LANCS & SOUTH CUMBRIA BREAST NSSG
REFERENCE MANUAL
FOR THE MANAGEMENT OF
BREAST CANCER

Guidelines agreed by:

<table>
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<tr>
<th>Breast NSSG members</th>
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<tr>
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Please destroy all previous versions of this guideline
Section 1  NICE Guidance for Breast Cancer

Section 2  Clinical Guidelines for the management of breast cancer within Lancashire & South Cumbria

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- Diagnosis
- Staging investigations
- Role of other imaging modalities in breast cancer
- Male Breast Cancer
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- Prognostification and prediction
- DCIS
- Lobular Neoplasia
- The management of malignant breast disease – indications for surgery
- Reconstruction after Mastectomy
- Indications for radiation treatment
- Indications for systemic medical treatment – adjuvant chemotherapy
- Guidance on the endocrine treatment of breast cancer in adjuvant setting
- Endocrine treatment for advanced breast cancer
- Strategy for the assessment and management of osteoporosis following early menopause and the use of aromatase inhibitors
- Metastatic breast cancer – medical management using chemo and targeted (non-endocrine) therapy
- Follow-up arrangements
- Guidelines for patients with a family history of breast cancer
- Prophylactic (risk reducing) mastectomy - Family history patients
- Lymphoedema
- Referral of patients from Breast MDT to another MDT
- Diagnostic Algorithm for Suspected Metastatic Spinal Cord Compression (MSCC)
- Treatment Algorithm for Metastatic Spinal Cord Compression (MSCC)

Section 3  Appendices

Appendix I  List of Chemotherapy Protocols (Adjuvant and Neo-adjuvant)
Appendix II  Monitoring of Cardiac Ejection Fraction for patients with breast cancer received Trastuzumab
NICE and Breast Cancer

The following guidance has been published by NICE. This guidance is designed to cover most of the patients most of the time. They are not designed as a text book on breast cancer management and do not cover every eventuality. Topics covered are driven by the stakeholders.

NICE confines itself to peer reviewed published data and is exclusive of abstracts and conference presentations. All guidance issued should be applied to each individual patient. NICE guidance is available at www.nice.org.uk/index
SECTION 2

CLINICAL GUIDELINES
FOR THE MANAGEMENT OF
BREAST CANCER
WITHIN LANCS & SOUTH CUMBRIA
Introduction

- This manual sets out the guidelines on the management of breast cancer to be adopted by the cancer centre and units in the Lancashire and South Cumbria Cancer Network.
- All new patients with breast cancer should be discussed by a multi-disciplinary team.
- Patients should be considered for clinical trials.
- Patients may be treated outside this guidance but this must be agreed by the MDT and the reasons recorded in the patients notes.

The Breast MDT

The MDT lead should be a single named clinician who is also a core team member.

The MDT core team should include:

- Two designated breast surgeons
- Clinical Oncologist
- Medical Oncologist * (where the responsibility of chemotherapy is not undertaken by the clinical oncology core team member)
- An imaging specialist * (the role of imaging specialist can be met by a group of named specialists provided each meets the required workload)
- A histopathologist (taking part in the specialist EQA for breast cancer) * (the role of histopathology specialist can be met by a group of named specialists provided each meets the required workload)
- Two breast nurse specialists
- MDT co-ordinator/secretary
- At least one clinical core member of the team with direct clinical contact, should have completed the training necessary to enable them to practice at level 2 for the psychological support of cancer patients and carers, and should receive a minimum of 1 hours clinical supervision by a level 3 or level 4 practitioner per month
- An NHS employed member of the core or extended team should be nominated as having specific responsibility for users’ issues and information for patients and carers
- A member of the core team nominated as the person responsible for ensuring that recruitment into clinical trials and other well-designed studies is integrated into the MDT.

Conduct is governed by local policy but should be polite and respectful.
http://www.nhsiq.nhs.uk/media/2444560/ncatmdtcharacteristics.pdf

The MDT may be a forum for teaching and learning. The case presentations should be concise and relevant, the question addressed to the MDT should be clearly framed. Time thresholds for placing the patient on the MDT should be adhered to except in case of urgency. These cases should be discussed with the relevant clinician prior to the meeting. Adequate time should be allocated in clinicians’ timetables to attend. The meeting should be of a reasonable duration and a reasonable case load should be presented.
Imaging in the diagnosis of breast lumps

