West Yorkshire & Harrogate Cancer Alliance

Guidelines for the Management of Breast Cancer

Version 2.0
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# 1 Introduction

## 1.1 Background

Breast cancer is the most common cancer for women in England and Wales, with about 40,500 new cases diagnosed\(^1\) and 10,900 deaths\(^1\) recorded in England and Wales each year. In men breast cancer is rare, with about 260 cases diagnosed\(^2\) and 68 deaths\(^1,2\) in England and Wales each year.

Of these new cases in women and men, a small proportion are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body.

In addition, a considerable number of women who have been previously treated with curative intent subsequently develop either a local recurrence or metastases.

## 1.2 Purpose and Scope of these Guidelines

The West Yorkshire & Harrogate Cancer Alliance guidelines are based on national breast cancer guidance, and accompanying research evidence, with appropriate interpretation for our local service.

This document combines all individual specialty guidance for the management of breast cancer together into a single resource for MDTs.

The guidelines were written by members of the former Network Breast Cancer Site Specific Group and will be reviewed every three years.

## 1.3 Clinical Trials

The availability and importance of clinical trials should be discussed with all patients for both early and advanced disease at appropriate time points.

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2 Breast Cancer Pathways

The Yorkshire and Humber Clinical Network developed a timed Breast Cancer Pathway which was agreed by the Breast Cancer MDT Leads across the region in November 2015.

2.1 NHS England Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services

The NHS England Breast Clinical Reference Group (CRG) have also developed a breast optimal pathway and breast cancer service specification. The document entitled Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services has now been finalised and approved by NHS England in August 2017.
3 Patient Information

Clinical teams offer all newly diagnosed cancer patients information specific to their site, treatment and relevant to their individual need. Patients can also access NHS choices for an information prescription and clinical teams will offer help to do this, if required.
4 Referral

4.1 Breast Cancer Referral Guidelines for Patient, Within or Outside the Network

At a meeting of the former YCN Breast NSSG on 26 April 2006, the group agreed that all patients with breast cancer can be reviewed and treated in local MDT’s and can be referred to other MDT’s within or outside the Network if specific expertise is required in individual patient circumstances. This is uncommon for breast cancer patients.

This was re-agreed in April 2012.
5 Imaging

5.1 Introduction

These guidelines have been drawn up from and entirely in line with Royal College of Radiology Breast Imaging guidelines (http://www.rcr.ac.uk/publications/) and NHS Breast Screening Programme guidelines (http://www.cancerscreening.nhs.uk/breast/)

Diagnosis of breast disease should occur in a multidisciplinary setting using the principles of triple assessment (clinical assessment, imaging and needle cytology/histology). This is best achieved in designated specialist breast clinics in which both radiologists and surgeons/clinicians work closely together. Direct access from GPs for breast imaging alone is not recommended.

These clinics should:

- Provide rapid patient access with measures to identify and prioritise those women with a higher suspicion of malignancy;

- Be organised to ensure that, where possible, all necessary diagnostic procedures are carried out at the initial clinic visit (where this is not achievable imaging should be performed and reported within five working days);

- Imaging should precede any needle aspiration or biopsy procedures. Occasionally there may be a clinical indication to perform FNAC first (e.g. in large cysts).

Imaging should be performed only where there is a clear clinical indication to do so. Inappropriate requests should be monitored and subjected to audit.

Conventional routine techniques for imaging the breast are x-ray mammography and ultrasound. Mammography is the most sensitive routine imaging technique for demonstrating malignant disease in the breast. However, it does involve ionising radiation and should be used only where there is a reasonable risk of malignancy. Breast cancer is uncommon under the age of 35 years and is rare under the age of 30 years. Mammography is also less sensitive for breast disease in younger women because, in general, the normal breast is denser and more difficult to interpret. For these reasons, the recommended protocols for the use of breast imaging are age-dependent.
5.2 Family History Screening

5.2.1 NICE Breast Familial Health Guidelines

Please note that NICE have produced Breast Familial Health Guideline (CG164)

This is a new challenge.

5.2.2 Very High Risk (gene positive or equivalent risk)

There is now compelling evidence in favour of MRI +/- mammographic screening of very high risk patient groups in line with the newly published NICE guidelines.

Access to this service is through the NHS Breast Screening Programme. To be eligible the patient has to have been assessed by our clinical geneticist colleagues as it is based on calculated risk. All high risk patients do not fulfil the NICE criteria for MRI screening.

Women accepted onto the NHS higher risk screening programme will be offered tailored annual screening with MRI and/or mammography.

Centres performing FH screening should be the centres that are already performing a significant amount of breast MRI. National guidelines advise reporting >100 scans per year.

The cancers in this young patient group often have a surprisingly benign appearance and are known to have a rapid doubling time and therefore follow up of lesions which can’t be biopsied in this group should probably be at 6 months rather than a year.

5.2.3 High Risk and Moderate Risk

National guidelines interpreting the NICE guidelines for these groups are still awaited. These patient groups should continue to be managed locally through symptomatic or family history clinics.

HIGH RISK: > 8% risk 10 years 40-50, > 30% lifetime risk (20% risk of BRACA gene)

ANNUAL MRI 30-50 advised : > 8% risk 10 years 30-40 which equates to 20% risk 10 years 40-50

ANNUAL MRI 40-50 advised if mammo dense : > 12% risk 10 years 40-
5.3 Imaging Protocols

5.3.1 Imaging of symptomatic patients over 40 years: Mammography and Target USS

- Mammography is the imaging technique of first choice. It is recommended that the standard mammographic examination should normally include a mediolateral oblique and a craniocaudal projection of each breast. Supplementary projections may be performed as directed by the supervising radiologist/radiographer;

- Target breast ultrasound provides useful additional information and should be used to complement mammography. Ultrasound may be used as the initial imaging technique where clinical examination suggests the presence of a benign process such as a simple cyst;

- Ultrasound is NOT regarded as a suitable technique for routine breast cancer screening. “baseline” mammography is not routinely required prior to commencing HRT. The majority of women receiving HRT are offered screening every three years as a matter of routine. In this age group there is no evidence to support more frequent screening.

5.3.2 Imaging of symptomatic patients under 40 years: Target USS +/- Mammography

- Ultrasound is the imaging technique of first choice in women under 40 years.

- With clinically benign or uncertain findings (P2,P3). If ultrasound confirms normal, benign or probably benign findings, e.g. cyst or circumscribed solid lesion, mammography is unlikely to provide additional diagnostic information.

- Mammography should be performed in women under the age of 40 yrs for lesions which are suspicious on clinical or ultrasound criteria P4/5 or U4/5.

- Mammography should be considered in patients aged 35-39 years with clinically indeterminate lesions (P3) in whom ultrasound is normal.

- Mammography may provide additional diagnostic information in the evaluation of some indeterminate B3 lesions.

- However, where malignancy is suspected, mammography with two views (mediolateral oblique and cranio-caudal projections) of each breast should be performed

Reference: Best Practice diagnostic guidelines for patients presenting with breast symptoms (Department of Health - Nov 2010).
5.3.3 **Localisation of impalpable lesions for surgical biopsy and excision:**

- Diagnostic localisation should allow accurate excision of the abnormality in order to obtain a diagnostic sample weighing less than 20 grams.
- The technique or techniques used are determined by the type and position of the lesion being targeted and by the preferences of radiologists and surgeons.
- Ultrasound guidance is recommended where lesions can be confidently seen on ultrasound. Skin marking may be preferred for superficial lesions.
- Wire localisation is recommended for more deep-seated abnormalities; the wire should pass within 10 mm of the margin of the lesion. It is recommended that check films should always be performed to confirm accurate localisation; if not the procedure should be repeated.
- Following excision, specimen radiography should be performed for all image-guided localisations for impalpable lesions to confirm that adequate excision or sampling has been achieved. Section radiography will aid histopathological assessment of these specimens. A dedicated specimen x-ray machine is preferred.
- ≥ 98% of impalpable lesions should be correctly identified at the first operation.

5.3.4 **Image-guided breast interventional procedures**

Percutaneous sampling of breast lesions is important to avoid unnecessary surgery for benign problems and provide pre-operative diagnosis of malignant lesions, allowing for informed patient counselling and treatment planning. The radiologist plays an important role in obtaining representative tissue, particularly from impalpable lesions. Needle aspiration and/or biopsy should be performed on all clinically or radiologically indeterminate, suspicious or malignant breast abnormalities.

- FNAC and WBCB are essential components of triple assessment and radiologists with a special interest in breast imaging should be skilled in these techniques.
- To ensure accurate sampling, image guidance may be the preferred technique for sampling palpable as well as impalpable lesions.
- Ultrasound guidance is recommended where lesions can be confidently seen on ultrasound.
- Stereotaxis is the recommended technique for guiding biopsy of lesions not clearly visible on ultrasound. For x-ray-guided biopsy, check films must be performed to confirm that the appropriate area is sampled.
- The recommended techniques for FNAC are fully described in the Guidelines for Non-Operative Diagnostic Procedures and Reporting in Breast Cancer Screening.
• For WBCB, the best results are likely to be achieved if 14-gauge needles are used with a spring-loaded biopsy device.

• Consideration should be given to clip insertion where appropriate.

5.3.5 Vacuum biopsy

The imaging team should have access to vacuum biopsy to increase the preoperative diagnosis and decrease the benign breast biopsy rate in accordance with NHSBSP guidelines.

5.3.6 Criteria for the safe avoidance of needle sampling in females < 25yrs with solid breast masses

Solid breast masses in young women are a common problem in symptomatic breast clinics and the majority are fibroadenomas. The diagnosis of carcinoma, phylloides and papilloma are uncommon under 30 and rare under 25yrs. In view of this it would seem reasonable to take the age of 25years as the cut-off below which the avoidance of needle sampling of certain solid masses can be considered safe.

It is important if biopsy is not performed that ALL of the following criteria are met to ensure safe practice. Omitting biopsy has to be carefully considered and discussed with the patient.

• Age <25yrs
• No known risk factors for breast malignancy
• Mass not rapidly enlarging
• Clinical examination: impalpable or smooth discrete mobile mass
• Ultrasound
• Well-defined homogeneously isoechoic or mildly hypoechoic mass
• <3.0 cm in greatest dimension
• Ovoid shape, aligned parallel to the skin surface
• Smooth or gently lobulated contour, two or three lobulations only
• No microlobulations
• Thin, echogenic pseudocapsule
• No calcification
• No acoustic shadowing


5.3.7 Breast Pain

Breast pain alone is not an indication for imaging, particularly if cyclical and of short duration. If persistent localised pain or if there are localised clinical signs follow 'lump protocol.
5.3.8 Nipple discharge

Age appropriate imaging should be performed for spontaneous single duct or serosanguinous discharge.

Routine imaging is not indicated in bilateral discharge.

5.3.9 Pregnancy

Triple Assessment with ultrasound and biopsy as first line. Mammography second line if malignancy is suspected.

5.3.10 Breast sepsis

Ultrasound +/- drainage in the acute phase. Mammography to rule out underlying malignancy >35yrs once acute episode settled.

5.3.11 Imaging of the Axilla

In a patient with suspected breast cancer, ultrasound of the ipsilateral axilla should be performed routinely.

If an abnormal lymph node or nodes are seen with ultrasound needle sampling is required. Pre-operative diagnosis of lymph node metastases will identify patients in whom sentinel node biopsy is not applicable.

Criteria for proceeding with lymph node sampling is one of the following:

- cortex > 2mm
- focal cortical bulge
- short axis ratio > 0.5
- loss of hilum

The method of sampling employed should be agreed locally. FNAC and core biopsy of axillary nodes are both accepted techniques.

If haematological malignancy is suspected FNAC is inappropriate; a core biopsy should be considered.

5.3.12 Surveillance Mammography

Surveillance of women at increased risk due to family history, previous breast cancer or atypia or previous mantle radiotherapy is being considered nationally and national guidelines are expected this year. This may offer these women regular screening through NHSBSP.
5.3.13 Male patients

Gynaecomastia, benign enlargement of breast tissue affecting one third of males in their lifetime, is the commonest cause of a breast lump presenting as a diffuse swelling or a discrete subareolar lump.

Carcinoma of the male breast is a rare cause of breast enlargement. It is extremely uncommon <50yrs. Accounts for <1% of breast cancers and <0.2% of cancers in males.

Routine practice varies widely from clinical assessment only to imaging and biopsy of all cases.

To avoid missed diagnosis of breast cancer, lymphoma or other pathologies consideration should be given to tissue sampling in cases of unilateral focal lumps.

Ultrasound is the imaging method of first choice.

Imaging is not routinely indicated less than 50 years.

Imaging can be reserved for selected cases in line with local protocols. The principal uses are to aid characterisation of clinically suspicious lesions and to guide biopsy.

5.4 MRI in Breast Imaging

5.4.1 Background

A patient presenting with a breast problem undergoes “triple assessment.” This comprises clinical assessment, imaging and tissue sampling. Imaging traditionally means mammography and ultrasound.

MRI has a proven role as an adjunct to triple assessment in selected cases, providing additional information which achieves a preoperative diagnosis and allows successful single stage surgery.

5.4.2 Equipment and Expertise

Breast MRI requires a 1.5 Tesla magnet, a dedicated breast coil and agreed access to MRI guided biopsy.

It requires trained / experienced radiographers to perform the contrast study and carry out the initial post processing.

