the hormonal status of the tumour. For pre-menopausal women receiving tamoxifen, non-hormonal methods of contraception will need to continue.

A guideline from the Society of Family Planning may be of use:

[Patel A, Schwarz B. Cancer and contraception. May 2012. SFP Guideline #20121.](#)

Contraception [Volume 86, Issue 3](#), Pages 191-198, September 2012.

There is a small amount of evidence that the use of GnRH agonists prior to and during chemotherapy may protect the ovaries from chemotherapy-induced follicle damage. This is a controversial area and should be a consultant decision.

The date of the last menstrual period should be recorded at each visit.

Patients need to have a realistic expectation and understand the risk of relapse and the importance of timing for neo-adjuvant and adjuvant chemotherapy. Fertility reserve needs to be considered in women of all ages when considering embryo or oocyte cryopreservation as regular menses do not necessarily imply good fertility reserve.

Women over 40 years old need to be aware of the low likelihood of successful pregnancy following IVF but embryo cryopreservation can still be considered. However, oocyte preservation (for women without a partner) is generally not advisable as pregnancy outcome is extremely poor in this group. There may not be NHS funding available for women over 40 years old or for women who already have a child or whose partners have a child.

When referring a patient to an assisted conception unit (ACU), it is good practice to try and estimate the risk of recurrence and the urgency of need to start chemotherapy as this will help the ACU team guide the patient's management.

6.2.9 Chemotherapy/trastuzumab in pregnancy

Chemotherapy should be avoided in the first trimester of pregnancy as there is an increased risk of fetal malformations and spontaneous abortions. In the second and third trimesters, cytotoxic chemotherapy does not appear to increase the risk of fetal malformations.

Although pre-eclampsia, pre-term labour, intrauterine death and low birth weight have been reported in case series, it is not known if these are higher than in the normal population. Complications of myelosuppression include maternal and neonatal sepsis and haemorrhage.

There is little data on the long-term effects on the fetus/child although the potential long-term effects of exposing the fetus to chemotherapy include gonadal dysfunction, impaired physical and neurologic development, cardiotoxicity after anthracyclines and germ cell mutagenesis resulting in carcinogenesis and teratogenicity in subsequent generations, as well as, theoretically, malignancy as a result of the treatment.

Although case series are small, it appears that anthracycline-based chemotherapy (such as AC) and taxane chemotherapy are safe in the second and third trimesters. The safety of GCSF in pregnancy is not known but can be used when considered necessary for the mother.

There is very little data on trastuzumab in pregnancy. However, from case studies, there may be a relationship with oligohydramnios or anhydramnios, with one hypothesis being that it relates to the role of epidermal growth factor receptor (EGFR) in fetal kidney development. Use of trastuzumab should be avoided in pregnancy for the adjuvant treatment of breast cancer.

6.2.10 Vaccinations in the immunocompromised

The Department of Health guideline (2006) immunisation against infectious disease outlines the risks associated with use of live vaccines in immunocompromised individuals. Patients may not be able to mount a normal immune response and can suffer severe manifestations with live vaccines such as BCG, measles, oral typhoid and yellow fever. Live vaccines should be avoided until 6 months after all chemotherapy or generalised radiotherapy. Live vaccines should be avoided until 3 months after high dose steroids (prednisolone 40mg OD for at least 1 week or equivalent).

Inactivated vaccines are not dangerous to patients receiving chemotherapy but, as an appropriate immune response may not be mounted, they may be ineffective.

Seasonal flu vaccines and pneumococcal vaccine should be offered to patients and administered before chemotherapy starts. If this is not possible, administer the vaccine dose on the day before or day 1 of the chemotherapy cycle.

6.2.11 Baseline cardiac assessments before cytotoxic chemotherapy

Patients receiving chemotherapy may be considered to be at increased risk of developing cardiac dysfunction. The following assessments are recommended before initiating chemotherapy, for all patients with HER2 positive breast cancer. Although these recommendations relate only to HER2 positive tumours, similar pre-treatment assessments would be desirable in any patient for whom cytotoxic chemotherapy is being considered.

- Medical history: to determine previous cardiac events and risk factors.
- Physical examination:
 - blood pressure (hypertension is a potent and modifiable risk factor for the development of cardiac dysfunction, and should be assessed before each cycle of treatment – a blood pressure of >140/85mmHg should be treated with an ACE inhibitor)
 - auscultation of the heart to identify murmurs (significant valvular heart disease is a risk factor for cardiac dysfunction)
 - signs of heart failure (raised venous pressure, crepitations over the lung fields or pedal oedema).
- 12-lead ECG – looking for possible markers of structural heart disease including left ventricular damage/dysfunction:
 - for arrhythmias (atrial fibrillation, atrial flutter, heart block)
 - for evidence of previous myocardial infarction (Q-waves, left bundle branch block)
 - for evidence of left ventricular hypertrophy.
- Left ventricular ejection fraction measurement using echocardiography or MUGA scan.

Serial LVEF assessments are required to guide treatment, and a high degree of reproducibility is essential; MUGA has some advantages in this respect, but requires the use of significant ionising radiation.⁶ The same monitoring modality should be used throughout the course of treatment and, where possible, this should also include the same operator, machine and calculation algorithm. Each institution should establish a normal range for the methods used. LVEF is a dynamic physiological function varying from day to day depending on heart rate and loading conditions, but every effort must be made to provide an accurate and precise assessment of LVEF to guide clinical decisions about trastuzumab therapy, in the same way as this information is essential for implantable cardioverter defibrillator⁷ and cardiac resynchronisation therapies.⁸ Clinicians interpreting LVEF values should consider confounding factors if they receive unexpected results.

Interventions at baseline

Referral to a cardiologist is recommended for patients who have evidence of LVSD, cardiac dysrhythmias, or structural heart disease, including evidence of previous infarction or significant modifiable cardiovascular risk factors, such as poorly controlled hypertension.

Modification of planned chemotherapy regimen

Assessment of baseline LVEF before chemotherapy in all patients informs the choice of cytotoxic regimen. Patients with low or borderline LVEF may benefit from a non-anthracycline-containing regimen. The combination of docetaxel and cyclophosphamide (TC) has been compared with doxorubicin and cyclophosphamide, and has shown at least equivalent efficacy.⁹ Prophylactic ACE inhibitor therapy may also be considered for such patients. Similarly, the combination of docetaxel, carboplatin and trastuzumab may be appropriate (TCH).

The use of ACE inhibitors to control hypertension

Blood pressure should be measured in all breast cancer patients at routine oncology clinic visits, and where readings are above the second Joint British Societies' guidelines¹⁰ target of <140/85mmHg, they should be treated with an ACE inhibitor licensed for the treatment of heart failure (see table below). Angiotensin-converting enzyme inhibitors are recommended as first-line anti-hypertensive agents. Trial data support their efficacy in reducing blood pressure, and for the prevention and treatment of left ventricular dysfunction and heart failure.^{11,12,13,14} There is also direct trial evidence for the efficacy of ACE inhibitors in preventing the decrease in LVEF observed in patients after high-dose chemotherapy.¹⁵

It is recommended that dose titration and renal function monitoring be performed in primary care in accordance with current cardiac guidance.¹⁶ Patients with breast cancer whose hypertension cannot be controlled with standard pharmacological treatment should be referred to a specialist.

ACE inhibitors licensed for heart failure, and their recommended dosing schedules.¹⁷

ACE inhibitor	Starting dose	Dose titration
Captopril	6.25–12.5mg BD	Maintenance: 25–50mg BD Maximum: 150mg daily in divided doses
Cilazapril	0.5mg OD	Maintenance: 2.5–5mg OD Maximum: 5mg OD
Enalapril maleate	2.5mg OD	Maintenance: 20mg OD Maximum: 10–20mg BD
Fosinopril sodium	10mg OD	Maintenance: 10–40mg OD Maximum: 40mg OD
Lisinopril	2.5mg OD	Maintenance: 20mg OD Maximum: 35mg OD
Perindopril erbumine	2mg OD	Maintenance: 4mg OD Maximum: 4mg OD
Quinapril	2.5mg OD	Maintenance: 10–20mg OD Maximum: 40mg OD
Ramipril	1.25mg OD	Maintenance: 2.5–5mg OD

Note: Refer to Trust formulary for locally available ACE inhibitors.

Lifestyle recommendations

Patients should be advised by their GP and oncologist about lifestyle changes that reduce their cardiovascular risk:

- Smoking cessation.
- Improving diet:
 - moderate alcohol consumption (up to 14 units a week for women – heavy alcohol consumption can both increase blood pressure and reduce cardiac function)
 - reducing dietary salt
 - reducing fat
 - increasing fruit and vegetable consumption (5-a-day).
- Increasing physical activity:
 - moderate intensity exercise
 - build up to 30 minutes 5 times a week (Department of Health guidelines).
- Weight loss where appropriate.

6.3 Trastuzumab

All women with breast cancer should have tumour tissue tested for HER2 expression. Patients with HER2 overexpression at the 3+ level by IHC or with gene amplification by fluorescence in situ hybridisation (FISH) or equivalent technique should be considered for therapy with trastuzumab as per NICE guidance. There may be a few patients with high risk tumours with borderline amplification of the HER2 gene where herceptin could be considered.

NICE guidance states that trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2 positive breast cancer following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy (if applicable). Trastuzumab should not be offered to women who have any of the following:

- a history of documented congestive heart failure
- high-risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular heart disease
- evidence of transmural infarction on ECG
- poorly controlled hypertension

Cardiac assessment, monitoring and management for patients receiving trastuzumab should be performed according to the guidelines¹⁸ produced by UK NCRI published in 2009 as follows, and is summarised in algorithms below.

6.3.1 Assessment of left ventricular ejection fraction before trastuzumab treatment

LVEF should be further assessed in all patients after completion of chemotherapy and before initiating trastuzumab therapy. Some patients (7% in the National Surgical Adjuvant Breast Project (NSABP) B-31) will experience a decrease in LVEF that precludes trastuzumab treatment.¹⁹ These patients are not eligible to commence trastuzumab and should be started on an ACE inhibitor and referred to a cardiologist. Repeat assessment of cardiac function should take place after 3 months (but before the time window for starting trastuzumab specified by NICE expires). A significant decrease in LVEF (e.g. 0.10 points) during the course of anthracycline chemotherapy is most likely to indicate a left ventricle that has been left in a damaged, haemodynamically compromised state, and is thus at increased susceptibility to trastuzumab. Prophylactic ACE inhibitor therapy may therefore be considered for such patients.

Initiation of trastuzumab therapy

Trastuzumab may be initiated in patients with LVEF above the LLN for the institution.

Monitoring frequency

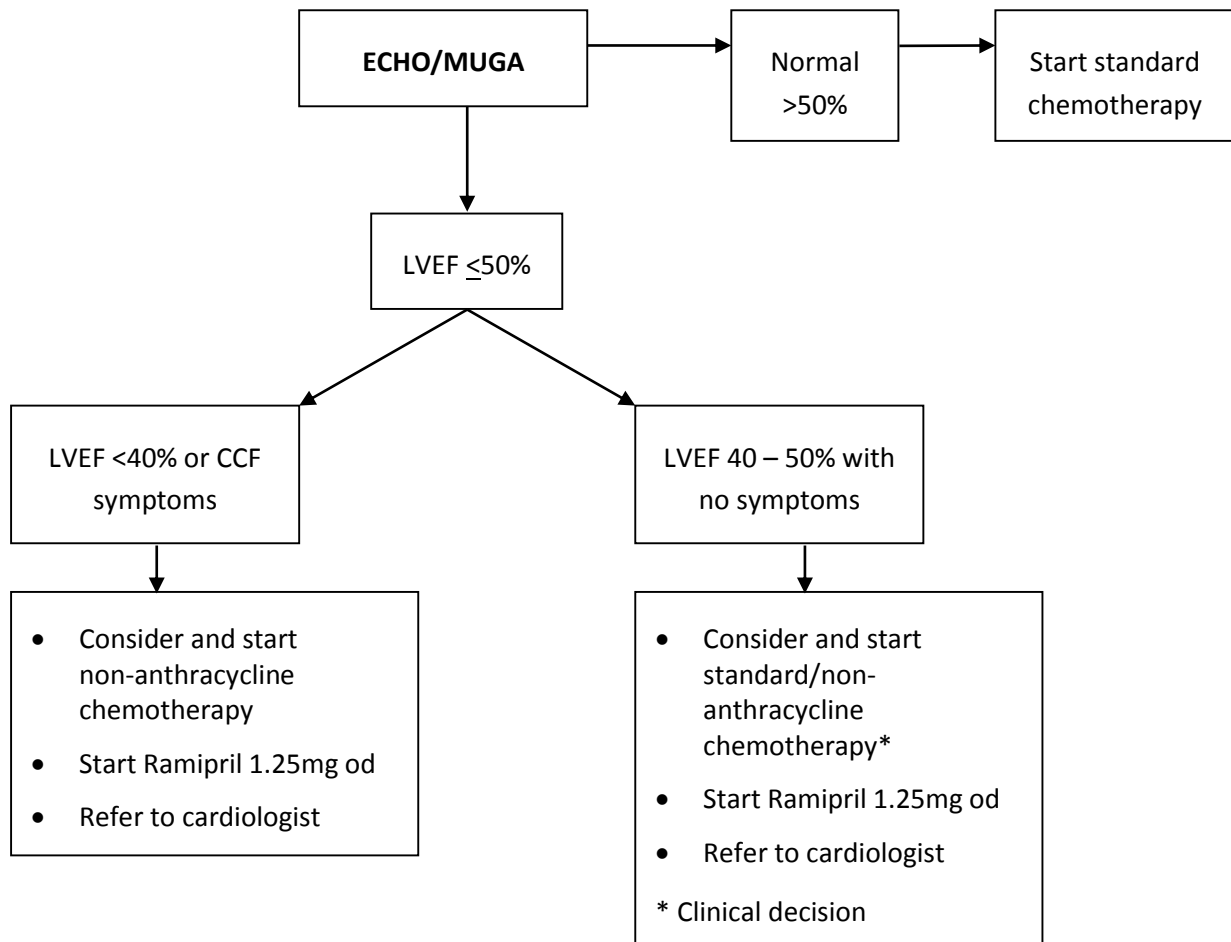
Routine LVEF monitoring is recommended at 4 and 8 months. A further assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment. The minimum number of LVEF assessments when following this recommendation is four, compared with five using the previous NCRI guidelines. Additional testing is required in patients who have LVSD.