- Age >40 years
  - Digital mammo
  - + Ultrasound

- Age <40 years
  - Ultrasound

Specific indications for ultrasound

- Assessing masses in young women where the breast is mammographically dense
- Identifying a discrete mass lesion in a nodular area
- Identification of multiple or recurrent cysts with blood-stained fluid
- Assessing lesions identified by mammography as an aid to sizing
- Monitoring malignant and benign lesions
- Image-guided core biopsies
- Ultrasound and FNAC assessment of axilla

**Diagnosis**

- All discrete masses presenting symptomatically must be assessed by imaging (see above) and fine needle aspiration (FNA) or biopsy, usually core biopsy. It is now accepted that we should rely primarily on core biopsies, which should preferably done under ultrasound guidance.
- If FNA result is C4 (suspicious), or C3 (atypical), consider repeat FNA or biopsy in the light of triple assessment
- If FNA result is C1 (inadequate/non-diagnostic), when the clinical and imaging findings are malignant, a repeat FNA or biopsy must be done to obtain a tissue diagnosis
- Core biopsy can be used in conjunction with FNA, particularly in multi-focal disease. Core biopsy should be performed in all suspected cancers (Baso Guidelines 2005). Ultrasound guided core biopsy is preferred where possible
- FNA of axillary lymph nodes that are suspicious on ultrasound

**Basic information**

- The information required on all patients is as follows:-
  - Histologically confirmed diagnosis (core biopsy as minimum)
  - Clinical history and examination
  - Age and menopausal status
  - Past or concurrent medical illnesses
  - Family history

**Staging investigations**

All patients should have:-

- Full blood count
- Biochemical profile (bone and liver function tests)
High risk patients consider:-
High risk is defined as definitely greater than 4 involved lymph nodes. Any patient deemed by the MDT to be high risk can be fully staged. Furthermore, chest x-ray is not the standard investigation for diagnosis of lung metastases, although they can be followed up, if visible, by this modality. It is appropriate to consider a CT scan of thorax and upper abdomen as a staging technique that will give information on soft tissue and bone involvement. The breasts and axillae should be included in the diagnostic field. If bone metastases are detected a bone scan should follow, along with plane films of areas of metastatic disease if at risk of fracture (e.g. hips/femorii). Any staging CT scan should be performed in the local cancer unit that is planning to treat the patient.

- CT, chest, abdomen and Pelvis if clinically appropriate.
- Isotope bone scan

- Other investigations e.g. isotope bone scan, skeletal x-rays, ultrasound liver scan should only be done as indicated by symptoms, signs or the biochemical profile

Reporting will follow the guidelines given in "Pathology Reporting of Breast Disease" NHSBSP publication no 58 issued January 2005 by RCPath and NHSBSP. http://www.rcpath.org/resources/pdf/PathologyReportingOfBreastDisease-CORRECTED-lowres.pdf

This covers scoring for ER and sentinel node reporting. The advice given in the recent national breast pathology update course was that centres already doing PR should continue to do so as it is a proven prognostic indicator.

- Tumour size
- Histological grade
- ER/PR status
- HER 2 status

- ER, PR and HER 2 will continue to be tested at present. This gives specific information as to the identity of ‘Triple negative tumours’ which are a separate sub group and may be treated differently.
- The ER and PR will continue to be expressed as an Allred score
- HER-2 status is recommended in all patients.
- HER-2: Every attempt will be made to make the result available within 2 weeks to help with medical treatment.
- All receptor requests should be processed routinely. An individual should be named within each pathology laboratory to ensure that cores are routinely sent for analysis. This person will also arrange to resend future specimens should the core not contain adequate cancer to enable receptor analysis.
- Nodal status; sentinel LN biopsy should form the standard of care for all patients (within RCS guidelines).
- At the time of the treatment MDT the patient’s grade, histological subtype, TNM and NPI should be agreed and entered onto the SCR system. (Clinical M stage is satisfactory, even if subsequent data may result in future modification). ER, PR and HER2 should be available in all circumstances except if the core is inadequate (in this case the pathology laboratory should employ a robust system to enable the report to be ready at the next possible opportunity).
- ER PR and HER2 should be available at the diagnostic MDT
- Oncotype DX should be offered if clinically appropriate.
- Ki67 may be requested for additional information where it will aid decisions regarding chemotherapy.

SCR (Somerset Cancer Registry) and Varian Databases
At present both data bases are in use; the former to record the anonymised patient data and management that will be up-loaded to form part of regional and national data, the latter to enable treatment planning and electronic record keeping.
The SCR is to be uploaded live at the time of the MDT.
The Varian System (via interface) contains records of all patients referred to Oncology. Staging will be completed at the time of the first patient referral.
Robust arrangements for regularly updating the system as the patient’s status changes, are currently being prepared.