Breast MRI scans require 45-60 minutes to perform. Reporting requires dedicated time on an MRI work station and double reporting is considered best practice.
5.4.3 Interpretation

It should be clear on the request card what information is required from the MRI examination.

To enhance the probability of accurate results, the information from the triple assessment and the mammographic / ultrasound images should be available when the MRI is reported.

The scan should be reported / interpreted by breast radiologists or in conjunction with breast radiologists, to achieve its full potential as an adjunct to triple assessment. This is important because false positive MR imaging is well documented and will lead to clinical errors if imaging is actioned without histological confirmation.

Management of equivocal lesions identified at MRI is difficult. The difference between mass lesions and areas of enhancement is an important distinction and the resolution of MRI is still such that ‘lesions’ < 5mm are difficult to action beyond follow up. Follow up at 1 year is appropriate in most cases if 2nd look USS is normal. Referral between centres for a second opinion is not only possible but appropriate to produce a uniformly high level of service.

5.4.4 Indications

The decision to request breast MRI should be made at the multi disciplinary team meeting after review of the completed triple assessment.

The main indications for breast MR imaging are as follows:

1. To diagnose or exclude breast cancer when triple assessment is inconclusive.
   a) Clinical and mammography/ultrasound non concordance.
   b) Metastatic carcinoma in axillary lymph nodes with normal mammography and ultrasound.
   c) Conventional imaging difficult to interpret because of previous treatment for breast cancer, previous benign surgery or occasionally when there is marked benign breast change.

2. To assess the extent of newly diagnosed breast cancer.

The negative result from the COMICE trial has meant that MRI is NOT required for all patients having conservative surgery but increasingly it is being used in selected cases when a breast cancer diagnosis has been made but the extent of disease is uncertain

   a) Clinical/radiological non-correlation of size of lesion.
   b) Multi-focality suspected radiologically but targetting 2nd biopsy difficult.
   c) Lobular carcinoma or mixed lobular carcinoma at core biopsy if conservative surgery planned.
   d) Other possible indications which are under investigation but up until now unproven are

   - FH of breast cancer
   - Mammographically occult carcinoma
   - High grade DCIS
3. To monitor response to neoadjuvant chemotherapy
   a) Pre treatment scan to delineate the extent of tumour, extent of disease.
   b) Post two cycles of chemotherapy to assess response to chemotherapy, plan surgery and, if necessary, position a marker clip.
   c) Post treatment if a wide local excision is planned to guide surgery.

4. Breast Implants

MRI is regarded as the best imaging test for assessing breast implants but it should only be used in exceptional cases where it is clear it will change management. Breast implant assessment is usually clinical.

5.5 PET/CT Imaging

All cases to be referred for PET CT only after discussion in a Breast MDT.

May be useful for assessment of suspected malignant infiltration with a painful brachial plexopathy and known breast carcinoma where conventional imaging is equivocal and the result of PET CT would make a difference to patient outcome. Similarly, for more accurate staging in patients with potentially operable advanced disease to exclude occult metastases when conventional imaging is equivocal or indeterminate.

PET-CT 2016 Evidence-based indications for the use of PET-CT in the United Kingdom 2016 For breast cancer see page 4 of the following link:


5.6 Future Developments

5.6.1 MRI Biopsy

More breast MRI will inevitably mean more MRI biopsy but the numbers will remain small.

National and international figures suggest approximately 3% of patients having MRI scans will need an MRI biopsy.

- Each biopsy takes between 1 and 2 hours.
- Centres choosing to provide a biopsy service should take on the responsibility of providing this service for neighbouring centres which would include reviewing cases and advising on management.
- Undertake the appropriate QA and audit as for mammography and ultrasound guided breast biopsies

Because of the small numbers involved, all sites performing MRI will not necessarily opt to perform MRI biopsy but the setting up of an MRI service should involve agreeing access to MRI guided biopsy.

5.7 Professional Standards

Radiologists with a special interest in breast imaging should:

- Assume responsibility for the provision and quality of imaging in symptomatic breast services
- Have undergone appropriate training in accordance with RCR guidelines
- Be personally involved in the interpretation and reporting of a minimum of 500 mammograms in the symptomatic service and or a minimum of 5,000 in NHSBSP
- Be part of a multidisciplinary team associated with a designated breast unit and have appropriate contracted time (identified in a personal job plan) to participate in regular (usually at least weekly) multidisciplinary clinical case management meetings
- It is anticipated that a specialist breast radiologist will require two, and preferably three, fixed sessions dedicated to breast imaging. This should include participation in diagnostic breast clinics organised to ensure that direct and timely consultation with the other members of the clinical team can take place.
- Ideally participate in both symptomatic breast imaging and the NHSBSP
- Possess the skills required to report mammography, perform and interpret breast ultrasound, supervise specialist mammography techniques and perform image-guided biopsy and localisation of impalpable breast lesions.
- Mammography and breast ultrasound reporting should use recognised and recommended descriptive terminology (RCR Breast Group breast imaging classification Clin rad 2009, June 64 (6) 624-7) and include details of site, imaging size and nature of any abnormality with an opinion as to the likely diagnoses and recommendations for any further diagnostic procedure or intervention;
- Have a working knowledge of the role and interpretation of breast MRI and large volume vacuum assisted biopsy.
- Participate in personal breast imaging audit and multidisciplinary breast service audit.
- Participate in CME as recommended by the RCR and ensure that this includes an appropriate breast imaging content.
5.8 Equipment

This section provides guidance on equipment used for imaging as part of the routine symptomatic breast assessment (x-ray mammography and breast ultrasound).

5.8.1 Imaging equipment sufficient for satisfactory diagnostic images

Radiologists involved in breast imaging should ensure that imaging equipment is of a sufficient standard to achieve satisfactory diagnostic images. Breast imaging in symptomatic practice should satisfy the technical and quality requirements laid down by the NHSBSP.

5.8.2 Mammography equipment for symptomatic breast imaging and breast screening assessment

For symptomatic breast imaging and breast screening assessment, mammography equipment should be capable of:

- Obtaining all conventional mammographic projections;
- Obtaining specialist projections including localised compression, magnification projections and stereotactic localisation (digital equipment for stereotaxis has significant advantages);
- Be subject to routine regular quality control assessment to the standards required by the NHSBSP.

5.8.3 Ultrasound equipment for breast imaging

Ultrasound equipment used for breast imaging should:

- Operate at a minimum of 10.0 MHz and preferably be capable of achieving 10-13 MHz operating frequency;
- Provide either hard copy images of appropriate diagnostic quality or the facility to archive and retrieve digital data;
- Be subject to routine regular quality control assessment to the standards required by the NHSBSP.
6 Surgery

The former YCN Breast NSSG supports the national Improving Outcomes in Breast Cancer guidance.

The network has a key role in the development of guidelines for the management of women with breast disease and to agree standards against which the performance of each unit can be assessed.

Units are encouraged to recruit to clinical trials; many are now open in the window of opportunity before surgery and should be offered at this point.

6.1 Prophylactic Mastectomy

6.1.1 Background

Patients with early stage breast cancer often enquire about the risk posed to them of developing cancer in the contralateral breast. They may go on to request a contralateral prophylactic mastectomy, with or without immediate breast reconstruction.

6.1.2 What is the risk of developing a breast cancer in the opposite breast?

A recent publication estimates the average risk of developing contralateral disease at 0.3% per year (a review of over 38,000 patients – this figure was not significantly higher for lobular breast cancers). In the vast majority of cases, the biggest risk is from the treated index cancer.

6.1.3 Will a prophylactic mastectomy improve survival?

A recent Cochrane review found there was no good evidence to support surgical removal of a healthy breast to improve survival.

It reported that patients did have reduced cancer worry following prophylactic mastectomy but commented that patients had previously over-estimated their risk and that this could be avoided with appropriate counselling.

Patients should be properly counselled about the risk of contralateral disease, which in most cases will be low. In addition, regular surveillance means that a new primary is likely to be screen-detected and therefore smaller.

6.1.4 Is there a drug to take to protect the opposite breast?

No drug is licenced for the prevention of breast cancer.
However, patients who have received adjuvant endocrine therapy for a previous ER positive primary cancer will be afforded some protection against development of a contralateral cancer.

6.1.5 Estimating family history risk

Patients affected with breast cancer and with a relevant cancer family history, particularly those with a confirmed predisposing gene (e.g. BRCA1/BRCA2/TP53) mutation, have an increased risk of contralateral breast cancer.

Estimating the risk in these patients is complex and standard risk tools (IBIS/BOADICEA) can be misleading.

Patients with an existing family history and a diagnosis themselves have already demonstrated a tendency and will be at potentially higher risk than an unaffected woman with a similar strength of family history. However, risk may be reduced for some women by adjuvant endocrine therapy, or adjuvant chemotherapy-induced menopause.

Wherever possible/practical, consider referral to clinical genetics for patients requesting contralateral mastectomy who have been diagnosed at a young age (<40 years), or at older ages with a positive family history.

There will be some apparently high risk patients who will turn out after formal assessment to have a family history that is not as strong as was originally thought (e.g. from cancer registry confirmations). Conversely, not all initially apparent moderate risk cases will be confirmed in this category. Some patients may change their views after breast care nursing/counselling input or genetic testing results. For patients undergoing neoadjuvant therapy, this additional information can be available in a timely fashion to plan surgery.

6.1.6 Summary

Prophylactic mastectomies in patients who are neither known to be a gene (e.g. BRCA1/BRCA2/TP53) carrier nor who have a high risk family history should be discouraged from undergoing prophylactic mastectomy, although this should not be prohibited.

6.1.7 References

1. Invasive lobular breast cancer – no increased risk of contralateral disease


3. NICE Improving outcomes in breast cancer 2002
7 Pathology

7.1 Introduction

These guidelines for the examination and reporting of breast cancer specimens are supplementary to the following national guidance:

• Pathology reporting of breast disease –


National Co-ordinating Committee for Breast Screening Pathology on behalf of The Royal College of Pathologists and the National Health Service Breast screening Programme. NHSBSP Publication No 58 (2005)

All breast cancer cases should be reviewed by a Breast Cancer Multidisciplinary Team (MDT) which has two histopathologists as core members. There should be a nominated Lead breast pathologist for the service but all pathologists reporting breast cancer specimens should participate in the breast MDT, in the NHSBSP EQA scheme and in local audit (including an assessment of consistency). If there is a significant discrepancy with the clinical/radiological findings the pathological material from diagnostic breast specimens should be reviewed, if possible, by a second pathologist with an interest in breast cancer.

Specimens should be reported in time for appropriate clinical decision making at the breast MDT, in accordance with the timeframe and pathway agreed by the local MDT.

7.2 Specimen Types

7.2.1 Diagnostic

Fine Needle aspirate
Core biopsy (clinical, ultrasound guided or stereotactic)
“Mammotome” biopsy
Open biopsy
Localisation (needle guided) biopsy
Nipple biopsy
Node biopsy
7.2.2 Therapeutic

Mammotome biopsy
Wide local excision (+/- cavity biopsies)
Mastectomy
Post treatment excision
Segmental excision (includes re-excision for margin clearance)
Sentinel node biopsy
Axillary sampling
Axillary clearance

7.3 Specimen Examination

Each pathology service should establish a defined protocol for each type of diagnostic and therapeutic breast specimen type received by the laboratory, taking into account the above guidance. The protocols should be regularly reviewed and updated by the Lead breast pathologist in consultation with other pathologists who participate in service delivery. They should include a code for specimen orientation as agreed with the local breast surgical team.

Access to specimen radiography (analogue or digital as appropriate) and specialist radiological opinion should be available for relevant cases.

Breast tissue should only be removed and stored for the purposes of research if it is surplus to the requirements of the diagnostic process. Appropriate patient consent and ethical approval should be obtained prospectively.

7.3.1 Macroscopic Examination

National guidance for the macroscopic examination of breast specimens is given in the NHSBSP Publication Number 58 “Pathology Reporting in Breast Disease”. The following comments supplement this guidance:

**Radiological-pathological correlation**

Examination of specimen slice X-rays is of great benefit in accurate identification, localization, assessment and sampling of impalpable abnormalities. This is particularly important in cases of mammographically detected calcification. Correlation with radiological appearances provides important feedback for the Breast Screening Programme.

**Estimation of whole tumour size**

Estimation of whole tumour size is imprecise, particularly in mastectomy specimens, but provides important information regarding disease extent needed for radiological and surgical audit. In mastectomy specimens, sampling of the nipple in the coronal plane to include full cross sections of all the nipple ducts allows assessment of nipple involvement by DCIS.
Calculation of whole tumour size if this is involved may then be based on the distance between the tumour and the nipple.

**Post treatment (neoadjuvant chemotherapy) specimens**

Thorough sampling is essential and more blocks are often required than from an equivalent specimen from a patient who has not received neoadjuvant treatment. Identification of residual disease may be facilitated by identification of a coil or marker inserted previously by the radiologist. Large blocks may be helpful in determining the distribution of residual tumour foci if residual disease is no longer contiguous. Specimen X-ray assists the identification of subtle alterations in tissue architecture in patients who have had a good response to treatment.

**Ductal carcinoma in situ (DCIS)**

The Sloane Project pathology protocol provides detailed guidance for the handling and examination of specimens containing DCIS and is recommended for all units participating in the Sloane Project. In both wide local excision and mastectomy specimens, specimen slice X-ray permits identification of the targeted lesion and appropriate sampling. Particular attention should be given to excision at the margin nearest the nipple and this margin should be separately identified by the surgeon.