Symptomatic heart failure

Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted, have ACE inhibitor therapy initiated by the oncologist and be referred to a cardiologist.

Monitoring procedures in early and metastatic breast cancer

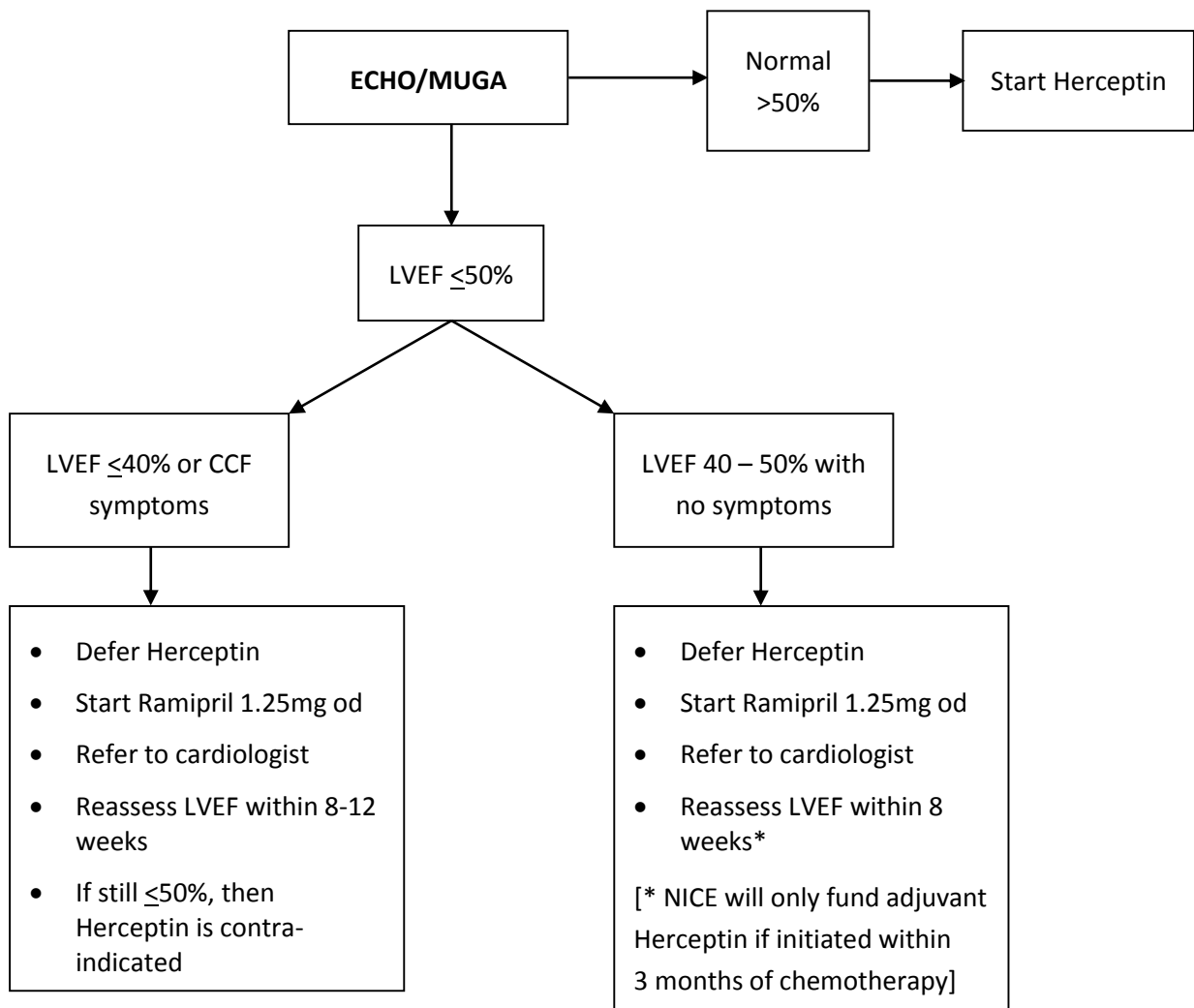
These recommendations were primarily developed for use in patients with early breast cancer who are expected to complete a full 12-month course of trastuzumab therapy. In patients with metastatic breast cancer, trastuzumab is continued until disease progression, but the recommendations are still suitable for monitoring cardiac effects during the first few months of therapy. During trastuzumab therapy, patients with metastatic breast cancer should be monitored for 8 months according to our recommendations. Assuming no complications have occurred, cardiac monitoring should be performed at the discretion of the treating physician, after discussion with the patient, and in accordance with local guidelines. Patients with metastatic disease have a very different oncology risk profile to those receiving adjuvant treatment; the monitoring strategy and thresholds for treatment discontinuation should thus be individualised in consultation with the oncologist and cardiologist when appropriate.

Figure 6.1: Cardiac monitoring with anthracycline-based chemotherapy and Herceptin*1. Pre-chemotherapy (baseline)*

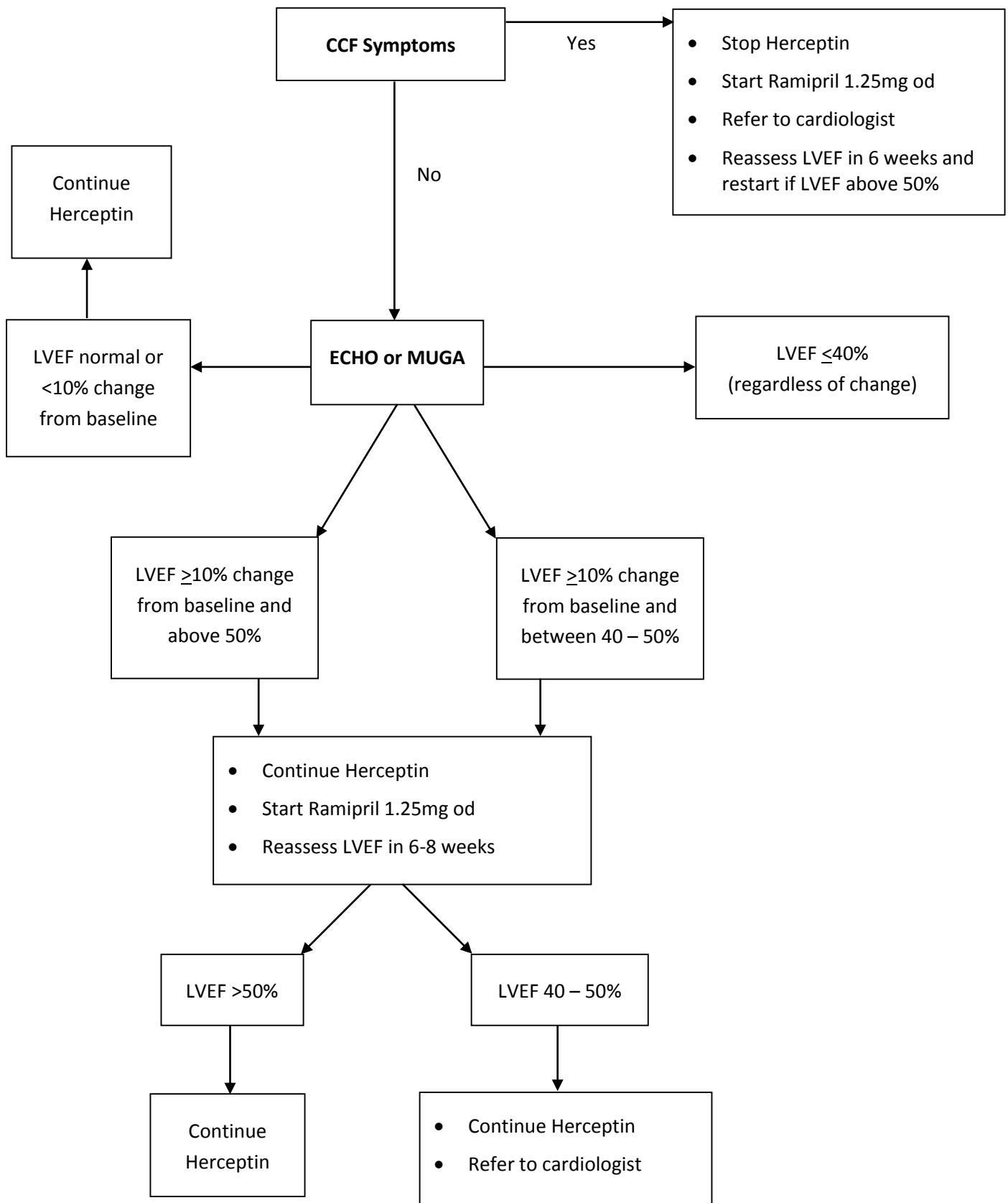
2. Herceptin cardiac monitoring for adjuvant and metastatic patients

- Herceptin should be monitored for all adjuvant patients AND for 8 months initially in the metastatic setting. Beyond this, monitoring should be at the discretion of the clinician, as clinically indicated.
- Routine LVEF monitoring at 4 and 8 months.
- A further LVEF test should be carried out for patients that require cardiovascular intervention during Herceptin treatment. Refer to flowchart.

a) Pre-Herceptin



b) During Herceptin



6.3.2 Administration of trastuzumab

The recommended initial loading dose is 8mg/kg body weight and subsequent doses are trastuzumab 6mg/kg body weight 3-weekly.

6.3.3 Side effects of trastuzumab

Infusion-related symptoms: during the first infusion chills and/or fever are commonly observed. These are usually mild and occur infrequently with subsequent infusions. These symptoms are treated with an analgesic such as paracetamol or an antihistamine such as Piriton. Severe adverse reactions include hypotension, bronchospasm and respiratory distress; these can be serious and potentially fatal.

Serious pulmonary events: rare complications of pulmonary infiltrates, acute respiratory distress syndrome, pneumonitis, acute pulmonary oedema and respiratory insufficiency have been reported. They may occur as an infusion-related event or with a delayed onset. Patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy should not be treated with trastuzumab.

6.4 Bone health

The following advice is based on the UK Expert Group led by David M Reid, Professor of Rheumatology, University of Aberdeen, reviewed and supported by the NCRI Breast Cancer Study Group and the National Osteoporosis Society (November 2007).

The known major risk factors for osteoporotic fracture are:

- previous fragility fracture above the age of 50 years
- parental history of fracture
- a body mass index (BMI) of <22
- alcohol consumption of 4 or more units per day
- diseases known to increase fracture risk such as premature menopause, rheumatoid arthritis, ankylosing spondylitis, immobility and Crohn's disease
- prior oral corticosteroid use for more than 6 months.

6.4.1 Osteoporosis and adjuvant therapy

Bone health is an important issue in women undergoing adjuvant treatment for breast cancer. Two groups of women will be at risk of developing osteoporosis as a consequence of such therapy:

- women with a premature menopause as a consequence of chemotherapy or ovarian suppression, ablation or removal
- post-menopausal women receiving treatment with aromatase inhibitor.