**Sentinel lymph nodes**

Each sentinel node should be sliced along the short axis at 1-2mm intervals and processed in its entirety. Very small nodes can be bisected. At least one H&E section should be examined. Pathologists may choose to examine additional sections (e.g., levels) or perform immunohistochemistry for epithelial markers to improve the accuracy of identifying metastatic cells and to measure the largest size of a metastasis/micrometastasis/or isolated tumour cells (ITC) identified on initial examination. Classification of single node involvement should be done using the TNM classification (6th edition).

7.4 Minimum Dataset For Reporting

7.4.1 Diagnostic specimens:

**For all core biopsy specimens**

- Diagnostic category code (B1-5)

**For malignant core and diagnostic biopsy specimens**

- Presence of invasion/microinvasion and/or DCIS
- Invasive tumour type*
- Invasive tumour grade*
- Vascular invasion*
• *as far as can be judged in the material present
• Hormone receptor status (if not routinely assessed on resection specimens)

For breast fine needle aspiration specimens

• Diagnostic category code (C1-5)

7.4.2 Screening and symptomatic therapeutic resections:

• Minimum dataset: from NHSBSP Publication No 58 (2005)
# BREAST CANCER HISTOPATHOLOGY MINIMUM DATASET REPORT

<table>
<thead>
<tr>
<th>Surname</th>
<th>Foranames</th>
<th>Date of birth</th>
<th>Date of publication only</th>
<th>Version 2.0</th>
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<td>Date of reporting</td>
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<td>Side</td>
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<td>Specimen type</td>
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<td>Specimen weight</td>
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<td>Axillary procedure</td>
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<td>in situ carcinoma</td>
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<td>DCIS grade</td>
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<td>DCIS growth pattern(s)</td>
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<td>Size</td>
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<td>Microinvasion</td>
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<td>Invasive carcinoma</td>
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<tr>
<td>Type</td>
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<tr>
<td>Invasive grade</td>
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<tr>
<td>Tumour extent</td>
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<td>Vascular invasion</td>
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<tr>
<td>Axillary nodes present:</td>
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<tr>
<td>For single node positivity, specify</td>
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<tr>
<td>Other nodes present:</td>
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<tr>
<td>Excision margins (for DCIS or invasive carcinoma)</td>
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<tr>
<td>Oestrogen receptor status</td>
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</table>

**Valid at date of publication only**
7.4.3 Optional local additional items in use, as agreed with locality MDTs:

Comment if post-neoadjuvant treatment (& therefore limitations of prognostic factors as appropriate)
Presence of extensive in-situ carcinoma
Distance to deep margin/ all radial margins
Presence of skin invasion
For axillary and lymph node procedures
Status of apical node
Extracapsular spread
Size of largest nodal metastasis

7.4.4 Additional data items for screening cases:

(specific NHSBSP Breast Pathology Data form also available)

Presence of histological calcification & whether benign/ malignant
Specimen radiograph seen?
Mammographic abnormality in specimen?
Nature of significant benign lesions
Presence of epithelial proliferation, type and whether atypical
Final histological diagnosis; Normal  Benign  Malignant

The dataset items should be reported in a proforma either within, or separate from or instead of the free text part of the pathology report. Departments and MDTs should work towards recording and storing the dataset items as individually categorised items in a relational database, so as to allow electronic retrieval and to facilitate the use of pathology data in clinical audit, service planning and monitoring, research and quality assurance.

Laboratories should use an agreed diagnostic coding system (e.g. SNOMED). All malignancies must be reported to the Northern and Yorkshire Cancer Registry, in accordance with the service level agreement with their host Trust.

7.5 Grading And Staging Conventions

7.5.1 Tumour grading:

DCIS nuclear grade - NHSBSP system
Invasive carcinoma grade – Nottingham modification of Bloom and Richardson system
7.5.2 Tumour staging:

Invasive carcinoma – Nottingham Prognostic Index

Staging system used will depend on the choice of the locality MDTs.

7.6 Use Of Ancillary Laboratory Techniques

All invasive carcinomas should have their hormone receptor status assessed. Oestrogen receptor (ER) status should be determined on all cases and, if negative, progesterone receptor (PR) status determined. Some departments may choose to assess ER and PR status on all tumours. The NHSBSP guidelines recommend the Allred scoring method (score 0-8) for invasive carcinomas. Cases of ductal carcinoma in situ (DCIS) should have their hormone receptor status assessed if there is consideration of endocrine therapy or entry into clinical trials. In DCIS the intensity and percentage of positive cells should be recorded and current NHSBSP recommendations suggest that >5% positive cells should be regarded as positive.

Departments providing this service in-house must have at least conditional laboratory (eg CPA) accreditation and participate in an appropriate external quality assurance programme. Current satisfactory participation is essential. If laboratories refer cases to an external service provider, they must ensure that the service provider has at least conditional laboratory (eg CPA) accreditation and that they participate in an appropriate external quality assurance programme which demonstrates that laboratory performance is satisfactory.

Her2 status should be assessed on all invasive breast cancers except where this is unlikely to affect treatment. In these cases the need for testing should be reviewed at MDT.

Additional immunohistochemical procedures which may be of value include the following:

<table>
<thead>
<tr>
<th>Diagnostic scenario</th>
<th>Immunohistochemical markers</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distinction between epithelial hyperplasia of usual type and ADH/DCIS</td>
<td>CK5, CK14, ER</td>
<td>Note that CK5 positivity in HUT is heterogeneous.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beware CK5 and CK14-negative columnar cell proliferations</td>
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<tr>
<td></td>
<td></td>
<td>Note that CK5 may be useful in identifying clonal neoplastic proliferations within papillomas</td>
</tr>
<tr>
<td>Lobular carcinoma phenotype</td>
<td>E-cadherin</td>
<td>Note that 10-20% invasive lobular carcinomas may be E-cadherin positive; Identification of LISN is facilitated by use CK5/6 together with E-cadherin.</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Basal carcinoma phenotype</td>
<td>CK5,CK14</td>
<td>Usually also triple negative ie ER,PR &amp; HER2 negative</td>
</tr>
<tr>
<td>Apocrine carcinoma phenotype</td>
<td>BRST-2, AR</td>
<td>Apocrine carcinomas usually ER negative, AR &amp; BRST2 positive.</td>
</tr>
<tr>
<td>Invasive micropapillary carcinoma</td>
<td>EMA</td>
<td>Identifies reverse polarity</td>
</tr>
<tr>
<td>Assessment of stromal invasion</td>
<td>SMM,p63,CK5,CK14</td>
<td>Remember that “encysted” papillary carcinoma may lack a surrounding layer of myoepithelium and that adenosquamous carcinomas may have a positive periphery</td>
</tr>
<tr>
<td>Primary v metastatic carcinoma</td>
<td>CK7,CK20,ER,PR,BRST-2, TTF1,CEA,CA125,CA19.9,S100,HMB45,MelanA etc</td>
<td>Select panel depending on clinical situation</td>
</tr>
<tr>
<td>Pagets disease of nipple v melanoma v carcinoma</td>
<td>CAM 5.2,CK7,EMA,S100,HMB45, Melan A</td>
<td>Pagets also usually HER2 positive</td>
</tr>
<tr>
<td>Spindle cell lesions (epithelial v myoepithelial v myofibroblastic differentiation)</td>
<td>CK5,CK14,SMM,CK7,CAM 5.2, MNF116,AE1/3,CD99,CD31,CD34, S100, Melan A,HMB45.</td>
<td>Note that spindle cell (metaplastic) carcinomas show variable expression of luminal cytokeratins but are often positive for basal cytokeratins. Also remember that cytokeratin expression may be seen in myoepithelial and other mesenchymal lesions</td>
</tr>
<tr>
<td>Solid papillary (endocrine) DCIS</td>
<td>Synaptophysin,Chromogranin,CK5</td>
<td>CK5 distinguishes between solid papillary DCIS (negative) and usual-type hyperplasia.(positive)</td>
</tr>
</tbody>
</table>
7.7 Audit

All pathologists reporting breast cancer specimens should participate in the National Breast Pathology EQA scheme and in local audit (including an assessment of consistency where more than one pathologist participates in service provision). Audit may take the form of

- review of compliance with procedures for specimen examination and reporting
- completeness of datasets
- systematic logging of diagnostic agreement/disagreement during review of cases for MDTMs
- review of diagnostic consistency between pathologists using data for example from cases in EQA circulations, blind circulations or screening service data.

The results of the audit process should be discussed with all pathologists who participate in service delivery and used to inform the development of reporting protocols.

7.8 Referral For Review Or Specialist Opinion

7.8.1 Referral for treatment

**Symptomatic (non-screening) cases**

All patients referred for treatment at a hospital within the West Yorkshire & Harrogate Cancer Alliance following diagnosis elsewhere must be reviewed and discussed at the treating hospital’s multidisciplinary team meeting (MDTM).

The complete diagnostic pathology report must be available at the MDTM, and wherever possible, the histological/cytological material should be reviewed prior to the meeting. This is particularly important if there is a significant discrepancy with the clinical/radiological findings. Pathological material should be received at least 3 days before the relevant MDTM to allow sufficient time for review.

A formal report should be issued by the reviewing pathologist to the responsible clinician at the treating hospital. The results of the review should be sent to the original reporting pathologist, either by a copy of the review report or by letter.

Where patients have been referred for oncology treatment, requests for specialist biomarker studies (ER, PR, Her2 etc) will be co-ordinated between the treating oncology service, their local pathology service and the referring hospital’s pathology service, as appropriate. The oncology service must agree a mechanism for requesting tests and the relevant pathological material with their local pathology service. Requests for pathological material should be made in good time to ensure that results are available at the MDTM where the patient is to be discussed.
NHSBSP (Screening) cases

Pathology results from patients referred by the Breast Screening Service (BSS) must also be routinely discussed at the treating hospital’s MDTM. Pathology reports must be available for discussion at the treating hospital’s MDTM, with slides for review as appropriate. If the screening and symptomatic services are not integrated, or the pathologists reporting the screening service diagnostic biopsies are not part of the treating hospital’s MDT, a formal report should be issued by the reviewing pathologist to the responsible clinician at the treating hospital of any altered diagnosis.

The results altered following such review should also be sent to the original reporting pathologist, either by a copy of the review report or by letter.

7.8.2 Referral for specialist opinion

All breast lymphomas should be referred to the Haematological Malignancy Diagnostic Service for phenotypic analysis and confirmation of diagnosis.

Most other cases of breast cancer do not need central review. In cases of diagnostic difficulty, referral will usually be made to a pathologist of a relevant specialist MDT in the network, although referral to other specialists within or outwith the network may be appropriate in individual cases. Cases referred for individual specialist or second opinion will be dealt with by the individual pathologist and a report issued by them. Where relevant, tissue blocks should be made available to allow any further investigations that are deemed appropriate. The result of the review should be communicated to the referring pathologist by letter and additionally by fax/telephone if appropriate. The referring pathologist will inform their local MDT.

In instances when the patient is referred for an opinion or treatment by a Specialist Multidisciplinary Team, the case should be referred to the Lead Pathologist of the appropriate MDT who will ensure the case is dealt with by an appropriate individual and dealt with according to the Specialist MDT guidelines.

Specialist referral outwith the West Yorkshire & Harrogate Cancer Alliance may incur a fee for service.

7.9 References


Current practical applications of diagnostic immunohistochemistry in breast pathology.

Breast carcinoma with basal differentiation: a proposal for pathology definition based on basal cytokeratin expression. Rakha EA, El-Sayed ME, Green AR, Paish EC, Lee AH and Ellis IO.


Pinder, SE, Provenzano, E, Earl, H and Ellis IO. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. Histopathology 50, 409-417 2007.

Sobin LH and Wittekind C (Eds.). UICC (2002). Guidelines on inter-departmental dispatch of samples from patients sent to another hospital or centre for assessment and/or treatment. The Royal College of Pathologists (2004).

TNM Classification of Malignant Tumours (6th edition)

8 Early Breast Cancer

8.1 Ductal Carcinoma In-situ

8.1.1 Background

These guidelines provide recommendations from the former YCN Breast Group of the on management of DCIS including surgery and adjuvant treatments.

DCIS is a non-invasive epithelial proliferation that is confined within the basement membrane of the breast ducts. DCIS is most often diagnosed from age 50-54 onwards in the UK, corresponding with the start of screening mammography. Left untreated, this may develop into invasive breast cancer and therefore, is usually managed by surgical excision either by wide local excision, or mastectomy. Mastectomy produces very high rates of local control, but will be over-treatment for many patients.

After wide local excision alone, local recurrences occur at a rate of 2-3% per year of follow-up, or up to 20-30% over 10 years (1,2). Half of recurrences are further DCIS and half are invasive cancer. Possible risk factors for recurrence are positive margins, age <40, tumour extent, high grade, and comedonecrosis. However, these have not been reliably determined. Although, some studies have shown lower risk of recurrence of low grade lesions with clear margins (2,3), others have shown similar rates of recurrence at 2-3% per year (4). Although local recurrence is common, risk of death from breast cancer is low, with 10-year breast cancer-specific survival after surgical excision of DCIS of around 97%.

A meta-analysis of three large randomised trials, has shown a 52% relative reduction in ipsilateral recurrences (DCIS or invasive cancer) with adjuvant radiotherapy after breast-conserving surgery (5). No groups have been reliably identified that derive no benefit from radiotherapy. The absolute benefit will depend on the risk of recurrence and may be modified by use of endocrine therapy. No survival benefit has been identified from use of adjuvant radiotherapy. Radiotherapy has well recognised acute and potential late toxicities. The UK has traditionally taken a selective approach for use of adjuvant radiotherapy for patients perceived at highest risk of recurrence. However, international opinion is moving towards consideration of radiotherapy in all but the lowest risk groups (2), and use of higher total treatment doses (6).

Combined analysis of the two randomised trials assessing adjuvant tamoxifen for DCIS showed a relative reduction of all breast events of 28% (5). However, these trials included ER negative cases which are likely to have reduced the apparent benefit of tamoxifen. In one of these trials (NSABP B-24), analysis of a subgroup of ER positive cases alone showed a 59% relative reduction in events, including contralateral disease (7). No survival benefit has been demonstrated with adjuvant endocrine treatment for DCIS. Side effects of tamoxifen include frequent menopausal symptoms, and ~2-3x relative risks of venous thromboembolism (~2-4% incidence with 5 years tamoxifen) and endometrial cancer (~0.3-0.8% incidence with 5 years tamoxifen) (8,9).

Ongoing trials are assessing the role of radiotherapy in lower risk groups, and aromatase inhibitors as adjuvant treatment.
8.1.2 MDT Discussion and Patient Involvement

The decisions regarding management of DCIS are not straightforward with a balance between risks of recurrence, and benefits versus side-effects of treatment. Cases should be discussed at an appropriate MDT and patients should be involved in decision-making.

Recommendation:

- All cases of DCIS should be discussed at a breast MDT with membership including the relevant specialities, and outcomes of discussions should be recorded.
- Patients with DCIS should be provided with information regarding DCIS and potential treatments to help with the decision-making process.

8.1.3 Neo Adjuvant Systemic Therapy

As stated in the ‘NHS Clinical Advice to Cancer Alliances for the Provision of Breast Breast Cancer Service’ Neoadjuvant chemotherapy or endocrine therapy is being used in increasingly large numbers of patients who have a biologically aggressive tumour, for those who are HER 2 positive and can therefore access pertuzumab or for downsizing to allow for breast conservation, or more limited axillary surgery. Neoadjuvant therapy will also be used within trial protocols where an in vivo assessment of sensitivity to treatment is required. The rationale for primary surgical and medical treatment decisions should always be recorded in the notes (Domain 1).

The option of neoadjuvant chemotherapy (if appropriate) can also be considered in patients who are eligible for genetic testing (based on tumour type, young onset and/or strong family history) when this will allow adequate time to appropriately inform patients about future new primary cancer risk based on family history assessment and genetic test outcome. Information about genetic status may impact on the patient’s subsequent choice about breast surgery and reconstruction (Domain 1).

8.1.4 Surgery Recommendations

- Breast conserving surgery with clear margins should be the aim for the majority of patients with DCIS.

Relative indications for mastectomy include:

- Extensive disease
- Persistent positive resection margins
- Recurrence following previous WLE and radiotherapy
- High risk family history/gene mutation carrier
- Patient preference
Nodal surgery:

- Nodal staging is not routinely recommended for DCIS in the absence of confirmed or suspected invasive disease. Sentinel lymph node biopsy or axillary node sampling may be considered for patients with increased risk factors for invasion, for example those undergoing mastectomy due to extensive disease.

**Valid at date of publication only**

8.1.4.1 Adjuvant Chemotherapy

As cited in the ‘NHS Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Service’ Adjuvant chemotherapy reduces the risk of metastatic disease, but the actual benefit to any individual patient is dependent on their baseline risk of developing metastatic disease as predicted by standard prognostic factors at diagnosis. All patients with early breast cancer should have their risk of recurrence assessed and benefits of systemic therapies discussed in the MDT meeting following primary surgery as per section 5.2.28. The final plan of systemic therapy should be made in the oncology clinic using this and other patient information and taking into account their views (Domain 5).

A number of online tools are available to assist e.g. NHS PREDICT, and for those with ER positive disease a number of molecular tests can give further refinement of the likely benefit from chemotherapy e.g. Oncotype DX, IHC4 and EndoPredict. NICE now recommends the use of Oncotype DX in in ER positive, HER2-ve, node negative patients where the benefit of adjuvant chemotherapy is uncertain. A proportion of patients who might otherwise have had adjuvant chemotherapy can avoid this on the basis of these further tests (Domain 5).

Anthracyclines should be avoided if there is a significant history of cardiac disease and used with caution in those over 60 or with significant hypertension, with a pre-treatment left ventricular ejection fraction carried out (Domain 1 & 5).

8.1.5 Adjuvant Radiotherapy Recommendations

Recommendations:

- Entry into relevant trials should be considered.
- Outside clinical trials, adjuvant radiotherapy should be considered for women with DCIS treated with breast-conserving surgery. Radiotherapy may be omitted in cases considered to be at low risk of recurrence, or where there are other relevant patient factors, where this has been discussed by the MDT and with the patient.
- Radiotherapy after mastectomy for DCIS is not recommended. Potential advantages and disadvantages for exceptional cases e.g. extensive high grade DCIS with widespread involved margins should be discussed at the MDT meeting and with the patient.

8.1.6 Adjuvant Endocrine Therapy

Recommendations:
- ER (+/- PR) status should be assessed for all cases of DCIS according to guidance recommended by the Sloane Project:
- ER negative DCIS should not be treated with adjuvant endocrine therapy
- Entry into relevant trials should be considered.
- The NICE guidelines indicate that adjuvant Tamoxifen should not be routinely offered for DCIS after breast conserving surgery. Tamoxifen should be used only when the case has been discussed by the MDT and potential benefits versus adverse effects have been discussed with the patient.
- Aromatase inhibitors should not be used for DCIS outside clinical trials
- Patients treated with mastectomy for DCIS with clear margins should not be treated with adjuvant endocrine therapy outside clinical trials.

It should be considered that use of endocrine therapy will modify risks of recurrence and potential benefit of radiotherapy, and vice versa.

Please also see the Clinical Advice for the Provision of Breast Cancer Services Adjuvant Endocrine Therapy 5.2.34 to 5.2.40 for further detail.

8.2 Invasive Breast Cancer

8.2.1 Adjuvant Chemotherapy

As noted in the NHS Breast Service Guidance - Adjuvant chemotherapy reduces the risk of metastatic disease, but the actual benefit to any individual patient is dependent on their baseline risk of developing metastatic disease as predicted by standard prognostic factors at diagnosis. All patients with early breast cancer should have their risk of recurrence assessed and benefits of systemic therapies discussed in the MDT meeting following primary surgery as per section 5.2.28. The final plan of systemic therapy should be made in the oncology clinic using this and other patient information and taking into account their views (Domain 5).

A number of online tools are available to assist e.g. NHS PREDICT, and for those with ER positive disease a number of molecular tests can give further refinement of the likely benefit from chemotherapy e.g. Oncotype DX, IHC4 and EndoPredict. NICE now recommends the use of Oncotype DX in in ER positive, HER2-ve, node negative patients where the benefit of adjuvant chemotherapy is uncertain. A proportion of patients who might otherwise have had adjuvant chemotherapy can avoid this on the basis of these further tests (Domain 5).

Anthracyclines should be avoided if there is a significant history of cardiac disease and used with caution in those over 60 or with significant hypertension, with a pre-treatment left ventricular ejection fraction carried out (Domain 1 & 5).
8.2.2 Anti-HER2 Therapy

All patients with invasive HER2 positive disease 1cm or greater should be offered adjuvant trastuzumab for 1 year along with adjuvant chemotherapy. The benefit of such treatment for HER2 positive cancers <1cm is less certain and the decision should be left to the oncologist in charge (Domain 1 & 5).

Single agent paclitaxel with trastuzumab appears as effective as standard chemotherapy for small node-negative cancers (2cm or less) and is a lot less toxic and expensive. It should also be encouraged where there is a contra-indication to standard chemotherapy e.g. because of age or co-morbidity (Domain 1 & 4).

Cardiac monitoring should be carried out based on standard guidelines.

Recently, the addition of 4-6 courses of neoadjuvant pertuzumab to trastuzumab and chemotherapy has been shown to improve significantly both pathological complete remission rates and 5 year survival outcome, and this is recommended for patients with higher risk cancers. In contrast, the evidence from the APHINITY trial does not suggest a clinically worthwhile benefit for yearlong adjuvant pertuzumab, despite the trial statistically meeting its primary endpoint.

8.2.3 Adjuvant Bisphosphonates

Based on strong evidence, adjuvant bisphosphonate therapy with zoledronate 4mg by IV infusion 6 monthly or oral ibandronate 50mg daily, for a minimum of 3 years, should be offered to postmenopausal women with early breast cancer to reduce the risk of bone recurrence and fractures, and improve breast cancer survival. For lower risk patients, however, the absolute benefit is likely to be very small and may be outweighed by the potential side effects (in particular a 1% risk of osteonecrosis of the jaw). This is being reviewed by NICE. Note that switching between zoledronate and ibandronate is an option (appendix 4; Domain 1; Cancer Strategy Recommendation).

Please see the Prescribing Guidance in the appendix (Chapter 11)

8.2.4 Selection and Duration of Adjuvant Endocrine Therapy

Endocrine treatment reduces recurrence and breast cancer specific mortality rates in women with ER/PR positive early breast cancer. The most recent EBCTCG overview showed a 30% reduction in breast cancer mortality throughout the first 15 years following 5 years of adjuvant treatment with tamoxifen. (RR=0.71 for yrs 0-4 & 0.66 for yrs 5-9). The proportional reduction in risk of relapse for all time periods was 39% (RR=0.53 for yrs 0-4 & 0.68 for yrs 5-9). This benefit was independent of patient and tumour characteristics.
Currently, tamoxifen and aromatase inhibitors are the mainstay of adjuvant treatment in women with ER+ early breast cancer.

**Duration of endocrine therapy:**

**Duration of Tamoxifen:**

Breast cancer, especially ER+ positive disease is well recognised to have a long natural history with a 2% annual rate of relapse up to 15 years following diagnosis. Therefore, the challenge has been to determine the optimal duration of adjuvant endocrine treatment. The 1980’s Swedish trial which compared 5 years to 2 years of tamoxifen showed that 5 years was superior in terms of EFS(RR=0.82) and OS(RR=0.82) . Overall survival at a median follow up of 5.5 years was 80% vs 74%. This result was confirmed by the CRUK trial.

NSABP B-14 extension study was the first large trial to assess the benefit of continuing tamoxifen beyond 5 years in the adjuvant setting. 1152 ER positive patients who had completed 5 years of tamoxifen were randomised between further 5 years of treatment or placebo. The trial was closed prematurely as the first interim analyses showed no benefit with longer treatment. In fact, there was a reverse trend. The DFS @4 years was 92% in the 5 year arm compared to 86% in the 10 year arm. This adverse effect with longer treatment was attributed to the agnostic action of tamoxifen which comes into play with longer term use.

Following the NSABP B-14, 5 years of tamoxifen was established as standard treatment in the adjuvant setting. However, it was increasingly recognised that 5 years of endocrine treatment had long carry over benefit and to see any improvement from extended treatment follow up period would have to be long. The NSABP B-14 was criticised for small numbers and premature termination resulting in short follow up duration.

**ATLAS and aTTOM** trials were started in the 1990’s to re-examine the question.

ATLAS Trial: A very large trial which recruited 12,894 patients who had completed 5 years of tamoxifen between a further 5 years or placebo. 53% were node negative and 53% had T size< 2cms. There was no grade analysis. Compliance after 2 years of randomisation was 84% in the treatment arm and 9% in the placebo arm. The 6,846 patients with ER+ disease were analysed for RFS and breast cancer specific survival, but all patients were analysed for side effects.

In ER+ women allocated to extended treatment there was a further reduction in risk of relapse(p=0.002), breast cancer specific mortality(p=0.01) and all cause mortality. This difference became apparent after 10 years following diagnosis. Out t year 10 RR for recurrence was 0.75, an absolute difference of 3.7% and RR for breast cancer mortality was 0.71, an absolute difference of 2.8%. This benefit was independent of patient age, menopausal status, tumour size or nodal status. As there was no increase in other cause mortality, there was an increase in all cause mortality.

The aTTom trial (REF) in UK had a similar design and recruited 6,539 women with ER+ or unknown EBC. The risk ratio(RR) for recurrence was 0.85 with an absolute reduction of 4% with longer treatment. There was a 2% reduction in mortality (RR=0.88) and these benefits were time dependent becoming apparent 7-10 years after diagnosis. These results from ATLAS and aTTOM along with results from trials of 5 years of tamoxifen SUGGEST 50% reduction in risk of mortality with 10 years of tamoxifen compared to no treatment.
Clearly, in both trials extended treatment arm was associated with increased morbidity. There was increased risk of PE (RR = 1.87) and endometrial carcinoma (RR = 1.74) but the mortality was not significantly different.

**Role of Ovarian Ablation/ Suppression in Pre-Menopausal Women:**

The 1995 EBCTCG meta analysis of the ovarian ablation trials started prior to 1980 showed that in women below the age of 50, ablation of functioning ovaries by irradiation or surgery reduced risk of relapse and improved survival when used as sole treatment. Addition of ablation to cytotoxic chemotherapy was much less useful. Since then, several randomised trials have further assessed the role of ovarian suppression in the adjuvant setting in pre-menopausal ER+ breast cancer.