Both groups of women should be given general advice on maintenance of bone health, including adequate calcium intake in diet or with supplementation (target intake 1g/day) and adequate vitamin D intake in diet or with supplementation (target intake 400–800IU/day) – a measurement of vitamin D3 level should be considered to assess this. If vitamin D levels are found to be extremely low (i.e. below the simply insufficient range), then a loading dose of colecalciferol 20,000 units capsules (1 capsule weekly for 12 weeks) should be considered before commencing the maintenance dose.

Other recommendations for maintenance of bone health include:

- weight-bearing exercise such as walking – refer to physiotherapy if patient requires specialist advice on exercise.
- avoidance of smoking
- moderation of caffeine intake
- sensible exposure to sunlight.

Referral to a dietician is advised in at-risk women.

No specific monitoring or treatment is required for women who continue to menstruate after treatment for early breast cancer or post-menopausal women above 45 years of age who do not require endocrine treatment or who are receiving tamoxifen.

6.4.2 Measurement of bone density

Both groups of at-risk women should be referred for a baseline measurement of bone mineral density (BMD) by a DXA scan. BMD should be done at the lumbar spine and at one or both total hip sites.

For premature menopausal women, a baseline BMD assessment should be obtained within 3 months of commencing ovarian suppression therapy or oophorectomy and within 12 months of developing post-chemotherapy amenorrhoea. For post-menopausal women receiving aromatase inhibitors, a baseline BMD assessment should be obtained within 3 months of commencing AI.

Osteoporosis is defined as a BMD ≥ 2.5 standard deviations (expressed as a T-score) below peak bone mass or the mean bone density for young adult women. Osteopaenia is defined as a T-score -1 to -2.5 below the normal score for young adult women.

6.4.3 Management

(See algorithm below.)

For post-menopausal women receiving adjuvant treatment with AI, three risk groups are defined:

- High-risk group: baseline T-score of < -2 or known vertebral fracture should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation. DXA should be repeated after 24 months to assess compliance and response. Poor compliance and secondary osteoporosis explain most cases of poor response.
- Medium-risk group: baseline T-score between -1 and -2 should receive lifestyle advice plus calcium and vitamin D supplementation. DXA should be repeated after 24 months to exclude a clinically significant reduction in BMD (T-score of < -2 or $> 4\%$ per annum decline in BMD). Patients who exceed these limits should be treated as per high-risk group.
- Low-risk group: baseline T-score of > -1 (normal BMD) should receive lifestyle advice only and no follow-up DXA is required.

For premature menopausal women receiving a concomitant AI, only two groups are defined:

- High-risk group: T-score of < -1 or known vertebral fracture should receive bone protection with bisphosphonates as described above.
- Medium-risk group: T-score of > -1 should follow recommendations for all medium-risk groups.

The choice of bisphosphonate should be based on local protocols. Weekly oral alendronate 70mg or risedronate 35mg, monthly oral ibandronate 150mg, 3-monthly intravenous ibandronate 3mg, or 6-monthly intravenous zoledronic acid 4mg are all considered appropriate. The patient should be referred to the osteoporosis clinic if intravenous bisphosphonate is to be considered.

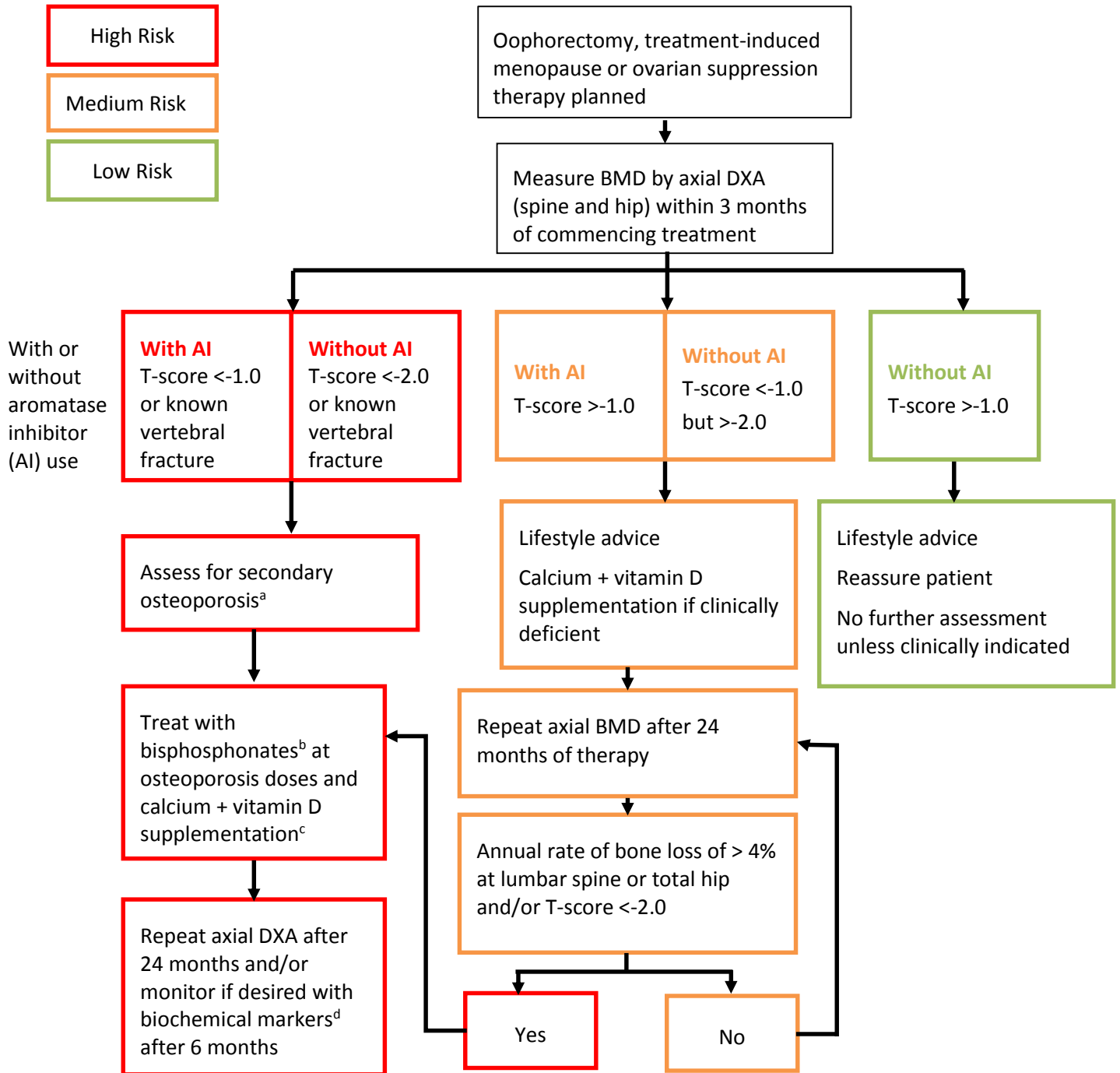
Bisphosphonates are contraindicated in patients with low glomerular filtration rate ($<30\text{ml}/\text{min}/1.73\text{m}^2$) or hypocalcaemia. Oral bisphosphonates should be used with caution in patients with oesophageal disease although intravenous bisphosphonates will be appropriate in such patients.

Calcium supplementation should be given at a dose of 1g/d and vitamin D3 at a dose of 400–800IU/d. Consideration should be given to measuring vitamin D3 levels if likely to be deficient (e.g. poor diet, lack of sun exposure, skin pigmentation). If vitamin D3 levels are found to be extremely low (below the insufficient range) then a loading dose of colecalciferol 20,000 units capsules (1 capsule weekly for 12 weeks) should be started before the maintenance dose.

Consider referral to a specialist menopause clinic for women with premature menopause and/or poorly tolerated symptoms despite the above measures.

Figure 6.2: Algorithms for management of bone loss in early breast cancer

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause



Courtesy of the National Osteoporosis Society

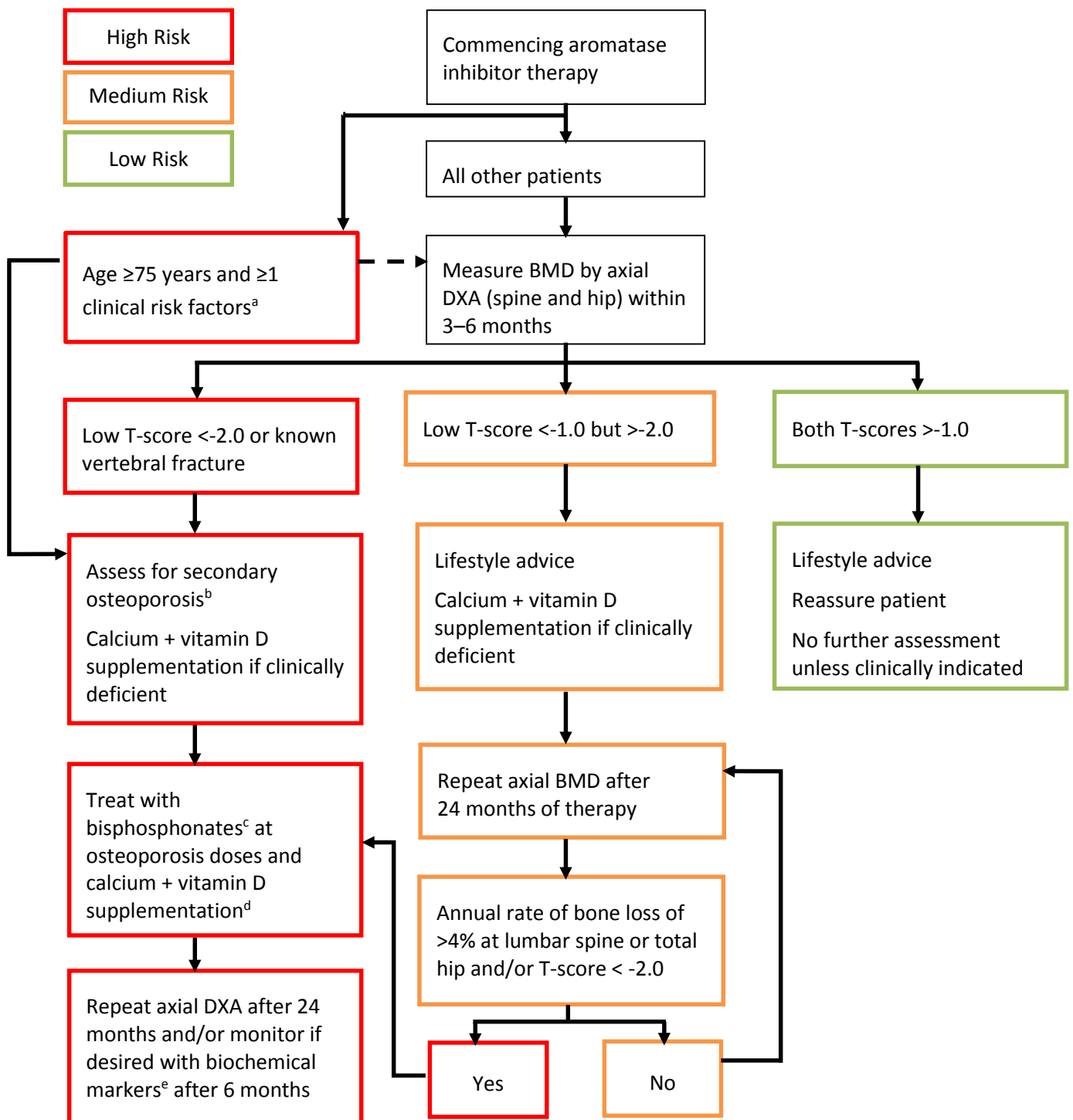
^a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST/γGT), serum creatinine, endomysial antibodies, serum thyroid-stimulating hormone

^b Alendronate 70mg per week, risedronate 35mg per week, ibandronate (150mg PO monthly or 3mg IV 3-monthly), zoledronic acid 4mg IV 6-monthly

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

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

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors



^a Previous low-trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, low BMI (<22)

^b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST /γGT), serum creatinine, endomysial antibodies, serum thyroid-stimulating hormone

^c Alendronate 70mg per week, risedronate 35mg per week, ibandronate (150mg PO monthly or 3mg IV 3-monthly), zoledronic acid 4mg IV 6-monthly

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

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

6.5 Male breast cancer

Most data regarding treatment of male breast cancer are retrospective in nature and come from small single-institution series; the choice of treatment modalities is generally guided by extrapolation of data from female breast cancer.