ZEBRA trial was a large randomised trial that directly compared ovarian suppression to CMF chemotherapy and found the two treatments to be equivalent. This led to the conclusion that OS could be used as a reasonable alternative to cytotoxic chemotherapy. Since then we have moved on to second and third generation chemotherapy regimens which include anthracyclines and taxanes and this result is therefore, of less relevance to current practice. Four main trials namely INT0101, ABCSG-VII, IBCSG11-93 and Zipp explored the role of OS in combination with cytotoxic chemotherapy. All failed to show a significant advantage with this strategy. There may be an advantage in combining tamoxifen with OS in younger women who remain pre-menopausal even after chemotherapy. SOFT trial is investigating this question, but results of this arm of the trial are awaited. At ASCO 2014, a joint analysis of the TEXT and exemestane arm of the SOFT trials were presented. OS+ Exemestane significantly reduced risk of recurrence compared to OS+ Tamoxifen. This is not practice changing OS is not yet standard treatment in the adjuvant setting.

**Aromatase Inhibitors:** (AI)

**Upfront or early switch:** Third generation AIs such as anastrazole, letrozole and exemestane are powerful alternatives to tamoxifen in postmenopausal women with ER+ breast cancer.

A recent meta analyses of all the adjuvant AI trials published by Dowsett et al concluded that AI used either as upfront treatment or following 2-3 years of tamoxifen resulted in significant reduction in risk of recurrence and a non-significant reduction in mortality. At a median follow up of 5.8 years, the absolute decrease in recurrence rates with 5 years of AI compared to 5 years of tamoxifen was 2.9% (9.6% vs 12.6%) with a non significant 1.1% decrease in breast cancer mortality. The switch strategy resulted in a recurrence rate difference of 3.1% (5.0% vs 8.1%) at mean of 3.9 years of follow up. The absolute decrease in breast cancer specific mortality was 0.7%.

A recent 10 year update of the ATAC trial which compared 5 years of tamoxifen to 5 years of anastrazole showed a relapse rate difference of 2.7% at 5 years and 4.3% at ten years in favour of the AI group. There was no significant improvement in overall survival despite a decrease in breast cancer specific mortality. There are concerns regarding increase risk of cardiovascular event with anastrazole.
AI after 5 years of Tamoxifen:

The seminal trial that explored this question was the NCIC-CTG MA.17 trial. 5,187 patients with ER+ breast cancer who had completed 5 years of adjuvant tamoxifen were randomised between placebo or 5 years of letrozole. All were postmenopausal at randomisation. At 4 years, there was an absolute difference of 4.6% in DFS in favour of extended treatment with letrozole. The statistically significant decrease in DFS and DDFS in the letrozole arm remains even at 64/12 follow up with adjustments made for crossover (HR=0.52 for DFS& 0.61 for OS). These benefits were seen regardless of the menopausal status of the patient at time of diagnosis. In fact, premenopausal status at time of diagnosis seem to confer additional benefit. There have been smaller trials which have investigated the same question with similar conclusions.

However, hot flashes, arthralgia, myalgia were more common in the AI arm resulting in a compromise in QOL. There was also increased risk of osteoporosis (5.8% vs 4.5%).

Unanswered Questions:
Duration of AI therapy:

Majority of our postmenopausal patients are on AI right from the start of endocrine therapy. At present there is no level-I evidence to support the use of AI beyond 5 years. Phase -III data is awaited. In the meanwhile, based on evidence so far, it may be reasonable to continue AI beyond the standard 5 years in high risk postmenopausal woman. In the absence of toxicity data this needs careful discussion with patient.

5 years of additional tamoxifen or switch to AI:

There is no head to head randomised trial to answer this question. The HR for overall survival (OS) in MA.17 at 64/12 follow up is 0.61(0.52-0.71) and in the combined ATLAS/aTTOM trials the HR for OS is 0.91(0.84-0.97). This suggests that switch to AI following 5 years of tamoxifen may be more beneficial. In the absence of direct comparisons, this data should be interpreted with caution and should not be used to make treatment decisions.

Selection of women for switching from tamoxifen to AI:

As most of our patients who are post menopausal at diagnosis is commenced on upfront AI, the question of switch is essentially for women who are pre/peri menopausal at diagnosis and become postmenopausal during treatment on tamoxifen. Determining menopausal status in this group can be tricky as the standard parameters used to define menopause are often inaccurate. In the MA.17 trial, patients who were pre-menopausal at diagnosis were regarded as having gone through menopause if they remained amenorrheic for 1 year or more with FSH/LH/serum estradiol levels in the postmenopausal range. Using these criteria only 5/5187 resumed regular menses on AI.

Who needs extended endocrine treatment:

All the extended endocrine trials show that the majority of patients remain relapse free after 5 years of endocrine treatment resulting in small gains from extended treatment. None of the studies were able to identify any clinical or molecular marker that predicts for response to extended treatment. It is likely that patients who are at higher risk of relapse as identified by
standard clinico-pathological criteria will have a higher absolute benefit from treatment. Standard prognostic tools such as NPI and ‘adjuvant on line’ are helpful, but deciding on the right cut off so that treatment is both clinical and cost effective is a challenge.
Guidelines for Adjuvant Endocrine therapy in Early Breast Cancer.

General Points:

1) Adjuvant endocrine therapy should be considered in tumours with ER and or PR score greater than or equal to 3.

2) For the purpose of these guidelines a woman can be considered post menopausal if
   • > 60 years of age.
   • Has had a bilateral oophrectomy.
   • < 60 years but amenorrhea for 12 months or more in the absence of HRT, Mirena coil, hysterecomy, tamoxifen use or recent chemotherapy.
   • Has FSH/LH and serum estradiol levels in the post-menopausal range in the absence of tamoxifen use or recent chemotherapy.
   • Following chemotherapy, or with tamoxifen use, there is amenorrhea for 12 months or more and serum FSH/LH serum estradiol levels are in postmenopausal range. In patients below 45 years of age, this should ideally be confirmed on serial measurements especially if switch to an AI is being considered.

3) In all patients choice, duration and sequencing of treatment should be decided only after careful consideration of benefit and risks of each treatment. Patient preference should be integral to this decision making.

4) Nottingham Prognostic Index Calculation:

<table>
<thead>
<tr>
<th>Score</th>
<th>Prognostic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.08-2.4</td>
<td>EPG</td>
</tr>
<tr>
<td>2.42-&lt;=3.4</td>
<td>GPG</td>
</tr>
<tr>
<td>3.42-&lt;=4.4</td>
<td>MPG I</td>
</tr>
<tr>
<td>4.42-&lt;=5.4</td>
<td>MPG II</td>
</tr>
<tr>
<td>5.42-&lt;=6.4</td>
<td>PPG</td>
</tr>
<tr>
<td>6.42-6.8</td>
<td>VPPG</td>
</tr>
</tbody>
</table>

5) Decision regarding duration of endocrine therapy should be part of the therapeutic MDT discussion and clearly recorded in patient's MDT record.

6) Implementation of extended endocrine treatment can be logistically challenging. Each breast unit should discuss and develop a pathway that is appropriate for them.

Patients who are Pre-menopausal at diagnosis:
Patients with NPI<4.42.

- Recommended duration of endocrine therapy is 5 years.
- Commence Tamoxifen 20mg soon after surgery unless patient is to receive chemotherapy, in which case Tamoxifen is commenced after chemotherapy.
At 3 years:
- If a patient is deemed post menopausal, consider switch to an aromatase inhibitor until 5 years of treatment is completed
- If a patient remains pre-menopausal continue Tamoxifen until 5 years of treatment is completed.

Patients with NPI>= 4.4 or Node positive at diagnosis

Recommended duration of endocrine therapy is 10 years.
- Commence Tamoxifen 20mg soon after surgery unless patient is to receive chemotherapy, in which case Tamoxifen is commenced after chemotherapy.

At 5 years
- If a patient is deemed post menopausal consider switch to an aromatase inhibitor until 10 years of treatment is completed.
- If a patient remains pre-menopausal continue Tamoxifen until 10 years of treatment is completed.

Role of ovarian suppression/ablation:
- Not regularly recommended in addition to Tamoxifen and/or chemotherapy.
- Maybe considered as an alternative to chemotherapy in patients not suitable/declines chemotherapy.
- Ovarian suppression+AI is an option if there are concerns regarding use of Tamoxifen.

Patients who are Post-menopausal at diagnosis

- Upfront AI for 5 years is recommended.
- In patients with high risk disease (NPI>5.42) extending treatment beyond 5 years is reasonable.

8.2.5 Risk of osteopenia and osteoporosis

All the aromatase inhibitors increase the risk of bone density reduction and its complications. Patients who are prescribed an AI should be advised regarding these implications, although bone density itself should not prevent their prescription. A baseline bone density scan (DEXA scan*) should be performed at baseline within the first 3-months of treatment. Further DEXA scans should be subsequently performed according to the results of the baseline scan and recommendations from the bone metabolic unit if subnormal. Lifestyle advice includes a balanced diet, regular weight bearing exercise, cessation of smoking. Please refer further to the National Guidelines (Title: Evaluation, monitoring and treatment of bone loss in early breast cancer, a quick reference guide from a UK expert group).
8.2.6 Other issues

Use of an AI should be the product of a consultation between the patient and the clinician and needs to take into account the presence of co-morbidities, risk factors for skeletal, thromboembolic and gynaecological toxicities, patient choice, breast cancer recurrence risk and reduction in risk of future new ipsilateral or contralateral breast cancers. Follow up protocols are in the process of change and these guidelines need to be considered in relation to changing practices.

Ongoing and future trials of adjuvant, endocrine and other interventions in early breast cancer should continue to be supported.

*Additional Information

Cost of single baseline Dexa Scan with report: £100 - in some centres it is as low as £35.

8.2.7 Licensed indications

<table>
<thead>
<tr>
<th>Anastrazole</th>
<th>Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women, either as sole therapy or following 2–3 years of tamoxifen therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemestane</td>
<td>Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy.</td>
</tr>
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</table>

8.2.8 Adjuvant Radiotherapy for Invasive Early Breast Cancer:

Introduction

NICE guidelines recommend that patients not receiving adjuvant chemotherapy should start their adjuvant radiotherapy as soon as clinically possible. The effect of the interval between surgery and start of adjuvant radiotherapy on long term outcome remains unknown. A recent systematic review showed an increase risk of LRR with RT delay of greater than 8 weeks. Recently, IBCSG investigated the association between the interval to adjuvant RT after BCS and clinical outcome. All patients included in their analysis were on endocrine therapy. They concluded that a delay of up to 20 weeks between BCS and RT did not influence outcome. Majority had good prognosis tumours. Canadian retrospective review of 568 patients with T1/T2 N0 breast cancer and no systemic treatment showed that a delay of up to 16 weeks did not increase risk of LRR after a median follow up of 11.2 years. These points may be useful.
when discussing with patients effects of delay in treatment due to problems with wound healing or decreased arm movement.

Patients receiving adjuvant chemotherapy should start radiotherapy approximately three weeks after their last cycle of chemotherapy. Data suggest that concurrent administration of chemotherapy and radiotherapy increases toxicity and is to be avoided. However, available data suggest that radiotherapy can be given concurrently with Trastuzumab. Adverse event data from the phase III NCCTG trial did not show increase risk of cardiac events with concurrent Herceptin and RT.
Following Breast Conserving Surgery:

All patients should be considered for adjuvant radiotherapy to whole breast after breast conserving surgery (BCS) outside clinical trials.

Several randomised trials and meta analyses have confirmed that whole breast radiotherapy (WBRT) following BCS reduces the risk of loco-regional relapse by a 1/2 to 2/3. The strongest evidence comes the EBCTCG meta analyses, the most recent of which was published in 2011. This showed that overall, adjuvant radiotherapy to conserved breast tissue reduced risk of loco-regional recurrence at 10 years from 35% to 19.3% and breast cancer specific mortality at 15 years from 25.2% to 21.4%. Both were highly significant. Overall survival at 15 yrs was improved by 3% (p=0.03).

The magnitude of benefit varied according to nodal status. In node positive the absolute LRR risk reduction was 21.2% and breast cancer mortality was reduced by 8.5%. Corresponding figures for node negative patients was 15.4% and 3.3%. In the N0 group, younger age, larger tumours, ER poor status, lack of use of tamoxifen all increased risk of relapse and these patients had a higher absolute benefit from adjuvant radiotherapy. In fact, the high risk pN0 patients had a higher benefit from WBRT than the N+ group.

Although, the proportional benefit from WBRT was seen to be higher in the ER positive patients treated with tamoxifen (60% RR) cf to ER-, higher grade tumours (35% RR), the absolute benefit can be very low as the baseline risk of relapse is low. In some of these low risk patients the benefit from adjuvant radiotherapy could be outweighed by the side effects and long term risks of treatment especially cardiac toxicity. In the past two decades several trials have attempted to identify a favourable sub group of patients for whom adjuvant radiotherapy following BCS could be avoided. In general, these trials have randomised patients with low risk factors such as older age, lower grade, smaller tumours which are ER+ to endocrine therapy +/- WBRT. Almost all has shown that omission of RT reduces local control. CALGB-9343 group recently updated the results after a median follow up of 12.5 years. This was a randomised phase III trial conducted between 1994-1999. 636 women aged 70yrs or above with T1N0M0 ER+ breast cancer were randomly assigned to tamoxifen alone or tamoxifen + WBRT. All patients had lumpectomy with clear margins, defined as no tumour at inked margin. At 10 years, loco-regional control rate was 98% in the tamoxifen+RT arm cf to 90% in the tamoxifen only arm. This was statistically significant. However, there was no difference in BCS or overall mortality or even breast preservation rate. Of the 636 women only 3% died from breast cancer @10 years as opposed to 49% death from other causes. A further sub-group analysis within the study population was not possible.