Endocrine therapy is an important part of the management as 90% of cases are ER positive. The standard endocrine therapy should be tamoxifen, as this is the most extensively studied. Other hormonal therapies which can be considered are goserelin, orchidectomy and megestrol acetate.

Case studies have described the use of aromatase inhibitors alone but there are no data supporting this approach. In fact, there is concern and some reported cases of AIs increasing circulating testosterone in turn leading to an increase in androgen available for conversion to oestrogen. If AIs are considered for the treatment of metastatic tamoxifen-resistant disease, they should only be administered in combination with surgical or medical orchidectomy (LHRH agonist).

6.6 Treatment and management of metastatic disease

6.6.1 General principles

If at all possible, histological confirmation of metastatic disease and up-to-date receptor status (ER and HER2) should be obtained. This is particularly important for patients with unusual sites or presentations of metastases or with a long disease-free interval. The ER and the HER2 status of the metastatic tumour may be different from the primary as it can be influenced by prior therapies and clonal outgrowth.

The aim of treatment is symptom relief. Prophylactic palliation may be justified in some patients with minimal or no symptoms. Age, performance status, sites of disease and previous therapy affect the first-line modality used.

Local therapy with radiation or limited palliative surgery should be considered where local symptoms predominate.

In a small number of patients with oligometastatic disease and long disease-free intervals a more radical approach to the management of metastases may be appropriate. This should always be a consultant and/or MDT decision. Approaches to consider include metastatectomy, radiofrequency ablation and stereotactic radiotherapy (tomotherapy, Cyberknife, Gamma Knife).

Before introducing a change in systemic therapy, document the nature and severity of the symptoms for subsequent subjective assessment of patient response. Avoid any treatment with side effects worse than those caused by the patient's cancer. Nominate marker lesions for objective assessment of patient response. Ensure bi-dimensional measurements are documented, making use of diagrams and photographs as appropriate.

Endocrine therapy often works slowly and patients with stable disease do almost as well as those whose tumours achieve a partial response. Treatment with endocrine therapy should, therefore, be continued for as long as the patient is well, with relief of symptoms, and without evidence of progression, whether or not there is objective evidence of tumour regression.

In contrast, chemotherapy is generally reassessed after 2–3 courses and treatment should be continued beyond this only if there is clear-cut evidence of symptom relief and/or tumour regression. This should be

seen as a guideline rather than a hard-and-fast rule, based on a balance between clinical benefit and the side effects of treatment.

In general, patients with metastatic disease should be considered for any appropriate clinical trials. Standard treatment should be given only if there is no appropriate trial or the patient declines entry. Chemotherapy should be used only for patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Exceptions can be made for younger patients by the consultant in charge. Occasionally, remarkable responses which are clinically valuable are seen in patients with PS3 secondary to liver metastases. The great majority of such patients, however, do badly and are better treated in conjunction with the palliative care team.

It is important to liaise with the palliative care team as early as possible in the course of metastatic disease. Patients who develop unpleasant symptoms, particularly pain, should be referred early and their disease managed jointly by the two units.

There are many potential options for the treatment of metastatic breast cancer and the individual management of a patient will need to take into account many factors. Therefore, the following represent a general framework rather than specific guidelines.

6.6.2 Endocrine therapy

Women who have ER positive breast cancer (defined as in the adjuvant setting as an Allred score of 3 or more) should be considered for systemic endocrine therapy.

Post-menopausal women who have not had an aromatase inhibitor

- first-line therapy: letrozole 2.5mg OD or anastrozole 1mg per day
- second-line therapy: tamoxifen 20mg per day or exemestane 25mg per day
- third-line therapy: fulvestrant 500mg IM every 4 weeks with additional 500mg after initial dose
 - Fulvestrant is currently available through the Cancer Drugs Fund for post-menopausal women with ER positive locally advanced or metastatic breast cancer which has relapsed on or after adjuvant anti-oestrogen therapy or progressed on therapy with an anti-oestrogen and has had two lines of hormonal treatment with at least one AI.
- Fourth line therapy: megestrol acetate 160mg per day. Consider this in patients with a long natural history and/or with slow indolent disease.

Women who have had an aromatase inhibitor in the adjuvant setting

- can be re-challenged with the same treatment if there is a long disease-free interval (usually taken to be greater than 1 year). Otherwise:
 - tamoxifen 20mg OD or
 - exemestane 25mg OD
 - fulvestrant 500mg IM every 4 weeks with additional 500mg IM 2 weeks after the initial dose.

Pre-menopausal women

These women can be treated with tamoxifen if they have not previously received this agent or if there is a significant interval after adjuvant therapy. Otherwise, endocrine options include ovarian suppression with goserelin plus or minus the addition of an AI.

6.6.3 Trastuzumab

All women with advanced breast cancer should have tumour tissue (from either original primary or ideally a fresh biopsy) tested for HER2 expression. Patients with HER2 overexpression at the 3+ level by IHC or with gene amplification by FISH should be considered for therapy with trastuzumab as per NICE guidance (see below):

- As monotherapy in patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy will generally have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments.
- In combination with docetaxel or paclitaxel in patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

Patients should be of performance status 0–2 and have a life expectancy of >3 months.

The standard first-line treatment recommended for HER2 positive patients in the metastatic setting is combined taxane/trastuzumab regimen followed by trastuzumab monotherapy (once taxane treatment is completed) until disease progression. The use of trastuzumab with other cytotoxics for firstline treatment of HER2 positive metastatic disease (e.g. in combination with vinorelbine) can be highly effective, but is currently outside NICE guidance; however, it is occasionally considered on an individual patient basis.

On disease progression outside the CNS, trastuzumab should be discontinued and the patient treated with cytotoxic chemotherapy alone or capecitabine and lapatinib. There is also evidence that continued trastuzumab therapy beyond progression can improve response rates and progression-free survival. However, this is not currently uniformly funded in the NHS. Patients can be made aware of co-payment or private arrangements.

Investigations and management of cardiac dysfunction

As per UKNCRI recommendations (see [section 6.3.1](#)).

Administration

The recommended initial loading dose is 8mg/kg body weight and subsequent doses are trastuzumab 6mg/kg body weight IV 3-weekly. Dose reduction in the trastuzumab is not normally necessary. In patients who cannot tolerate trastuzumab, the treatment will be stopped. Concomitant anti-emetics before trastuzumab are not necessary.

6.6.4 Chemotherapy

The exact choice of regimen will depend on a number of factors, including:

- prior chemotherapy and previous response
- cumulative anthracycline exposure
- patient choice and fitness.

It is not possible, therefore, to recommend which regimen should be used in which circumstance (except to note the NICE guidance).

The following regimens are all acceptable:

- Anthracycline naïve or retreatment
 - Note: maximum allowable dose for doxorubicin is 450–550mg/m² and for epirubicin 950mg/m², although less if other cardiac risk factors are present or prior mediastinal radiotherapy
- Single agent epirubicin – 3-weekly
 - Dose usually 60–90mg/m² IV day 1
- Single agent epirubicin – weekly
 - Dose usually 20–30mg/m² IV day 1
- EC (epirubicin and cyclophosphamide)
 - Dose usually 60–90mg/m² and 600mg/m² respectively IV day 1 3-weekly
- FEC (as per adjuvant)
- CMF (as per adjuvant)
- Taxanes given according to NICE guidance²⁰
- The use of docetaxel in combination with an anthracycline in first-line treatment of advanced breast cancer is not currently recommended. As paclitaxel is not licensed for first-line use with an anthracycline, its use has not been considered in this indication.
- Docetaxel and paclitaxel are recommended as an option for the treatment of advanced breast cancer where initial chemotherapy (including an anthracycline) has failed or is inappropriate.

Doses

- Docetaxel: starting dose 100mg/m² or 75mg/m² IV day 1 depending on patient factors. Primary prophylaxis with GCSF should be strongly considered with docetaxel 100mg/m²
- Paclitaxel
 - 70–90mg/m² IV day 1 weekly
 - 175mg/m² IV day 1 3-weekly

Other chemotherapy agents for advanced breast cancer

Capecitabine

1250mg/m² PO BD on days 1–14 every 21 days

Then above is the licenced starting dose; however, consider commencing at 1000mg/m² for frailer patients.

Lapatinib and capecitabine

Lapatinib in combination with capecitabine is recommended for HER2 positive patients who had previous treatment with anthracycline and taxane and trastuzumab in the metastatic setting and with LVEF within normal limits.

Lapatinib 1250mg PO OD continuously until disease progression

Capecitabine 1000mg/m² PO BD on days 1–14 every 21 days

(Available through the national Cancer Drugs Fund)

Eribulin

1.23mg/m² (1.4mg/m² eribulin mesylate) IV over 2–5 minutes day 1 and day 8 every 21 days until disease progression

(Available through the national Cancer Drugs Fund)

Vinorelbine intravenous therapy

25–30mg/m² day 1 and day 8 every 21 days

Vinorelbine oral therapy

Cycle 1: 60mg/m² day 1 and day 8

Cycle 2: 60mg/m² day 1 and escalate to 80mg/m² on day 8 if no grade 4 neutropenia (<0.5 x 10⁹/l) or febrile neutropenia

The subsequent cycles should be given with the same dose as day 8 cycle 2.

(An off-licence schedule of vinorelbine every 14 days is currently used in Imperial healthcare.)

Combination therapy

Combination treatment is sometimes considered for the treatment of advanced disease.

Docetaxel and capecitabine

Docetaxel 75mg/m² day 1

Capecitabine 1000mg/m² BD days 1–14 every 21 days

MVP

Mitomycin-C 8mg/m² IV day 1 on cycles 1, 2, 4 and 6 only

Vinblastine 6mg/m² (max 10mg) IV day 1

Cisplatin 50mg/m² IV day 1

MVCarbo

Mitomycin-C 8mg/m² IV day 1 on cycles 1, 2, 4 and 6 only

Vinblastine 6mg/m² (max 10 mg) IV day 1

Carboplatin typically at AUC 5 IV day 1

Gemcitabine and carboplatin (where funding available)

Gemcitabine 1000mg/m² day 1 and day 8

Carboplatin AUC 5 day 1 every 21 days

Gemcitabine and paclitaxel

Gemcitabine 1250mg/m² day 1 and 8

Paclitaxel 175mg/m² day 1 every 21 days

Metronomic chemotherapy

Cyclophosphamide 50mg PO OD

Methotrexate 2.5mg BD day 1 and day 2 weekly

Bevacizumab and paclitaxel

A 28-day cycle of bevacizumab 10mg/kg day 1 and 15 and paclitaxel 80mg/m² days 1, 8 and 15 can be considered if funding is available (through an application to the CDF) for patients with ER and HER2 negative disease and also for patients previously treated with a taxane in the adjuvant setting.

(The use of capecitabine and bevacizumab is also licensed but funding is not currently available through the NHS.)

Myocet and cyclophosphamide

When Myocet is administered in combination with cyclophosphamide (600mg/m²) the initial recommended dose of Myocet is 60–75mg/m² every 3 weeks.

Managing common chemotherapy-related toxicity

Follow guidelines for the adjuvant setting. Please note that in the metastatic setting, chemotherapy should only be given if the neutrophil count is $\geq 1.5 \times 10^9/l$, unless PS 0 when neutrophil count of greater than $1.0 \times 10^9/l$ is acceptable.

6.6.5 Metastatic bone disease

Patients with metastatic bone disease (lytic and/or sclerotic lesions) should be treated with intravenous bisphosphonates such as zoledronic acid or pamidronate for 6–9 months then changed to an oral bisphosphonate providing the disease remains clinically stable. Patients should be informed at the start of bisphosphonate treatment the intent to switch to an oral bisphosphonate such as clondronate 800mg BD or ibandronate 50mg OD following 6–9 infusions of zoledronic acid and refer to the GP to commence the oral bisphosphonate.

Recently, denosumab 120mg SC given every 4 weeks has been licensed for the prevention of skeletal-related events in patients with bone metastases and can also be considered as an alternative to intravenous bisphosphonates and used in accordance with NICE guidance.

Potent bisphosphonates and denosumab are known to be associated with osteonecrosis of the jaw and all patients commencing such treatment should be made aware of this risk. Where possible, patients are recommended to have a dental check-up before commencing therapy.

¹ www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf

² Cuzick J, Ambroisine L, Davidson N, et al. *Use of luteinising- hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials.* Lancet 2007; 369:1711-1723.