UK BASO II trial was a factorial 2x2 design trial that randomised patients with low risk breast cancer after BCS to WLE alone, Tamoxifen alone, Radiotherapy alone or combination of WLE+RT+Tamoxifen. After a median follow up of 167 months the LRR in the WLE group was 2.2%/annum as opposed to 0.8%/PA in the RT alone or Tamoxifen only arm. The LRR was lowest at 0.2%/PA in the combination arm. Although, BASO II was not an equivalence trial, results suggest that Tamoxifen may be used as a safe alternative to RT in low risk breast cancer.

The results of the UK PRIME-II study which randomised 1380 patients >65 years with T1- T2< 3cms, grade I or II ER+ tumours to tamoxifen +/- RT after BCS is still awaited.
As no trial has successfully identified a cohort where RT can be successfully avoided all patients should be considered for Adjuvant RT following BCS. In the light of the CALGB 9343 and BASO II trial showing no survival benefit, the risk: benefit ratio should be carefully considered at individual level and endocrine therapy alone may be a reasonable option for at least some of these patients.

8.2.9 Adjuvant Radiotherapy after BCS:

1) All patients should be offered whole breast radiotherapy after BCS outside clinical trials.
2) Patients age of 70 years, with T1 G1 ER positive tumours can be considered for endocrine therapy alone. This has to be carefully discussed within the MDT and with the patient. Compliance with endocrine therapy should be assured.
3) Indications for radiotherapy to glands as for PMRT.
4) See policy for tumour bed boost.

8.2.10 Boost Policy:

Breast boost should be considered in the following circumstances:

- Positive resection margins, where further surgery is not appropriate.
- Age at or below 40 years.
- Age between 40-55 years and two or more of the following factors
  - Tumour size > 3 cms.
  - Grade III tumours.
  - ER negative tumours.

BCS following down staging with neo adjuvant chemotherapy

Technique:

Modality:

Electron therapy: Energy of the electron beam used will depend on the depth of the tumour bed as assessed on CT. For majority of patients electron therapy using 8Mev or 10 Mev electrons should be sufficient.

Energies greater than 10 Mev could compromise cosmetic outcome more significantly. Use of photons should be considered.

Field definition:

Electron:

The boost should be planned prescribed and verified along with the tangential field planning using CT data. The field should include the lumpectomy cavity as defined by architectural distortion and/or tumour bed clips with a radial margin of 1.5 - 2cms. In most cases this will include most, if not all, of the scar, but it is not essential to include the entire scar unless clinically indicated. No bolus should be adopted. Occasionally very laterally placed tumours may not be suitable for CT planning. For these patients, clinical mark up will be appropriate.
Photon: Mini tangents with 6MV is appropriate.

**Dose prescription:**

A standard dose of 10 Gy in 5 fractions over a maximum of 7 days is prescribed at 100%.

The 90% depth should be recorded.

References:

1) Effect of Radiotherapy after Breast Conserving Surgery on 10 year Recurrence and 15 year breast cancer death; Meta analyses of individual patient data for 10,801 women in 17 randomised trials.


2) Lumpectomy Plus Tamoxifen with or without Irradiation in Women Aged 70 Years or Older with early Breast Cancer: Long term Follow Up of CALGB9343.

JCO Jul1 2013. 2382-2387

3) Should a woman aged 70-80 years receive radiation Therapy after Breast Conserving Surgery?

JCO Jul1 2013 2377-2381. Jarslow et al

4) Radiotherapy or Tamoxifen after Conserving Surgery for Breast Cancer of Excellent Prognosis: BASO II Trial.


6) Tamoxifen with or without Breast Irradiation in Women 50 years or Older with Early Breast Cancer. Fyles et al

NEJM, 2004 Sept2 351(10) 963-70

8.2.11 Post Mastectomy Radiotherapy:

A number of randomised trials and the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) meta analyses have shown that post mastectomy radiotherapy reduces risk of loco regional relapse (LRR) by a proportion of 60-70%. Clearly, higher the risk of recurrence, greater is the absolute benefit. There is now increasing evidence that this improvement in local control translates into an increase in breast cancer specific and maybe overall survival in the longer term. In the EBCTCG overview, a 20% improvement in local control at 5 years corresponded to a 5% improvement in breast cancer specific survival at 15 years, suggesting a 4% Relationship between loco-regional (LR) control and breast cancer specific survival.

Based on this all guidelines and consensus statements would recommend PMRT in patients with a high, characteristically defined as 20% or more risk of LRR. There is consistent agreement that patients with pT4 tumours or 4 or more positive nodes fall into this category. In fact, subset analysis of the Danish trials and the EBCTCG overview showed a 22.3% absolute improvement in LR control (40.6% vs 12.9%) at 5 years in patients with 4 or more nodes. The survival gain at 15 years was 5.2%.

Tumour size of 5cms or more is generally regarded as a high risk factor. Rates of LRR for T3N0 tumours seems to vary significantly with some studies showing a 15% failure rate whilst
others as high as 50%. The level of evidence for PMRT in this group is less strong, but most
guidelines would recommend chest wall irradiation in this group.
T1-T2N0 tumours have been shown to have a LRR of <10% and is regarded as the low risk
group. Recent analysis of the IBCSG trials I-VII(ref) suggest certain tumour related factors
can increase failure rate in this group. This is being explored further in the now closed
SUPREMO trial. Until further evidence PMRT is not recommended in this group outside
clinical trials.

The most controversial group is the T1-T2 N1(1-3+) patients. This is regarded as the moderate
risk group. The LRR rate in this group varies greatly between studies. The Danish Breast
Cancer Co-operative Group (DBCG) showed a LRR of approximately 30% at 10 years in this
group. PMRT reduced this to 5-6%. The other major trial from British Columbia (BCCA trial)
demonstrated a 20% absolute reduction in LRR from 33%-13% at 15 years. Survival gain of
up to 9% was seen in both studies.

EBCTCG sub set analysis of the 1-3 node positive group presented at SABCS2007 showed
that ¾ of recurrences occurred in the first 5 years. PMRT reduced loco-regional failure from
24% to 5.3%, an absolute reduction of 15.7% at 5 years. This translated into a survival gain of
5.3% at 15 years. This was very similar to the gains obtained from many of the modern
adjuvant chemotherapy regimens and PMRT was recommended for all node positive patients.

The EBCTCG overview and its three main component trials were criticised for the following
reasons:

- Inferior systemic treatments.
- Inadequacy of axillary surgery.
- The LRR rate in the control arm of 30% was much higher than expected.
- The concern about toxicity from large field radiotherapy.

However, even when EBCTCG restricted the data to be consistent with modern surgical and
systematic treatment, benefits in local control and survival was maintained but smaller.

Dr Darby et al (SABCS2009):
10 OR MORE LYMPH NODES RETRIEVED FROM AXILLARY SURGERY

<table>
<thead>
<tr>
<th></th>
<th>NO RT</th>
<th>RT</th>
</tr>
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<tbody>
<tr>
<td>1-3 NODES POSITIVE</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>4 OR MORE NODES</td>
<td>41%</td>
<td>13%</td>
</tr>
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</table>
likely to outweigh risks. The challenge is to identify this group of patients. Hopefully, the now closed SUPREMO trial will answer this question.

In the meanwhile, multiple retrospective studies and retrospective analysis of randomised studies have looked at patient and tumour related factors that indicate a higher relapse risk.

The accepted risk factors are:
- Young age <40-45 years.
- ER/PR- tumours particularly Triple negative tumours.
- Grade III.
- Increasing tumour size.
- Incremental increase in size/number of positive nodes.
- extensive LVI.

It should be noted that data for any single factor remains limited.

**Controversies about Optimal Radiation Target Volume:**

The commonest site of local recurrence after mastectomy is the chest wall(53%) followed by SCF/ICF (26%) and axilla (13%). IMN recurrence is reported to be as low 1-2%. In the DBCG and Canadian Trials which demonstrated a survival benefit with PMRT, the target volume included chest wall and regional lymph nodes. The above mentioned MA.20 NCIC trial from Canada also demonstrated the advantage of regional node irradiation in addition to whole breast. Due to concerns about the potential toxicity of large field irradiation this remains controversial.

**SCF/ICF radiation:**

Most guidelines recommend supraclavicular radiotherapy for 4 or more positive nodes. Toxicity associated with SCF radiotherapy is low, but it can increase the risk of lymphedema, shoulder stiffness and causes apical lung fibrosis. In UK, SCF radiotherapy is not routinely offered to all node positive patients. With mounting evidence in favour of nodal radiation this needs to be reconsidered. A recent study from the GKT group in London tried to identify patients in the 1-3 positive node group who are at high risk of SCF recurrence and warrant SCF RT. At a median follow up of 9.7 years, the SCF relapse rate was 9.2%. Number of positive nodes and higher Grade were predictors of SCF relapse.

**Axillary radiotherapy after axillary clearance:**

None of the published guidelines support the use of axillary RT after level II clearance for any level of nodal involvement. Extra capsular extension (ECE) is regarded as a risk factor for LRR and distant metastases and role of axillary RT is debated when there is extensive ECE. However, very few studies have evaluated its role as an independent prognostic factor. Based on current evidence, ECE alone cannot be used as a decision making tool for axillary RT.

**Axillary Radiotherapy after positive SNB:**

Best evidence for axillary RT as an alternative to surgery following macrometastases in sentinel lymph node comes from the recently published AMAROS study. Patients were randomised between axillary dissection and axillary radiotherapy after a positive SNB. 60% had macro metastases. At a median follow up of 6.1 years both treatments offer comparable local control.
Lymphedema was worse on the surgical arm and increased rate of shoulder stiffness was seen in the RT arm. Median follow up may be too short to assess RT toxicity.

IMN radiotherapy:
With the available data not recommended unless proven involvement of IMN on diagnostic or planning scan.

8.2.12 Indications for Post Mastectomy Radiotherapy

Radiotherapy to Chest Wall:

- Any T4 tumour.
- 4 or more positive nodes.
- Loco-regional relapse after previous mastectomy with no previous radiotherapy.
- 3 positive nodes + one other risk factor.
- 2 positive nodes + two other risk factors.

Risk factors to be considered.

Young age 40 or below.
Triple negative tumours.
Grade III tumours.
Increasing tumour size (3cms or more).
Extensive LVI.

Relative Indication:
Tumour size of 5cms or more with no nodal involvement.

Radiotherapy to glands:

Supraclavicular/ Level III nodes:

4 or more positive nodes.

Apical node involvement.
3 nodes + grade III/ ER-.

Axillary+ SCF/ICF radiotherapy:

Positive SNB where further local treatment is considered necessary by MDT as alternative to surgery. Only appropriate if there are indications for chest wall radiotherapy.

Axillary recurrence.

After axillary clearance, when surgical resection not thought complete. This will be after discussion at MDT and recorded in MDT notes.
References:


Is the benefit of post mastectomy irradiation limited to patients with four or more positive nodes as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&C trials. Radiotherapy and Oncology 82(2007) 247-253.


Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients : Final analysis of the EORTC AMAROS trial Journal of Clinical Oncology 2013. vol 31, no:18_suppl(June 20 supplement)2013

One to three versus Four or more Positive Nodes and Post mastectomy Radiotherapy: Time to End the Debate. Journal of Clinical Oncology vol 26 no:13 May 1 2008.


Selecting Breast Cancer Patients With T1-T2 tumours and one to three positive nodes at High Postmastectomy Loco regional recurrence Risk for Adjuvant radiotherapy: Int. J.Radiation Onclopgy, Biology, Physics Vol61 No:5 pp 1337-1347 2005.


Risk factors for Regional Nodal Relapse in Breast Cancer Patients With one to Three Positive Axillary Nodes.

8.2.13 Post Mastectomy Radiotherapy after Neoadjuvant Chemotherapy:

Use of neoadjuvant therapy, particularly chemotherapy (NACT) has become more common over the last few years. Although, NACT has so far not demonstrated a clear survival advantage, it can increase the choice of loco-regional treatment options and also enable us to tailor chemotherapy based on tumour response.

NACT generally induces significant changes in the pathological extent of the disease and therefore, the traditional post pathological parameters used in post mastectomy radiotherapy (PMRT) decision making may not be valid here. It has generally been accepted that the use of PMRT should be based on pre-NACT clinical staging. Based on this most guidelines recommend PMRT for clinical T3/T4 N1 disease.

There is increasing evidence that response to NACT can influence loco-regional control. Combined analysis of the two NSABP neoadjuvant trials (NSABP-B18 &B27) showed that in addition to age and clinical stage at presentation, pathological response to NACT predicts for LRR. All their patients had operable breast disease prior to NACT and none received PMRT. The 10 yr LRR rates were 14.3% and 12.2% respectively suggesting a positive impact with docetaxel. Their data suggests that patients with pCR in breast and axilla have a very low risk of LRR (6%) irrespective of clinical nodal involvement. This was seen in the retrospective series from M.D.Anderson (ref:2). Retrospective series from France concluded that breast only radiotherapy in patients who undergo breast conserving surgery after NACT did not increase loco-regional relapse in patients with ypN0 disease. After reviewing available literature on the role of PMRT after NACT, the Athena Breast Health Network from California concludes that patients above 40 years with pCR or 0-3 nodes without LVI or ECE have little or no benefit from PMRT.