³ www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf

- ⁴ Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet. 2012; 379(9814):432-44.
- ⁵ NICE, 2013. <http://guidance.nice.org.uk/DG10>
- ⁶ Healthcare Commission, 2000. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib17#bib17
- ⁷ NICE, 2006b. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib25#bib25
- ⁸ NICE, 2006c. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib26#bib26
- ⁹ Jones et al, 2006. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib20#bib20
- ¹⁰ British Cardiac Society et al, 2005. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib5#bib5
- ¹¹ SOLVD Investigators, 1992. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib40#bib40
- ¹² AIRE Investigators, 1993. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib1#bib1
- ¹³ Moyé et al, 1994. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib22#bib22
- ¹⁴ Arnold et al, 2003. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib3#bib3
- ¹⁵ Cardinale et al, 2006. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib7#bib7
- ¹⁶ NICE, 2003. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib23#bib23
- ¹⁷ BNF, 2007.
- ¹⁸ AL Jones et al. British Journal of Cancer (2009) 100, 684-692
- ¹⁹ Romond et al, 2005. www.nature.com/bjc/journal/v100/n5/full/6604909a.html#bib34#bib34
- ²⁰ NICE, 2009. <http://guidance.nice.org.uk/CG81/NICEGuidance/pdf/English>

7 Survivorship and Follow-up

As cancer treatments become more effective, more people are living with and beyond cancer with specific needs as a direct result of the cancer and its treatment. The consequences of cancer treatment are dependent on multiple factors and affect each person differently. Consequences may be physical (e.g. cardiovascular conditions, impact on fertility, bone health and gastro-intestinal); emotional and psychological (e.g. anxiety, self-confidence and depression); social; spiritual; or cognitive. They can have an impact on every aspect of a person and on their family's lives, from the ability to work, through to the ability to have a family or to participate in social activities. It is widely acknowledged that cancer survivors have a multitude of unmet needs following treatment, with a majority still having some needs 6 months later. Good survivorship care enables the person to live as full and active a life as possible.

Survivorship can be defined as:

“cover[ing] the physical, psychological and economic issues of cancer, from diagnosis until end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get healthcare and follow-up treatment, late effects of treatment, second cancer and quality of life.

Family members, friends and caregivers are also part of the survivorship experiences.”

National Cancer Institute, accessed 18/04/2012

The National Cancer Survivorship Initiative (NCSI) vision document (2010)¹ mandated five shifts in care for individuals completing cancer treatment. NCSI advocates cancer being treated as a chronic illness, with patients empowered and supported to take an active role in their care. *Improving Outcomes: A Strategy for Cancer* (2012)² states that people living with and beyond a cancer diagnosis should have their full needs addressed to prevent long-term disability, enabling them to live a full, active, good quality life for as long as possible. Work within the NCSI has to date focused on survivorship from the end of treatment, but its March 2013 report *Living With and Beyond Cancer*³ acknowledges that survivorship care from the point of diagnosis is also vital. It challenges services to develop further and focuses on five new areas:

- information and support from diagnosis
- promoting recovery
- sustaining recovery
- managing consequences
- supporting people with active and advanced disease.

The importance of good survivorship care is well known: those who have unmet needs are 20% more likely to visit their GP and twice as likely to attend A&E than their healthy counterparts. They are more likely to be unemployed and many report economic hardship. Much has been achieved both nationally and locally to address this agenda. It is essential that in the LCA our patients have access to high quality, equitable survivorship services on a par with the best in the country. We will continue to build on the successes to date.

The Consequences of Cancer and its Treatment (CCaT) collaborative group (a Macmillan Community of Interest) produced a ‘10 Top Tips’ guidance document for patients. These cover the key components of good survivorship care, and the LCA expects services to address these areas. The following nine points for professionals are based on the CCaT’s work.

7.1 Discuss a person's needs

The holistic needs assessment (HNA) has been shown to be effective in identifying a person's areas of concern. It can take many forms and the LCA has developed its own tool, based on the concerns checklist and distress thermometer. The tool allows patients to specify what is of most concern to them, and so directs subsequent discussion and intervention to addressing these needs. It has scope to cover physical, emotional, spiritual, finance and welfare, and practical concerns. It is anticipated that as the HNA becomes embedded within the pathway, patients will start to ask for an HNA and professionals need to be able to respond to this.

Recommendation: Every patient should be offered an HNA at key pathway points, including at diagnosis and end of treatment, and whenever a person requests one.

7.2 Provide a treatment summary and care plan

These are two related but distinct documents.

A treatment summary provides a summary of the cancer treatments received by the end of first treatment, planned follow-ups (including mechanisms for these) and signs and symptoms of which to be aware. The aim is to provide information not only to the patient, but also to the GP about the possible consequences of cancer and its treatment, signs of recurrence and other important information.

A care plan is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation: An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

7.3 Provide a main contact

Several pieces of UK-wide work have shown the necessity of a key contact, or key worker, not least the national Cancer Patient Experience Survey. It is now agreed that both patients and GPs (and other healthcare professionals) benefit from having a named person to contact if they need help or advice about issues related to the consequences of cancer and its treatment.

Recommendation: The treatment summary should include the details of a key worker in addition to details of who to contact out of hours. This should be sent to the GP, the patient and any others whom the patient identifies as necessary.

7.4 Identify post-treatment symptoms

As discussed above, cancer and its treatments can have far-reaching consequences and people with associated unmet needs are more likely to access healthcare services than their healthy counterparts. Providing information on likely post-treatment symptoms (e.g. lymphoedema), and how these can be managed or avoided, allows people to seek the right help from the right people at the right time.

Recommendation: Information on anticipated or possible consequences of cancer treatment and what to do if they occur should be routinely provided to all patients. This should be done from the time of discussion of treatment onwards, with the information clearly reiterated during the end of treatment consultation.

7.5 Provide support about day-to-day concerns

Life changes following a cancer diagnosis. It is recognised that people need help and support to find a 'new normal'. This may cover any one of a multitude of aspects, from work and education, through to financial worries and needing help with caring responsibilities. Help should be offered at all key points in the pathway, but may be of particular relevance at the end of treatment and may well be highlighted in the HNA. There are various options for written information provision (e.g. Macmillan information leaflets and information prescriptions) as well as some specialist services (e.g. Citizens' Advice Bureau). Reports published by the NCSI, available on the NCSI website, may be of use to professionals.

Recommendation: Patients should be routinely asked about whether they need support with day-to-day issues and referrals made to specialist services when necessary.

7.6 Talk about how you feel

Having a cancer diagnosis has an emotional impact, and at the end of treatment people experience a wide range of emotions. Sometimes, these can be dealt with by the person alone or with support from the key worker and others, but some people will need referral to psychological support services. This may be true not only for patients but for their family and carers too.

Recommendation: Use an HNA to identify emotional concerns. Further screening tools (e.g. the HAD (Hospital Anxiety and Depression) scale) should be considered, with subsequent referrals made as necessary.

7.7 Healthy lifestyle

There is a growing body of evidence which supports the adoption of a healthy lifestyle for those who have had a cancer diagnosis.

7.7.1 Smoking cessation

Tobacco smoking is the main cause of preventable morbidity and premature death in England. End of treatment provides an opportunity to deliver stop smoking interventions at a point at which an individual may be more susceptible to health advice and hence more motivated to quit.

Recommendation: All current smokers should be asked about their smoking habit and offered smoking cessation advice with onward referral to local services as necessary.

7.7.2 Diet

The role that diet can play in cancer incidence has been widely documented. Research has now moved to look at its influence beyond treatment. The nutritional issues during or following treatment include weight loss or gain; changes in body composition (e.g. loss of muscle mass); and particular eating difficulties

(e.g. swallowing problems and limited capacity for food). There are also long-term symptoms (e.g. changes in bowel habits) for those who have had pelvic radiotherapy.

Receiving advice from an appropriately trained professional has been shown to improve quality of life, reduce the risk of recurrence and the risk of developing a new primary or other chronic disease, such as heart disease or diabetes. The aim of dietary advice is also to counter the adverse effects of cancer treatment. To date, most of the work has been done in breast, colorectal and prostate cancer. The WCRF (2007)⁴ recommends the following eight-point plan for all cancer survivors:

1. Be as lean as possible within the normal body weight range.
2. Be physically active as part of everyday life.
3. Avoid sugary drinks and limit the consumption of energy-dense foods.
4. Eat mostly foods of plant origin.
5. Limit intake of red meat and avoid processed meat.
6. Limit alcoholic drinks.
7. Limit consumption of salt. Avoid mouldy cereals or pulses.
8. Aim to meet nutritional needs by diet alone.

Recommendation: Patients should be provided with dietary advice, based on the WCRF recommendations, at the end of treatment, with referral to specialist dieticians as required.

7.7.3 Physical activity

There has been a dramatic rise in the amount of high quality published research on the role of exercise in cancer in recent years. Physical activity results in improvement in quality of life, fitness and function and symptoms related to cancer and its treatments. It reduces cancer recurrence, incidence of second cancers and reduces both all-cause and cancer-specific mortality.

There is wide consensus that cancer survivors should exercise to the same level as the general population for health benefits. Research suggests that a combination of cardio-vascular and muscular strength training has additional benefits over and above undertaking only one type of exercise.

Recommendations: Patients should be encouraged to maintain or increase their level of physical activity both during and after treatment in line with national guidance. They should be referred for specialist assessment by a physiotherapist as necessary.

Patients should also be offered access to a health promotion event, such as a health and wellbeing clinic, at the end of treatment.

7.8 Self-managed follow-up

There is a move towards increased self-management and follow-up closer to home. This has clear benefits to patients, including reduced anxiety in the lead-up to routine appointments and less interference in their day-to-day life caused by travelling to hospitals. In addition, research has shown that recurrence is more likely to be detected by the patient themselves between appointments, rather than at the outpatient appointment. By reducing unnecessary appointments, Trusts are able to see new patients more quickly and spend more time with more complex patients.

For self-management to be effective, patients need to be given the right information about the signs and symptoms of recurrence and clear pathways to follow if they have concerns. They should also be guaranteed a fast, explicit route to re-access services if necessary. A telephone helpline is suggested, which should be run by senior, experienced staff.

Recommendation: In addition to the use of treatment summaries (as described above), services should investigate the feasibility of rolling out self-managed/patient-led follow-up.

7.9 Encourage survivors to share their experience

Sharing the experience of living with and beyond cancer can be beneficial to the patients themselves, their carers and others who have a cancer experience. Providing feedback on their experience, and volunteering and participation in research can all have a positive impact on the patient.

Recommendation: Patients should be offered information about local support groups and where they can access further information on sharing their experiences.

¹ Department of Health (2010) *National Cancer Survivorship Initiative Vision*. www.ncsi.org.uk/wp-content/uploads/NCSI-Vision-Document.pdf

² Department of Health (2012) *Improving Outcomes: A Strategy for Cancer*. www.gov.uk/government/publications/improving-outcomes-a-strategy-for-cancer

³ National Cancer Survivorship Initiative (2013) *Living With and Beyond Cancer: Taking action to improve outcomes*. www.gov.uk/government/uploads/system/uploads/attachment_data/file/181054/9333-TSO-2900664-NCSI_Report_FINAL.pdf

⁴ World Cancer Research Fund (2007) *WCRF/AICR's Second Expert Report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*.

8 Family History and Referral to Clinical Genetics Services

8.1 Referral criteria

8.1.1 Women affected with breast cancer

As part of their management, all women with breast cancer should be asked if they have either a maternal or paternal family history of breast and/or ovarian cancer. Where appropriate (see [Referral to tertiary care, section 8.1.4](#)) they should be referred for consideration of genetic testing and assessment of surveillance for family members.

Women fulfilling the following criteria should be offered referral to tertiary care even if they do not have a family history of breast or ovarian cancer:

- bilateral breast cancer with both cancers diagnosed <50 years
- breast **and** ovarian cancer
- triple-negative breast cancer diagnosed <50 years (triple-negative refers to the pathological classification of a breast cancer that does not express ER, PR or HER2 receptors; defined as an immunohistochemical (IHC) score of <3/8)
- Jewish ancestry.

Women with breast cancer who have a family history of other tumour types may also warrant referral to clinical genetics services, for example:

- sarcoma diagnosed <45 years
- thyroid or endometrial carcinoma
- brain, adrenocortical or any childhood cancer
- multiple other tumour types at a young age.

8.1.2 Women at risk of breast cancer based on family history

The lifetime risk of developing breast cancer is approximately 11–12.5% for the British female population. Women with relatives who have had breast cancer may have a higher risk. The possibility of identifying those women at increased risk has implications for the ability to prevent or reduce morbidity and mortality.

NICE Guideline 14¹ and its update Guideline 41² were developed for use by primary care physicians to facilitate referral of women with an above population risk of breast cancer due to a family history of breast and/or ovarian cancer. This has been recently updated with CG164 (vi). Two groups requiring referral were identified:

- **raised/moderate risk** – can be managed by family history clinics (secondary care)
- **high risk** – should be referred to the clinical genetics services (tertiary care).

The criteria below cover the majority of women who warrant referral, but further advice can be obtained from local secondary or tertiary care services for families that do not fit these criteria.

8.1.3 Referral to secondary care

- one first-degree relative with breast cancer diagnosed <40 years
- two or three close relatives with breast cancer at any age (at least one must be a first-degree relative)
- four close relatives with breast cancer at any age (at least one must be a second-degree relative).

8.1.4 Referral to tertiary care

- known breast cancer susceptibility gene mutation in the family (e.g. BRCA1, BRCA2, TP53)
- one first-degree relative with breast cancer diagnosed <30 years
- two close relatives with breast cancer, average age at diagnosis <50 years (at least one must be a first-degree relative)
- three close relatives with breast cancer, average age at diagnosis <60 years (at least one must be a first-degree relative)
- four close relatives with breast cancer at any age (at least one must be a first-degree relative)
- at least one first-degree relative with breast cancer and any of the following:
 - bilateral breast cancer
 - male breast cancer
 - ovarian cancer
 - Jewish ancestry
 - family containing breast cancer and any of the following:
 - sarcoma diagnosed <45 years
 - brain, adrenocortical or any childhood cancer
 - multiple other tumour types at a young age.

Please note:

- Women with a significant paternal family history of breast and/or ovarian cancer may still warrant referral even if a first-degree relative is not affected with cancer.
- Ideally, a family member who has had breast and/or ovarian cancer should be referred to the clinical genetics services, although in practical terms this may not always be possible.

8.2 Genetic testing

The lifetime breast cancer risk for BRCA mutation carriers is ~80% and the lifetime ovarian cancer risk for BRCA1 carriers is estimated to be 40–60% and for BRCA2 carriers 10–30%.

Testing for mutations in these genes is available as an NHS diagnostic service for eligible families. Genetic testing was previously undertaken in individuals with at least a 20% risk of carrying a mutation. A threshold of 10% has been adopted by NICE CG164.

All families fulfilling moderate or high-risk NICE referral group criteria that are reviewed in secondary or tertiary care can be assessed for eligibility for testing of the BRCA1 and BRCA2 genes. At present, genetic testing should be undertaken only after consultation and counseling by the genetics service.

Currently in the London Cancer Alliance (LCA) region, BRCA mutation testing should be offered to:

- a woman diagnosed with breast cancer who has:
 - bilateral breast cancer with both cancers diagnosed <50 years
 - triple negative breast cancer diagnosed <50 years
 - ovarian cancer
 - bilateral breast cancer and a relative with breast cancer diagnosed <60 years
 - a relative with breast cancer and both diagnosed <45 years
 - relatives with breast cancer and/or ovarian cancer and a Manchester score ≥ 15 *
- a man diagnosed with breast cancer who has:
 - a relative with ovarian cancer or male breast cancer
 - relatives with breast cancer and a Manchester score ≥ 15 .*

* Assessing the risk of a mutation being present is complex and dependent on the family structure and the number and types of cancer in the family. In the UK, the Manchester scoring system is the most widely used assessment tool for determining eligibility for BRCA1 and BRCA2 mutation testing.³

NICE CG164 also recommends the BOEDICEA model which can also be accessed online.⁴

Initial testing for a family is typically undertaken in a blood/DNA sample from an individual affected with breast cancer. The result of full testing of the BRCA1 and BRCA2 genes takes up to 8 weeks.

There are three known founder mutations in BRCA1 and BRCA2 that have an increased prevalence in individuals with Ashkenazi Jewish ancestry. This increased population prevalence means that these patients may have a 10% likelihood of having a mutation with a more limited family history. Referral to the clinical genetics services for individual discussion and assessment is advised.

Women with a TP53 mutation are at high risk of breast cancer. TP53 mutations classically cause Li-Fraumeni syndrome, a very rare cancer predisposition syndrome that includes younger-onset breast cancer, sarcoma, brain tumours and childhood cancers such as adrenocortical tumours and leukaemia. However, TP53 mutations may also be found in women with young-onset breast cancer, diagnosed <30 years, who have no other relevant family history, particularly if there is bilateral disease. Any family in which Li-Fraumeni syndrome is being considered should be referred to the clinical genetics services for evaluation.

8.3 Management and surveillance guidance

8.3.1 Women at risk of breast cancer based on family history

NICE guidelines for mammography in women with a family history of breast cancer are available at www.nice.org.uk/CG164. In the guidance women are assigned into three groups:

- **Population risk:** 10-year risk of less than 3% for women aged 40–49 years and a lifetime risk of less than 17%
- **Raised (moderate) risk:** 10-year risk of 3–8% for women aged 40–49 years or a lifetime risk of 17% or greater but less than 30%
- **High risk:** 10-year risk of greater than 8% for women aged 40–49 years or a lifetime risk of 30% or greater and/or 20% or greater chance of a faulty BRCA1, BRCA2 or TP53 gene in the family.

Annual mammography between 40 and 49 years is advised for women with at least a moderate risk of developing breast cancer. Individualised risk strategies are recommended for women at high risk.

High risk

These women should have their risk formally assessed and be managed by tertiary care.

BRCA1, BRCA2 and TP53 mutation carriers and women at a 50% risk of carrying a BRCA1 or TP53 mutation in a tested family **or** women at 50% risk of carrying a BRCA1 or TP53 mutation from untested or inconclusively tested families with at least a 60% risk of a BRCA1 or TP53 mutation (i.e. a 30% chance of carrying a mutation themselves) should have:

- annual MRI from 20 to 49 years (for TP53 carriers or greater than 30% risk **only**)
- annual MRI from 30 to 39 years
- annual MRI and mammography from 40 to 49 years
- annual mammography +/- MRI from 50 to 59 years (greater than 30% risk BRCA carrier)
- annual mammography +/- MRI from 50 to 69 years (BRCA carrier).
- ATM **homozygote** mutation carriers should have annual MRI from 25 years (no mammography)

See [Appendix 3](#) for the NHSBSP high risk screening protocols

(www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.pdf). It should be noted that this table includes ATM **heterozygotes** in the high-risk group, whereas genetic recommendations are that they should follow moderate risk protocols.

The following women are also eligible for MRI based on NICE clinical guideline 41:⁵

- women aged 30-39 at a 10-year risk of greater than 8%*
- women aged 40-49 at a 10-year risk of greater than 20% or greater than 12%* where mammography has shown a dense breast pattern

* Fulfilled by women with the following family histories:

- two close relatives with average age at diagnosis <30 years
- three close relatives with average age at diagnosis <40 years
- four close relatives with average age at diagnosis <50 years

Note: All relatives must be on the same side of the family and one must be a first-degree relative of the consultee.

Please note:

- It is important that women potentially at high risk are assessed by clinical genetics services so that their family history and risk can be verified before referral into high-risk screening.
- Although it is being addressed, availability of MRI surveillance remains inconsistent across the LCA region, which may be an issue for some high-risk eligible women.

Moderate risk

These women can be managed in secondary care and referred to tertiary care if assessment regarding genetic testing in the family is indicated (see [Genetic testing, section 8.2](#)).

Moderate risk women should have:

- annual mammography from 40 to 49 years
- 3-yearly mammography from 50 years onwards

- ATM heterozygote mutation carriers should have:
 - 18-monthly mammography from 40 to 50 years
 - 3-yearly mammography from 50 years onwards.

8.3.2 Women affected with breast cancer

Women who have had breast cancer and are known to be BRCA1, BRCA2 or TP53 mutation carriers or are at equivalent risk of carrying a mutation, as outlined above, should be offered high-risk surveillance (see [Appendix 3](#) and high risk, section above), if they have residual breast tissue.

Women recently diagnosed with breast cancer who have a significant family history of breast or ovarian cancer may need to be managed differently from women without a family history. The potential risk of further breast cancer primaries and ovarian cancer in these women means that options for ongoing surveillance and risk-reducing surgery may be different from those outlined for women with early and locally advanced breast cancer in NICE clinical guideline 80.⁶

All women considering risk-reducing mastectomy should be able to discuss their breast reconstruction options with a specialist in breast reconstructive skills.

8.3.3 BRCA1 and BRCA2 mutation carriers

Advice to women with BRCA1 or BRCA2 mutations should include:

- Information about breast awareness.
- Annual MRI from 30 to 49 years.
- Annual mammography from 40 years onwards.
- Discussions about risk-reducing oophorectomy: risk-reducing salpingo-oophorectomy after childbearing is highly effective and reduces the risk of ovarian cancer by ~90%. It also reduces the risk of breast cancer; the magnitude of breast cancer risk reduction depends on the age at which oophorectomy is undertaken but is estimated to be ~50% if performed prior to menopause. All mutation carriers should be offered discussions with the relevant professionals regarding risk-reducing oophorectomy once they have completed their families. Please note that there is no current evidence that ovarian screening is beneficial.
- Discussions about risk-reducing mastectomy: risk-reducing mastectomy is highly effective and reduces breast cancer risk by ~90–95%. However, it is a significant surgical procedure and women need to have detailed discussions with the relevant professionals before undertaking surgery. (Please also see [section 4.12 on Risk-Reducing Mastectomy](#).)
- Offer of referral to a BRCA carrier clinic for ongoing coordination of management.
- Discussions about suitability for participation in clinical trials, for example those assessing the risks and benefits of PARP inhibitors in this patient population.

8.3.4 Other gene mutation carriers

Women with mutations in certain other genes, such as TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), STK11 (Peutz-Jeghers syndrome) and CDH1 are at increased risk of breast cancer.

Mutations in such genes are very rare in the general population and therefore are relevant only to a few women in the region. Affected families should have individualised management, coordinated by a clinical genetics service, which will include management of breast cancer risk.

8.3.5 Chemoprevention for high-risk women

Randomised clinical trials have demonstrated that tamoxifen and raloxifene reduce the risk of developing primary invasive breast cancer in high-risk women. This has led to the increasing use of these drugs as chemopreventive agents in women at high risk of breast cancer, especially in North America. Studies are under way to address the effectiveness of chemoprevention in women without breast cancer who have a family history of breast or ovarian cancer. However, use of these drugs in this context in the UK is currently limited because there is no European Medicines Evaluation Agency (EMA) approval for preventive use.

The NICE Familial Breast Cancer update,⁷ has recommended that tamoxifen or raloxifene should be offered to postmenopausal women with a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.

¹ NICE, 2004. McIntosh A et al, *Familial breast cancer (CG14)* www.nice.org.uk/CG14

² NICE, 2006. *Familial breast cancer (CG41)* www.nice.org.uk/CG41

³ Evans et al, 2004. *J Med Genet* 41(6):474-80(2004)

⁴ Boedicea homepage <http://ccge.medschl.cam.ac.uk/boadicea/>

⁵ NICE, 2006. *Familial breast cancer (CG41)* <http://publications.nice.org.uk/familial-breast-cancer-cg41>

⁶ NICE, 2009. *Early and locally advanced breast cancer: Diagnosis and treatment (CG80)* <http://publications.nice.org.uk/early-and-locally-advanced-breast-cancer-cg80>

⁷ NICE, 2013. Familial Breast Cancer update (CG164) www.nice.org.uk/CG164

Appendices

Appendix 1: London Region Quality Assurance Reference Centre Guidance on Management of Indeterminate Breast Lesions

(January 2012)

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Background

In 2008/09, 275 women in London were referred for diagnostic surgery following NHS Breast Screening Programme (NHSBSP) screening mammography. Eighty-two women had a final diagnosis of malignant disease, and 193 women had benign changes. Most of these operations were precipitated by a pre-operative diagnosis of an indeterminate lesion such as papilloma, radial scar or atypia, which carry an associated risk of malignancy. The vast majority of these diagnoses were made with needle core biopsy (NCB) which, by necessity, will have only sampled a small volume of tissue. The increasing use of vacuum-assisted wider bore biopsies (VABs) means that it is now possible to manage these cases without surgery.¹ However, the management of the patient following a biopsy diagnosis of indeterminate pathology may be complex, and the Quality Assurance team concluded that clarification would be helpful.

Aims

It is recognised that cases are considered on a case-by-case basis. The aim of this document is to provide guidance for the multidisciplinary team in the management of these cases.

If malignancy is identified either pre- or post-operatively, the management is determined by the nature of the malignant pathology. If atypia is seen with other lesions (papilloma, radial scar) then the recommendations for atypia should be followed (excision of a representative sample of the atypia).