None of this data is from randomised trials and in all studies the pCR group is small. Therefore, these conclusions should be interpreted with caution. Still it may be time to factor in response to NACT into the PMRT decision making process.

Recommendations for Post Mastectomy Radiotherapy after Neoadjuvant Chemotherapy.

Radiotherapy to chest wall:

Absolute Indications:

A) Locally advanced carcinoma at presentation irrespective of response:
   i) any T4 tumour.
   ii) Palpable lymphadenopathy or bulky lymph nodes on USG axilla.

B) Residual disease in axilla after NACT - Positive axillary clearance.

C) Invasive residual disease in the breast after NACT.

Relative Indications:
T1-T3 N1(positive FNAC or SNB)tumours at presentation with pCR in breast and glands (ypT0/is ypN0.)

T3N0 tumours
Consider if two or more factors:
Age \(\leq 40\) years.
ER/PR negative tumours.
Grade III
More than one positive SNB.

**Indications for SCF radiotherapy:**

**Absolute indications:**

a) Any residual disease in lymph nodes after NACT- positive ANC.

**Relative Indications:**

a) Positive SNB at presentation with residual disease in breast but negative axillary clearance.

Consider if two or more factors:
Age \(\leq 40\) years.
ER/PR negative tumours.
Grade III
More than one positive SNB.

**PMRT not indicated:**

T1/T2/ N0 tumours at presentation with complete pCR in breast and glands.

**References:**

1) Predictors of Locao-regional recurrence after neoadjuvant chemotherapy: Results from combined NSABP B-18 and B-27. JCO Nov10 2012:3960-3966 (Accompanying Editorial).

2) Role of Postmastectomy Radiation After Neoadjuvant Chemotherapy in Stage II-III breast Cancer IJROBP Vol 83 No2 pp 494-503.


9 Recurrent/Advanced Breast Cancer

9.1 Surgical Management

The role of surgery for advanced breast cancer is less than for early breast cancer. However, with each diagnosis of advanced disease consideration should be given to potential surgical aspects of treatment. These may include:

- Toilet mastectomy/palliative resection of locally advanced disease where disease is uncontrolled by other measures
- Orthopaedic stabilisation of lytic bone metastases at risk of fracture
- Resection of solitary brain metastases in the absence of other sites of disease
- Spinal surgery for spinal cord compression in good performance status patients with residual neurological function
- Brain metastases

9.2 Radiotherapy

Palliative radiotherapy should be considered where advanced breast cancer is causing symptoms at specific sites. Potential indications for palliative radiotherapy include:

- Painful localised bony metastases refractory to analgesics
- Painful/fungating/bleeding local disease
- Cerebral metastases and stereotactic radiotherapy
- Spinal cord compression
- Choroidal metastases
- Radiation induced menopause as part of hormonal treatment

The choice of total dose/fraction size will depend on the individual clinical situation. For bone metastases including spinal cord compression a single 8 Gy fraction is often sufficient. Brain metastases may be treated with 12 Gy in 2 fractions on consecutive days, though longer courses such as 20 Gy in 5 fractions, or 30 Gy in 10 fractions may be considered for good performance status patients. Spinal cord compression is considered a radiotherapy (or surgical) emergency and should be confirmed by MRI scan and treated within 24 hours. Steroids should be given to patients with spinal cord compression and symptomatic cerebral metastases prior to radiotherapy.
9.3 Endocrine treatment

9.3.1 First-line Endocrine Treatment

Suitable postmenopausal women should be offered Cyclin Dependent Kinase 4 and 6 (CDK) inhibitors as initial endocrine-based therapy for hormone-receptor positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic (secondary) breast cancer. (NICE TA 495, 496)

Premenopausal women naïve to endocrine treatments can also be offered this combination in conjunction with Ovarian Suppression.

Single agent Aromatase inhibitor therapy can be offered to less fit patients, or those patients with low volume metastatic disease which may include those with bone only disease. Patients should be monitored with clinical assessment, biochemistry, tumour markers and imaging. When progression occurs, second-line hormonal therapy or chemotherapy may be considered dependent on the clinical situation.

9.3.2 Second-line and Subsequent Endocrine Treatments

Aromatase inhibitors and anti-oestrogens show a significant degree of non-cross resistance. In patients without rapidly progressing, or life-threatening disease, up to 3-4 types of hormonal therapy may be used in sequence including anastrozole, exemestane, letrozole, tamoxifen, fulvestrant and megestrol acetate. There is no strong evidence for any specific order of treatments over another.

Premenopausal women who have progressed with tamoxifen, may be offered ovarian suppression with goserelin, or ablation with radiotherapy, or surgical oophorectomy as a treatment option, and to allow subsequent use of aromatase inhibitors or fulvestrant.

9.4 Chemotherapy and HER2 Targeted Therapy

Chemotherapy should be discussed with patients who have advanced breast cancer in the following categories:

- Hormone receptor negative disease
- Refractory to hormonal treatments
- Rapidly progressive or life-threatening disease visceral disease

The potential benefits and side-effects should be discussed. The choice of whether to use chemotherapy, and the regimen used will depend on the extent of disease, performance status, previous treatment experience and the patient’s wishes. In general, chemotherapy regimens will be given sequentially with regular assessment of response and side-effects. On progression, change to second and subsequent lines of treatment will be considered after reassessment and discussion with the patient.
Chemotherapy should only be prescribed by specialist non-surgical oncologists, working with chemotherapy nurse specialists, expert pharmacy and laboratory support. It should generally be administered in designated day-care facilities or on an oncology ward. Specialist inpatient support for chemotherapy complications should be available.

Patients, their carers, and primary care staff should be given specific written information about their treatment, its likely side-effects, contact details for help and advice if they should suspect a chemotherapy-related problem, and information on where patients would be admitted if necessary.

9.5 Metastatic bone disease

Metastatic bone disease

As taken from the London Cancer Alliance Breast Guidance - Patients with metastatic bone disease (lytic and/or sclerotic lesions) should be treated with intravenous bisphosphonates such as zoledronic acid on a 4-6 weekly basis. Extended dosing interval 6-12 weekly after 1 year of treatment may be considered.

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.
10 Palliative & End of Life Care

Palliative Care Section was updated in May 2017

10.1 Definitions

Palliative care is part of supportive care. It embraces many elements of supportive care.

Palliative & End of life care is care that helps all those with advanced, progressive, incurable illness to live as well as possible until they die. It enables the supportive and palliative care needs of both patient and family to be identified and met throughout the last year(s) of life and into bereavement. It includes management of pain and other symptoms and provision of psychological, social, spiritual and practical support.

The Department of Health (2008) definition of end of life care states that it includes:

- Adults with advanced, progressive, incurable illness (e.g. advanced cancer, heart failure, COPD, stroke, chronic neurological conditions, dementia);
- Care given in all settings (e.g. home, acute hospital, ambulance, residential/nursing care home, hospice, community hospital, prison);
- Care given in the last year(s) of life
- Patients, carers and family members (including bereavement care).

End of Life Strategy, Department of Health 2008
National Council for Palliative Care Services 2006

10.1 Who Provides Palliative / End of Life Care?

Palliative / end of life care is provided by two distinct categories of health and social care professionals:

- All health care and social care professionals providing the day-to-day care to patients and carers in any care setting
- Those who specialize in palliative care (consultants in palliative medicine and clinical nurse specialists in palliative care, for example) who care for palliative care patients who have complex needs

Those providing day-to-day care should be able to:

- Assess the care needs of each patient and their families across the domains of physical, psychological, social spiritual and information needs
- Meet those needs within the limits of their knowledge, skills, competence in palliative care
- Know when to seek advice from or refer to specialist palliative care services
Training and education in the skills required for palliative / end of life care should be available to and undertaken by all health and social care professionals.

The national strategy *Ambitions for Palliative and End of Life Care 2015-2020* sets out the vision to improve end of life care through partnership and collaborative action between organisations at local level throughout England.

More information can be found at: [http://endoflifecareambitions.org.uk/](http://endoflifecareambitions.org.uk/)

For more information about local improvements, frameworks, tools to support best practice please contact your local End of Life Care Lead or Specialist Palliative Care Team.

One aspect of care is to discuss with individuals, if they wish, their preferences regarding the type of care they would wish to receive and where they wish to be cared for in case they lose capacity or are unable to express a preference in the future. This is the process of Advance Care Planning (ACP).

An ACP discussion might include:

- the individual’s concerns and wishes,
- their important values or personal goals for care,
- their understanding about their illness and prognosis,
- their preferences and wishes for types of care or treatment that may be beneficial in the future and the availability of these.

Such discussions can also inform shared decision-making regarding treatments with palliative intent. Local arrangements for recording this information for each individual patient will differ. Many services are developing/have developed Electronic Palliative Care Co-ordination Systems (EPaCCS) where by this information can be shared across professionals and settings (e.g on SystmOne). Contact your local specialist palliative care team for more information.

### 10.2 Specialist Palliative Care

Is provided by specialist multidisciplinary palliative care teams in services or units whose core specialty is palliative care (for example hospices, community or hospital palliative care teams). The specialist teams should include palliative medicine consultants and palliative care nurse specialists together with a range of expertise provided by physiotherapists, occupational therapists, dieticians, pharmacists, social workers and those able to give spiritual and psychological support.

Eligibility for referral to specialist palliative care services is based on patient need not diagnosis. The agreed criteria for referral are as follows:

1. The patient has active, progressive and usually advanced disease for which the prognosis is limited (although it may be several years) and the focus of care is quality of life.

2. The patient has unresolved complex needs that cannot be met by the caring team, for example:
- Uncontrolled or complicated symptoms (e.g. symptoms not adequately controlled within 48 hours by the referring team, or sooner if causing overwhelming distress).
- Complex psychological/emotional difficulties.
- Complex social or family issues.
- Difficult decision making about appropriate future care.

Patients fulfilling these criteria should be referred to and assessed by a member of the specialist palliative care team.

The subsequent care package will be dependent on this assessment and should be made in agreement with the patient, carer(s) and referring team. It is not appropriate for specialist palliative care services to be committed to patients by professionals outside these services. Equally, specialist services should ensure that the assessment process is accessible and responsive to patients in need.

The level of specialist palliative care support required may fluctuate. Shared care of patients between the specialist palliative care professionals and the referring team (for hospital patients) or the primary care team (for patients at home / care home) is usually appropriate. Timely and effective communication is essential in these situations. For these patients advice from specialist palliative care services on a 24 hour basis should be available in all care settings.

Sometimes the specialist palliative care consultant and team may take the lead role in patient care, usually in a specialist in-patient unit (hospice) or designated specialist palliative care beds.

Referral systems for specialist palliative care services vary in different areas. They should be clear to all local referring consultants and primary care teams.

10.3 Further Links and Information

Contact the local Specialist Palliative Care Team for further information

10.4 Directory of West Yorkshire & Harrogate Cancer Alliance
Specialist Care Services

The Directory was checked and updated in May 2017

Bradford, Airedale, Wharfedale and Craven
Bradford Teaching Hospitals NHS Foundation Trust
Airedale NHS Foundation Trust
NHs Bradford, Airedale, Wharfedale and Craven
Website: www.palliativecare.bradford.nhs.uk
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<td>01535 292184</td>
<td>01535 295016</td>
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<td>01535 295036</td>
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<td>Sue Ryder Care – Manorlands Hospice (Oxenhope)</td>
<td>01535 642308</td>
<td>01535 642902</td>
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<tr>
<td>Bradford Teaching Hospitals Palliative Care Team</td>
<td>01274 364035</td>
<td>01274 366851</td>
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<tr>
<td>Bradford Community Palliative Care Team</td>
<td>01274 323511</td>
<td>01274 215660</td>
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<tr>
<td>Marie Cure Hospice (Bradford)</td>
<td>01274 337000</td>
<td>01274 337095</td>
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<tr>
<td>Out of Hours Advice via on-call Palliative Medicine Consultant via Marie Curie Hospice / Manorlands Hospice</td>
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**Calderdale and Huddersfield**
Calderdale & Huddersfield NHS Foundation Trust
NHS Calderdale
NHS Kirklees

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<td>01484 342965</td>
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<td>Calderdale Community Palliative Care Team</td>
<td>01422 310874</td>
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<td>Overgate Hospice</td>
<td>01422 379151</td>
<td>01422 384210</td>
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<td>Kirkwood Hospice and Community Palliative Care Team</td>
<td>01484 557906</td>
<td>01484 557918</td>
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<td>Out of Hours Advice via Hospices</td>
<td>01422 379151</td>
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<td>Harrogate Hospital and Community Palliative Care Team</td>
<td>Tel 01423 553464</td>
<td>Fax 01423 555763</td>
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<tr>
<td>St Michael’s Hospice</td>
<td>Tel 01423 872658</td>
<td>Fax 01423 815454</td>
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<td>Leeds Teaching Hospitals NHS Trust Specialist Palliative Care Team</td>
<td>Tel 0113 2064563</td>
<td>Fax 0113 2064863</td>
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<td>Sue Ryder Care - Wheatfields Hospice and Community Palliative Care Team (West Leeds)</td>
<td>Tel 0113 2787249</td>
<td>Fax 0113 2302778</td>
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<tr>
<td>St Gemma’s Hospice and Community Palliative Care Team (East Leeds)</td>
<td>Tel 0113 2185500</td>
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<td>Tel 01924 816052</td>
<td>Fax 01924 543883</td>
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<tr>
<td>Dewsbury Day Support and Drop-in (Rosewood Centre)</td>
<td>Tel 01924 512039</td>
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<tr>
<td>Mid Yorkshire Hospitals NHS Trust Palliative Care Team</td>
<td>Tel 01924 543801</td>
<td>Fax 01924 543883</td>
</tr>
<tr>
<td>Pontefract Community Palliative Care Team (Prince of Wales Hospice)</td>
<td>Tel 01977 781456</td>
<td>Fax 01977 796209</td>
</tr>
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<td>Prince of Wales Hospice (Pontefract)</td>
<td>Tel 01977 708 868</td>
<td>Fax 01977 600097</td>
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York Hospitals NHS Foundation Trust
NHS North Yorkshire and York

https://www.yorkhospitals.nhs.uk/our_services/az_of_services/palliative_care/

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<td>01904 777049</td>
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<td>01904 708553</td>
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11 Appendix: Prescribing Guidance for Ibandronic Acid 50mg tablets in post-menopausal women with breast cancer

THE MID YORKSHIRE HOSPITALS NHS TRUST

Prescribing Guidance

For

Ibandronic Acid 50mg tablets in post-menopausal women with breast cancer

This guidance was developed by the Sheffield Teaching Hospitals NHS Trust and reproduced by The Mid Yorkshire Hospitals NHS Trust with their kind permission.