Non-pleomorphic lobular neoplasia is a coincidental finding in many cases. In such cases, the radiographic abnormality prompting assessment should be managed appropriately, but follow-up is indicated because of the increased risk of developing cancer.¹⁶

Pleomorphic lobular carcinoma in situ (LCIS) should be considered as malignancy (as ductal carcinoma in situ (DCIS) is considered as malignancy) and surgical management is indicated, although vacuum biopsy may be considered with a view to upgrading the pathology in selected cases.

The vacuum biopsy advisory group considered that there are separate roles for VAB in the primary diagnosis of certain groups of imaging findings and for the further diagnosis of abnormalities already biopsied by NCB or fine needle aspiration (FNA) cytology. The common principle for achieving adequate

diagnosis is retrieval of sufficient tissue. The recommendation of the vacuum biopsy advisory group is that for abnormalities that are often associated with an indeterminate diagnosis (mainly calcifications but also distortions and some asymmetries and small masses), the primary diagnostic approach should be to use VAB as the primary biopsy technique to either to excise the whole abnormality (e.g. 5mm cluster of calcification) or obtain a minimum of 2g of tissue (Table A1.1). For indeterminate lesions already diagnosed as indeterminate at NCB (e.g. atypical ductal hyperplasia (ADH), papillary lesion, mucinous lesion, radial scar) the option of VAB excision of a minimum of 5g of tissue should be considered, even if the histology shows atypia (to confirm that only atypia is present or to potentially upgrade to DCIS and/or invasive breast cancer).

Table A1.1: Lesions considered suitable for use of vacuum assisted biopsy as the primary diagnostic technique

Radial distortion with no mass on ultrasound
Calcification
Soft tissue lesion with presumed diagnosis of papilloma

The management recommendations for lesions that correspond to the mammographic abnormality are given in Table A1.2. However, on occasion, an indeterminate lesion is identified in a biopsy that was taken for a mammographic abnormality which proves to be benign, and such coincidental lesions are considered separately in Table A1.3.

Table A1.2: Recommended management of indeterminate lesions where the pathology corresponds to the mammographic abnormality

	Non-operative	Follow-up	Operative	Follow-up
Solitary papilloma, well-defined discrete lesions	Preferred: vacuum-assisted excision to remove lesion	None if imaging lesion is totally removed and no atypia	Local excision, fully excised	None
Multiple peripheral papillomas	Diagnostic vacuum excision of index lesion	Standard increased risk surveillance policy*	Remove lesion (consider risk-reducing surgery)	Standard increased risk surveillance policy*
Radial scar <2cm	Preferred for lesions <2cm: at least 12 VACB core biopsies to sample lesion. If atypia, then surgical excision recommended	None	MDM may elect to recommend excision for lesion >2cm**	None if no atypia. If atypia standard increased risk surveillance policy*
Atypical ductal proliferation (ADH) (1cm or less of calcification)	VACB – if no DCIS and lesion fully removed, consider further vacuum assessment of site	Standard increased risk surveillance policy* (marker to be placed)	Preferred – to remove area of mammographic abnormality	Standard increased risk surveillance policy*
Extensive calcification >1cm with Atypical ductal proliferation on initial biopsy	Vacuum biopsy of more than one area	If no DCIS, refer for diagnostic biopsy	Diagnostic biopsy of most suspicious area	If only atypia from representative surgical sample, standard increased risk surveillance policy*
Lobular neoplasia (atypical lobular hyperplasia/LCIS) not pleomorphic LCIS or LCIS with necrosis	Assess mammographic abnormality and manage accordingly	Standard increased risk surveillance policy*	LCIS – remove imaging abnormality unless already diagnosed as benign by vacuum	Standard increased risk surveillance policy*

* At present, the recommended follow-up for women at increased risk is five years annual mammography, after which women are returned to routine NHSBSP screening.²

** López-Medina et al.³ showed that the proportion of the radial scar volume involved by carcinoma ranged from 3.7% to 16.2% (mean, 8.3%) and was located invariably at the periphery of the lesion. As a consequence, even very extensive sampling might theoretically miss malignant foci.

Table A1.3: Recommended management of indeterminate lesions where the indeterminate pathology is coincidental and not predicted by imaging

	Non-operative	Follow-up	Operative	Follow-up
Solitary papilloma	Preferred: vacuum-assisted excision to remove radiologically visible lesion	None if imaging lesion is totally removed	Local excision	None
Multiple papillomas	Diagnostic vacuum excision of index lesion	Standard increased risk surveillance policy*	Remove lesion. For recurrent lesions consider prophylactic surgery	Standard increased risk surveillance policy*
Radial scar	No action needed if no corresponding mammographic abnormality	None	No action needed	None
Atypical ductal proliferation	VACB recommended to exclude DCIS, if minimal atypia only – follow up	Standard increased risk surveillance policy*	Operative biopsy preferred if severe atypia (pre-operative VACB may be used to identify DCIS)	Standard increased risk surveillance policy*
Lobular neoplasia (non-pleomorphic)	VACB suitable for lobular neoplasia	Standard increased risk surveillance policy*	Operative biopsy for mammographic abnormality if needed	Standard increased risk surveillance policy*

* At present the recommended follow-up for women at increased risk is five years annual mammography, after which women are returned to routine NHSBSP screening.⁴

Notes on management of lobular neoplasia and columnar cell change

Needle core biopsy

Issues relating to lobular neoplasia in needle core biopsies have recently been reviewed.^{5,6} The EUSOMA working group⁷ considered lobular neoplasia to be most frequently a co-incidental finding in a core biopsy and therefore advised that multidisciplinary discussion was essential to determine management, as is advocated by others.⁸ Diagnostic surgical excision of lobular neoplasia has been advocated.⁹

A recent review of the literature revealed an upgrade of 20% for LCIS and 13% for atypical lobular hyperplasia (ALH) to carcinoma when excised.¹⁰ Concerns have been raised about underestimation of cancer,¹⁰⁻¹² even with stereotactic vacuum-assisted biopsy,⁹ and this has led to the recommendation of diagnostic surgical excision for all such lesions from some groups.⁵ It must be appreciated that much of the data is retrospective and that not all studies have considered radiological-pathological discordance as a factor resulting in upgrade, as found by some.^{6,13-15} What is required are large prospective studies with all factors included.

There is general agreement, although limited robust data, that pleomorphic LCIS should be subjected to therapeutic excision; in essence treated as DCIS and therefore categorised as B5a on needle core biopsy. In one series of 12 cases diagnosed on needle core biopsy, ILC was found in three cases on subsequent excision.¹⁷ There is a need for larger studies to confirm that this does represent a more aggressive disease.

Columnar cell lesions in breast core biopsies

Cores bearing columnar cell lesions (CCL) are typically sampled for the histological assessment of mammographic microcalcifications. As for other such specimens, these should be examined at multiple (at least 3) levels. If columnar cell change or hyperplasia only is found, without atypia, the lesions should be regarded as within the constellation of fibrocystic change and categorised as B2, benign.

CCLs with atypia should be regarded as flat epithelial hyperplasia and classified as B3, of uncertain malignant potential. Lesions with more complex architecture should also be regarded as an atypical epithelial proliferation and also regarded as B3, of uncertain malignant potential. As for all such screen-detected lesions, multidisciplinary discussion should be undertaken to correlate radiological, clinical and histopathological findings. Data on risk of finding adjacent associated malignancy are extremely limited.

Acknowledgements:

This guidance was compiled with comments from:

Radiologists, pathologists and surgeons from the London Region NHSBSP services

European Working Group for Breast Screening Pathology:

Austria: Dr A. Reiner; P. Regitnig. Belgium: Dr M. Drijkoningen; Dr D. Faverly. Cyprus: Dr E. Iacovou. Czech Republic: Professor A. Ryska. Denmark: Dr B. Rasmussen. Finland: Dr P. Heikkila. France: Professor J.P. Bellocq; Dr J. Jacquemier. Germany: Professor W. Boecker; Dr T. Decker. Greece: Dr N. Apostolikas, Dr V. Zolota. Hungary: Dr G. Cserni; Dr J. Kulka. Ireland: Professor C. Quinn, Professor G. Callaghy. Italy: Dr S. Bianchi; Professor A. Sapino; Professor M. Pia Foschini. Latvia: Dr I. Liepniece-Karele. Luxembourg: Dr A-M Tanous. Malta: Dr J. DeGaetano. The Netherlands: Professor P.J. van Diest; Dr J. Wesseling. Poland: Dr E. Chmielik. Portugal: Dr M. Lacerda; Dr I. Amendoeira. Slovenia: Dr S. Grazio. Spain: Dr A. Córdoba. Sweden: Professor T. Tot; Dr D. Grabau. Switzerland: Professor B. Borisch; Professor Z. Varga. Turkey: Professor H. Kaya. United Kingdom: Professor I.O. Ellis; Dr C.A. Wells

UK Vacuum Biopsy Advisory Group:

Dr Robin Wilson; Dr Clive Wells; Dr Sarah Pinder; Dr David Evans; Dr Barbara Dall; Dr Peter Britton; Dr James Haselden; Dr Mike Michell; Dr Hilary Dobson; Dr Steve Allen; Dr Will Teh; Dr Andy Evans

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Appendix 2: Approved Indications for MRI of the Breast

Breast MRI is recognised as a diagnostic tool which should be used as an adjunct to conventional breast imaging after full discussion with a breast radiologist or within the context of the breast multidisciplinary team (MDT) meeting.

The following are recommended indications for breast MRI, which are supported by the published literature (NICE 2009, EUSOMA 2010):

- **Discordant conventional imaging**
Conventional triple assessment includes mammography and breast ultrasound. If imaging does not correlate with clinical assessment or with pathology, MRI may act as an additional problem-solving tool in assessing tumour characteristics such as size, extent or multifocality.
- **Pre-operative staging**
MRI of both breasts is not routinely used for pre-operative staging, but in selected patients (e.g. when conventional imaging may underestimate the extent of disease, such as invasive lobular carcinoma, or there is significant discordance between the imaging and clinical findings), MRI may be useful in further assessing tumour size, multicentricity and multifocality, and to evaluate the contra-lateral breast for occult disease.
- **Recurrence vs scar**
Mature scar can morphologically resemble malignancy. At approximately 9 months post-surgery, mature scar should not enhance, whereas recurrent tumour usually shows a typical malignant enhancement pattern.
- **Occult primary tumour/malignant axillary nodes**
The primary tumour may be occult on conventional imaging. Less than 1% of breast cancers present with involved axillary nodes but with normal conventional imaging.
- **Response to chemotherapy**
MRI can document tumour response to chemotherapy. A baseline pre-treatment MRI is required to document initial tumour location, size and imaging characteristics. An interim scan should be planned following 2/3 cycles of treatment. The tumour may require coil localisation or skin tattoo if there appears to be significant response, or potential for complete response. An end of treatment scan completes the assessment of response.
- **Breast implant imaging**
MRI may be used for assessment of implant integrity in cases of suspected leak or rupture, and to assess potential malignancy in an implanted breast.
- **Screening in high-risk groups**
NICE guideline 41 (October 2006) recommends annual contrast enhanced breast MRI for screening in a clearly defined cohort of women with a positive family history of breast cancer. The risk criteria of women who would qualify for screening are clearly set out in this guidance. This screening is also a requirement of the Cancer Reform Strategy (CRS, 2008). Breast MRI is recognised as a suitable screening investigation in the cohort of women who have had exposure to supra-diaphragmatic radiotherapy. The screening for this cohort of high-risk women will be undertaken by the NHS Breast Screening Programme (NHSBSP).
- **Post-operative assessment/post-radiotherapy**
MRI can be misleading in the immediate and short-term post-operative period, and within 18 months of radiotherapy. Scanning during this time should only be in selected patients, after discussion with a breast radiologist or following discussion within a breast MDT and consideration of the limitations of such imaging.