Guidance developed by:

Professor Rob Coleman, WPH, STHFT
Dr Matt Winter, Consultant Oncologist, WPH, STHFT Dr Anthony Gore, GP Clinical Lead, NHS Sheffield CCG Helen Taylor, MM Pharmacist, NHS Sheffield CCG

Thanks to: Neil Masters (Principal Pharmacist, WPH)

Date approved at APG: July 2016

Review Date: July 2019
**Valid at date of publication only**

**Ibandronic Acid 50mg tablets**

**in post-menopausal women with breast cancer**

**Summary:**
Post-menopausal women with breast cancer at sufficient increased risk of recurrence will be offered a bisphosphonate (by the hospital specialist) to reduce their risk of recurrence and mortality from breast cancer* (see appendix 1 pg 73)

Either as zoledronic acid 4mg IV 6 monthly OR ibandronic acid 50mg tablets (one daily) from the start of adjuvant therapy for a period of 3 years.

**Where chemotherapy is planned:**
Zoledronic acid 4mg IV 6 weekly for 3 cycles; after which ibandronic acid 50mg tablets (one daily) will be offered and initiated by specialist team from 6-36 months.

**Where chemotherapy is not planned:**
Ibandronic acid 50mg tablets (one daily) for 36 months will be offered

**Responsibilities of hospital specialist:**
- Discuss rationale for treatment with patient with the explanation that this is an unlicensed indication.
- Side effects to be discussed, including osteonecrosis of the jaw (dental examination advised prior to treatment) and atypical femoral fracture. Patients need to be able to comply with dosing instructions.
- Responsible for starting ibandronic acid 50mg (one daily); minimum 28 day script will be supplied
- Request GP to continue prescribing ibandronic acid for:
  - 30 months (after 3 cycles of zoledronic acid IV infusions during chemotherapy)
  - Up to 3 years (no previous zoledronic acid IV Infusion)

Patients are followed up at 2-3 years and 5 years from completion of initial adjuvant therapy

**Responsibilities of primary care clinician:**
- Prescribe ibandronic acid 50mg tablets (one daily) as per specialist letter (length of time stated on letter).
- Ensure any other bisphosphonate e.g. weekly alendronate or risedronate is stopped whilst patient is taking ibandronic acid or having IV zoledronic acid.
- Review current NSAID use (increased risk of GI side effects).
- Annual review by GP to include:
  - Medication review to check compliance; potential side effects; tolerability of ibandronic acid; ensure patient and/or carer understands how to administer tablets; check oral hygiene advice is being followed.
  - Annual blood tests: renal function and serum calcium

Ibandronic acid not tolerated or patient is unable to comply with dosing instructions – refer back to specialist (zoledronic acid IV 6 monthly will be offered as alternative to make up 3 years) Inform consultant if ibandronic acid is discontinued for any reason
**Statement of Purpose**
This guidance has been written to support primary care clinicians in the management of post-menopausal women with breast cancer initiated on ibandronic acid 50mg by secondary care specialists to improve breast cancer survival. Ibandronic acid is unlicensed for this indication.

**Introduction**

A large collaborative meta-analysis\(^1\) (involving 18,766 women of whom 11,767 were post-menopausal) found that for post-menopausal women with breast cancer adjuvant bisphosphonates reduced the rate of breast cancer recurrence and improved breast cancer survival.

The absolute reduction with bisphosphonate use in post-menopausal women at 10 years was 3.0% for breast cancer recurrence (from 25.8%); 3.4% for distant recurrence (from 21.2%); 2.2% for bone recurrence (from 8.8%); and 3.3% for breast cancer mortality (from 18.0%).

This benefit was only seen with certain bisphosphonates including zoledronic acid IV 6 monthly and oral ibandronic acid 50mg daily. Numbers were insufficient to assess the efficacy of the standard treatments for osteoporosis, oral alendronate and risedronate, for this indication\(^1\).

None of the bisphosphonates are currently licensed for this indication. The ‘off licence’ use of ibandronic acid 50mg tablets has been approved by the Medicines Safety Committee at Sheffield Teaching Hospitals.

There is clinical support for the introduction of bisphosphonates for this cohort of women\(^2\). It is included in the breast cancer CRG service specification and endorsed as a priority for implementation at the UK Breast Cancer Meeting (UKBCM)\(^3\) in November 2015.

**Indication / patient group**

Post-menopausal women with breast cancer who are assessed by a specialist to be at sufficient risk of breast cancer recurrence (see appendix 1).

**Medication / Dosage / Duration of treatments**

The hospital specialist will arrange the first prescription for ibandronic acid 50mg daily (minimum of 28 days will be supplied) and will request on-going prescribing by the GP. The specialist will specify the length of treatment (up to 3 years).

Elderly population (> 65 years): No dose adjustment is necessary\(^4\)

Patients with hepatic impairment: No dose adjustment is required\(^4\)

Patients with renal impairment\(^4\)

- No dose adjustment is necessary for patients with mild renal impairment (CrCl ≥ 50 and < 80 mL/min)
- For patients with moderate renal impairment (CrCl ≥ 30 and < 50 mL/min) a dose adjustment to one 50mg tablet every second day is recommended
- For patients with severe renal impairment (CrCl < 30 mL/min) a dose adjustment to one 50mg tablet once weekly is recommended

\(^1\)Creatinine clearance (CrCl) in this document may be approximated to eGFR\(^5\) in primary care for patients with a BMI between 18.5 and 30kg/m\(^2\). The values remain the same but the units become mL/min/1.73m\(^2\).

\(^2\)This is guidance on the management of a condition only.

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**Valid at date of publication only**

Version 2.0
Responsibilities of hospital specialist

- Discuss rational for treatment and make patient aware of unlicensed indication
  - Indication is not included in patient information leaflet for ibandronic acid 50mg tablets.
  - Verbal consent from patient regarding unlicensed use is acceptable.

- Instruct patient on how to take oral ibandronic acid safely and reliably (fasting, early morning, upright, swallowed whole with at least 200 ml of water etc). Ensure patient can follow administration recommendations. See ‘information for patients’

- Baseline blood tests – including renal function and serum calcium.

- Adequate intake of calcium and vitamin D is important in all patients:
  - All patients should be advised to take supplemental vitamin D 20-25 micrograms (800–1,000 IU) daily; brought over the counter (OTC) from pharmacies, supermarkets or health food shops.
  - If dietary intake of calcium is low, prescribe combined calcium and vitamin D preparation.
  - Include in GP letter whether calcium and vitamin D needs to be prescribed or patient has been advised to buy vitamin D

- Discuss potential side effects including:
  
  **Osteonecrosis of the jaw (MHRA warning):**
  - Patients should be advised to have a dental examination with appropriate preventative dentistry prior to treatment with bisphosphonates.
  - During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

  **Atypical femoral fractures (MHRA warning):**
  - During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain.
  - Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture.

  **Oesophageal reactions (MHRA warning):**
  - Patients should be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as difficulty or pain upon swallowing, chest pain, or new or worsening heartburn.
  - See above regarding importance of dosing instructions.

  **Very rare reports of osteonecrosis of the external auditory canal (MHRA warning):**
  - Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment.

Review current medicines:
  - Advise patient to stop any other bisphosphonate that they may be taking; for example: risedronate or alendronate.
  - For patients taking a regular NSAID consider whether this can be discontinued.

Responsibilities of the primary care clinician – see next page

This is guidance on the management of a condition only
Responsibilities of the primary care clinician

Issue on-going prescriptions for ibandronic acid 50mg daily for length of time specified by hospital specialist (consider adding stop date to dosing instructions). Ensure other bisphosphonates are stopped during this period.

For patients taking a regular NSAID review and consider whether this can be discontinued.

Annual review including:

- Blood tests: renal function and serum calcium:
  - If calcium is out of range or renal function becomes severe (eGFR < 30 mL/min/1.73m²) discontinue ibandronic acid and contact hospital specialist for advice.
  - Reduce dose if eGFR < 50 mL/min/1.73m² (see ‘patients with renal impairment’).
- Medication review: to check for compliance; side effects and tolerability; ensure patient and/or carer understands how to administer tablets; check oral hygiene advice is being followed.

Inform the consultant if the patient discontinues treatment for any reason. Any patient not able to comply with dosing instructions or unable to tolerate oral ibandronic acid can be offered zoledronic acid IV as an alternative.

To report any serious adverse reaction to the CHM and the referring consultant.

Follow up

Patients are routinely seen by the specialist twice during 5 year follow-up; once between 2-3 years and at 5 years post completion of initial adjuvant treatment (surgery +/- chemotherapy +/- radiotherapy).

Side effects / Contraindications

Full list of side effects / contraindications is given in the Ibandronic Acid 50mg tablets SPC (summary of product characteristics) available from www.emc.medicines.org.uk.

Contraindications:
- Hypocalcemia. This needs to be corrected before the start of the treatment and will be checked by the hospital specialist.
- Inability to stand or sit upright for at least 60 minutes.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- Hypersensitivity to the active substance or to any of the excipients (e.g. lactose intolerance).

Special warnings and precautions for use:
- The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction
- Use with caution in patients with active or recent upper gastrointestinal problems
- MHRA/CHM advice: Bisphosphonates use and safety (December 2014)*
- MHRA/CHM advice: Bisphosphonates: atypical femoral fractures (June 2011)*
- MHRA/CHM advice: Bisphosphonates: osteonecrosis of the jaw (November 2009)*
- MHRA/CHM advice: Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal (December 2015)*

*See ‘Information for patients’

Interactions

Full list of interactions is given in the Ibandronic Acid 50mg tablets SPC (www.emc.medicines.org.uk).

Since acetylsalicylic acid, NSAIDs and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

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Information for patients

- Patients need to be aware that this is an unlicensed indication (responsibility of specialist).
- Patients should be advised on how to take the medicines and be referred to the manufacturer’s Patient Information Leaflet for full details. Patients and carers should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.
- During treatment patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling, non-healing sores or discharge to a doctor and dentist.
- Patients should be advised to report any ear pain, discharge from the ear or an ear infection during treatment with a bisphosphonate.
- Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.
- Patients should be advised to contact their GP if they have any concerns with the medication.

Useful links / Additional information

GMC guidance on prescribing unlicensed medicines is available here: http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

NICE

There is no NICE guidance but NICE has published a Medicines Evidence Commentary.

References


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Appendix 1: Selection of patients suitable for adjuvant bisphosphonates

Post-menopausal*

No

Adjuvant/neoadjuvant treatment plan includes ovarian suppression therapy or oophorectomy

Yes

Chemotherapy planned

No

No oncological or cancer treatment reason for recommending bone targeted treatments

Yes

Prescribe IV zolendronic acid 4mg x 3 during adjuvant/neoadjuvant chemotherapy δ

Adverse prognostic factors >12% 10 year risk of breast cancer death

Yes

Patient offered:

Oral ibandronate 50mg Daily (1st line) until 36 months initiated in secondary care but δ continued in primary care

IV zolendronic acid 4mg (2nd line): for patient’s not tolerating or unable to comply with dosing instructions of ibandronic acid at (0), 6, 12,18,24,30 and 36 months delivered by secondary care δ

Assess fracture risk and use bisphosphonates /denosumub according to CTIBL guidelines

No

No

Patients already on weekly oral bisphosphonates for osteoporosis should be considered for a treatment change and follow algorithm

* If not clinically assessable i.e. hysterectomy/IUD then ensure age >55 +/- serum FSH is in post-menopausal range (patient must not be receiving concurrent therapies that can affect the HPG axis)

δ Include vitamin D 800-1000IU daily (+calcium 1000mg daily if low calcium diet)

CTIBL: Cancer Therapy Induced Bone Loss

IV: Intravenous

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