Appendix 3: High-risk Surveillance Imaging Protocols

See: www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.pdf

Risk	Ages	Surveillance protocol	Frequency	Notes
a) BRCA 1 or b) BRCA2 carrier or c) not tested, equivalent high risk	20–29 30–39 40–49 50+	n/a MRI MRI + Mammography Mammography +/- MRI	n/a Annual Annual Annual	Review MRI annually on basis of background density
TP53 (Li-Fraumeni)	20+	MRI	Annual	No mammography
A-T homozygotes	25+	MRI	Annual	No mammography
A-T heterozygotes	40–49 50+	Mammography Mammography	18-monthly Routine screening (3-yearly)	Routine screening from 50
Supradiaphragmatic radiotherapy-irradiated below age 30	30–39 40–49 50+	MRI MRI +/- Mammography Mammography +/- MRI	Annual Annual Annual	Surveillance commences at 30, or 8 years after first irradiation, whichever is the later. Review MRI annually on basis of background density

Notes:

- All mammography must be direct digital mammography to optimise dose and sensitivity.
- All MRI must be carried out in accordance with NHSBSP Technical Guidelines for Magnetic Resonance Imaging for the Surveillance of Women at High Risk of Developing Breast Cancer: publication number 68, January 2012.
- Background density assessment for continuation of MRI should be based on individual clinical judgement.
- Where a woman cannot tolerate MRI, she and her lead radiologist should discuss and agree potential alternatives (e.g. wide scanners).
- Screening should be suspended during pregnancy until about 6 weeks after cessation of lactation, due to the fact that the high density of the lactating breast inhibits interpretation of the image.
- Ultrasound should not be used as a routine screening or surveillance technique.
- For waiting time purposes, the 62-day wait period begins with the decision to recall for assessment. Where two screening examinations take place (mammography and MRI) the clock starts when the second examination is reported, provided that no other investigation has been deemed necessary after the initial mammography. If an abnormality is seen on the first examination then this should be investigated immediately, and the 62-day wait begins straight away.
- Supradiaphragmatic radiotherapy means any treatment in the area of the thorax.
- Untested but equivalent high risk would be as defined by a geneticist.

Appendix 4: London Cancer Alliance Histopathology Protocol for Potentially Mismatched Breast Screening Cases

This protocol relates to the London Cancer Alliance (LCA) pathology review process for B5 biopsies and C5 cytology where initial excision pathology shows no evidence of in situ or invasive malignancy and is supplementary to the National Guidelines¹ for dealing with mismatch cases.

All potential incidents should be reported to the local and screening Trust following its governance protocols.

To facilitate the audit process, the following steps are recommended to be undertaken in pathology departments.

1. Improve pathology department communications within the LCA
 - a. Breast screening multidisciplinary team (MDT) to directly send pathology reports to the pathology department of the hospital where the client is to have surgery. The breast screening staff will identify the referral hospital/surgeon and will send a copy of the report via safe haven fax or secure electronic messaging directly to a named person within that department.
 - b. Any potential mismatch case is identified at an early point directly by the reporting pathologist to the NHS Breast Screening Programme (NHSBSP) screening pathology department or the screening director.
2. Consistency of investigation of excisional breast tissue
 - a. All specimens should be handled according to NHSBSP guidelines.
 - b. All pathologists reporting breast cases derived from the NHSBSP should ideally undertake the national EQA for breast screening pathology.
 - c. All breast cancer cases reported should go through the breast MDT meeting.
3. Where a potential mismatch presents
 - a. Ensure the excision specimen has been thoroughly sampled. This may require multiple procedures such as blocking the whole specimen; selecting blocks from areas of abnormal calcification identified on X-ray of specimen slices; cutting additional levels; and turning blocks over and examining sections from the opposite face. NB Retain any wet tissue until the case is resolved.
 - b. Review clinical, radiological and pathological data with particular reference to size and site of the lesion at the local MDT.
 - c. Attempt to identify the biopsy site: an area of recent haemorrhage with haemosiderin-laden macrophages and associated with early granulation tissue or even fibrosis (according to time elapsed between biopsy and excision).
 - d. If the localisation is inaccurate or the biopsy site is not seen, re-image the patient to identify if the lesion is still in the breast.
 - e. If the case is not resolved by further local investigation or the local service is unable to undertake this further investigation, all the pathological material (including reports) should be sent urgently to the pathology department at the NHSBSP screening centre for correlation with the pre-operative pathology.

- f. After central review at the screening centre, consideration of DNA testing of biopsy vs resection tissue may be considered if the case remains unresolved.

Reference:

1. Reporting, Recording and Auditing B5 Core Biopsies with Normal/benign Surgery.
2. NHSBSP Good Practice Guide No 9. Nov 2007

Appendix 5: Example of Breast Pathology Synoptic Proforma

Patient's identifier: Report number:

Surgical specimen(s)

WLE Excision biopsy Localisation specimen Segmental excision Mastectomy
 Subcutaneous mastectomy Re-excision Further margins Microductectomy

Other

Malignant lesions

Malignant in situ lesion: Not present Present

In situ components: Ductal Lobular

DCIS grade: High Intermediate Low

DCIS growth pattern: Solid Cribriform Papillary Micropapillary Apocrine Flat

Other Specify other

Comedo-type necrosis: Not present Mild Moderate Marked

Pure DCIS size (mm):

Paget's disease: Present Absent Not applicable

Microinvasive: Present Absent Not applicable

Invasive carcinoma: Present Absent

Size and extent

Tumour size (mm):

Whole tumour size (mm):

Disease extent: Localised Multiple foci

Invasive tumour type

Pure (tick one box below) Mixed (tick all components below)

Tubular/cribriform Lobular Mucinous Medullary like Ductal/ NST

Micropapillary Other Other type/component:

Histological grade 1 2 3

Tubule formation 1 2 3

Nuclear pleomorphism 1 2 3

Mitoses 1 2 3

Lympho-vascular invasion Present Absent Possible

Receptor statusOestrogen receptor status: Positive Negative

Allred score =

HER2 status: Positive Negative Her2 IHC score: 0 negative 1+ negative 2+ 3+ Positive FISH/CISH ratio: Status: Amplified Non-Amplified **Excision status**

Distance from margin (mm):

Invasive: Superior..... Inferior..... Medial Lateral Deep..... Superficial.....

Nipple margin.....

DCIS: Superior..... Inferior.... Medial.... Lateral.... Deep..... Superficial

Nipple margin

Lymph node stageSentinel lymph node Axillary clearance

Total number of nodes present:

Total number of nodes positive:

Number with macrometastasis:

Number with micrometastases:

Number with ITCs: (Note ITCs only classified as node negative)

Size of largest deposit (mm)

TN(M) stage: pT.....pN.....

Date reported: Pathologist:

Appendix 6: Breast Cancer TNM

1. Primary tumour (T)

Designation should be made with the subscript 'c' or 'p' modifier to indicate whether the T classification was determined by clinical (physical examination or radiological) or pathological measurements respectively.

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, but presence of Paget disease should still be noted.
T1	Tumour ≤ 20 mm in greatest dimension
T1mi	Tumour ≤ 1 mm in greatest dimension
T1a	Tumour > 1 mm but ≤ 5 mm in greatest dimension
T1b	Tumour > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumour > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumour > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumour > 50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) (NB: Invasion of the dermis alone does not qualify as T4)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

If the tumour size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimetre reading that is closest to the cut-off (e.g. 1.1mm should be reported as 1mm; 2.01cm should be reported as 2.0cm).

2. Nodes (pN)

Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy.

Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for 'sentinel node', for example, pN0(SN).

pNX	Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for histological assessment)
pN0	No regional lymph node metastasis identified histologically
NB: ITCs are defined as small clusters of cells $\leq 0.2\text{mm}$, or single tumour cells, or a cluster of < 200 cells in a single histologic cross-section. ITCs may be detected by routine H&E or by IHC. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.	
pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) $\leq 0.2\text{mm}$ (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases OR
	Metastases in 1–3 axillary lymph nodes AND/OR
	Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases ($> 0.2\text{mm}$ and/or > 200 cells but none $> 2.0\text{mm}$)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis $> 2.0\text{ mm}$
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes OR
	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases.
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 deposit $> 2\text{mm}$)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases

pN3	Metastases in ≥ 10 axillary lymph nodes OR
	Metastases in infraclavicular (level III axillary) lymph nodes OR
	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected OR
	Metastases in ipsilateral supraclavicular lymph nodes.
pN3a	Metastases in ≥ 10 axillary lymph nodes (at least 1 tumour deposit >2.0 mm) OR
	Metastases to the infraclavicular (level III axillary lymph) nodes.
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.
pN3c	Metastases in ipsilateral supraclavicular lymph nodes.
Post-treatment ypN	
<p>– Post-treatment yp ‘N’ should be evaluated as for clinical (pre-treatment) ‘N’ methods above. The modifier ‘SN’ is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by ALND.</p>	
– The X classification will be used (ypNX) if no yp post-treatment SN or ALND was performed	
– N categories are the same as those used for pN	

Reference:

1. Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer, 2010, pp 347-76.
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Helpful rules of thumb

In the case of multiple simultaneous tumours in one organ, the tumour with the highest T category should be classified and the multiplicity or the number of tumours should be indicated in parentheses, e.g. T2(m) or T2(5). In simultaneous bilateral cancers of paired organs, each tumour should be classified independently.

If there is doubt concerning the correct T, N, or M category to which a particular case should be allotted, then the lower (i.e. less advanced) category should be chosen. This will also be reflected in the stage grouping.

Appendix 7: Hormone Receptor and HER2 Assessment

All centres undertaking ER and HER2 assessment must participate in the appropriate UK NEQAS ICC & ISH scheme with satisfactory results.

The hormone receptor overall status (positive or negative) as well as the components of the score (specifically, the percentage of cells staining and the average intensity) should be described in the histology report, as per UK NHSBSP Pathology Co-coordinating committee recommendations.

ER is scored using the Allred system, as in the NHS Breast Screening Programme (NHSBSP) National Reporting Guidelines. The methodology is as follows:

Proportion of staining	Average intensity of staining
0 = no nuclei staining	0 = None
1 = <1% nuclei staining	1 = Weak
2 = 1–10% nuclei staining	2 = Moderate
3 = 11–33% nuclei staining	3 = Strong
4 = 34–66% nuclei staining	
5 = 67–100% nuclei staining	

The proportion and the intensity are added to give the Allred score (range 0–8).

A score >2 is considered positive.

Scores of 0 or 2 (equivalent to less than 1% of cells) are considered negative.

Scores of 3–5 are considered, and should be reported, as weakly positive.

Scores of 6–8 are considered strongly positive.

Appendix 8: HER2 Protein Expression Measurement

The scoring system used for all Her2 immunohistochemistry (IHC) should be as per the UK Her2 guidelines, as follows:

0 = no staining or <10% membrane staining in tumour cells

1 = faint membrane staining is detected in >10% of tumour cells BUT cells are only stained in part of the membrane.

2 = Weak to moderate staining of entire membrane in >30% of tumour cells

3 = Strong staining of entire membrane in >30% of tumour cells

A score of 0 or 1 is considered NEGATIVE

A score of 3 is POSITIVE

Cases with a score of 2 are considered BORDERLINE and ISH analysis is undertaken to determine gene copy number (this may be either FISH or dual labelled CISH).

HER2 gene amplification measurement

ISH is used to determine the number of copies of the Her2 gene. The number of copies of the Her2 gene is presently assessed in relation to chromosome 17 copy numbers. Reports should include both the average copy number and the ratio of HER2 to chromosome 17. A ratio of HER2 to chromosome 17 signals is therefore reported as:

- ratio <1.8 – not amplified, Her2 negative
- ratio 1.8–2.2 is borderline and the count is repeated or the test repeated
- if the score remains as 1.8–2.0 the case is regarded as borderline, non-amplified and Her2 negative
- ratio 2.0–2.2 is regarded as borderline, but amplified and the tumour overall as Her2 positive
- a score >2.2 represents Her2 amplification and the tumour is regarded as Her2 positive.

It should, however, also be noted that the identification of multiple copies of chromosome 17 centromere by ISH is now recognised to rarely reflect polysomy of the whole of chromosome 17 and, even if the HER2:ch17 ratio is less than 2.00, multiple copies of HER2 (average more than 6/cell) should at the very least be recorded and would be regarded by some methodologies as HER2 positive.

Appendix 9: Algorithm for referral to physiotherapy for 23h cancer patients

Pre-operative →	Early post-operative → ($< 8/52$)	Late post-op ($> 8/52$) End of treatment / survivorship
Pre-existing shoulder problems Pain in shoulder Decreased shoulder movement pre-op – less than 120° elevation Co-morbidities affecting mobility Conditioning rehab (where available) for pre-adjuvant chemotherapy	Slow progression re. shoulder movement Cording causing limited function Patient concerns about ex progression Inability to achieve RT position Pain – acute Scar tissue management (if adherence) Persistent seroma	Persistent cording Fatigue issues Pain – in joints and soft tissue Needs individual ex advice Long-term poor shoulder function Specialist/cancer rehab needs Muscle imbalance relating to surgery Lymphoedema + exercise concerns Physical activity issues

Algorithm for referral to physiotherapy for breast cancer patients not on 23-hour breast pathway

As above, plus.

Post-operative

Review all patients as an inpatient for exercise advice and where appropriate mobility.

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Published by London Cancer Alliance

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