**The Role of other imaging modalities in breast Cancer**

**MRI Scanning**

**Indications**

- Screening of genetic high risk patients, according to family history guidelines.
  [http://guidance.nice.org.uk/CG164/NICEGuidance/pdf/English](http://guidance.nice.org.uk/CG164/NICEGuidance/pdf/English)
- Screening of patients following mantle radiotherapy.
- For diagnosis of occult breast primary cancer, suspected on clinical grounds, in patients for whom conventional imaging is unsuccessful.
- For patients with a discrepancy between clinical findings and imaging (size).
- Lobular and/or Multifocal Assessing possible recurrence after previous surgery+radiotherapy, if mammography is equivocal.
- To assess response to neo adjuvant chemotherapy if this is the best modality pre operatively.

**PET Scanning**

No routine indications exist presently.

**Pre-operative ultrasound of the axilla**

The role of SLNB is to reduce operative morbidity. Similarly, it is preferable to avoid two procedures (SLNB and subsequent clearance). Axillary ultrasound followed by FNAC of suspicious LN to demonstrate the presence of malignant involvement at the time of initial diagnostic core. Patients with an involved axilla can then proceed directly to axillary node clearance.

**Male Breast Cancer**

Men with breast cancer should be offered surgery which would take the form of a mastectomy. The axilla would be staged in the normal way with pre-operative ultrasound and sentinel node biopsy where nodes are not obviously involved.

Radiotherapy and chemotherapy would be offered in the normal way based on the results of pathological staging.

Tamoxifen is recommended if the tumour is oestrogen receptor positive but less information is available about aromatase inhibitors.

Consider discussion regarding family history risks.

Follow up should be annual mammograms for 5 years.
Breast Cancer Subtypes and risk stratification/prognosis/prediction

The clinico-pathological definition of breast cancer subtypes (Table 2) and their broad implications for systemic treatment selection (Table 3) are summarized below as defined in the 2013 St Gallen guidelines. Patients should be classified at mdt to one of these 4 intrinsic subtypes and subsequent treatment recommended accordingly. Ki-67 testing is not currently routine practice within the Network however it is hoped that this will become the case in the near future.

In addition to this use of the Oncotype DX 21-gene recurrence score is now a NICE-approved option for guiding adjuvant chemotherapy decisions for patients with the luminal subtype (ER positive and lymph node negative) who are assessed as being at intermediate risk (NPI>3.4) and for whom information on the biological features of the cancer provided by Oncotype DX will be likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy.

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Table 2. Surrogate definitions of intrinsic subtypes of breast cancer

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<thead>
<tr>
<th>Intrinsic subtype</th>
<th>Clinico-pathologic surrogate definition</th>
<th>Notes</th>
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<tr>
<td>Luminal A</td>
<td>‘Luminal A-like’</td>
<td>The cut-point between ‘high’ and ‘low’ values for Ki-67 varies between laboratories. A level of 16% best correlates with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between ‘Luminal A-like’ and ‘Luminal B-like’ subtypes derives from the work of Pratt et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.</td>
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<tr>
<td>Luminal A</td>
<td>‘Luminal B-like (HER2 negative)’</td>
<td>‘Luminal B-like’ disease comprises those luminal cases which lack the characteristics noted above for ‘Luminal A-like’ disease. Thus, either a high Ki-67 value or a low PgR value (see above) may be used to distinguish between ‘Luminal A-like’ and ‘Luminal B-like (HER2 negative)’.</td>
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<tr>
<td>Luminal B</td>
<td>‘Luminal B-like (HER2 positive)’</td>
<td>ER positive, HER2 over-expressed or amplified, Ki-67 ‘high’. The cut-off as described in the table above may also be used to distinguish between ‘Luminal A-like’ and ‘Luminal B-like (HER2 positive)’.</td>
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<td>Her2+ overexpression</td>
<td>‘HER2 positive (non-luminal)’</td>
<td>ER and PgR absent.</td>
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<td>Basal-like</td>
<td>‘Triple negative (ductal)’</td>
<td>ER and PgR absent, HER2 negative. There is an 80% overlap between ‘triple-negative’ and intrinsic ‘basal-like’ subtype. Some cases with low positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. ‘Triple-negative’ also includes some special histological types such as adenosquamous carcinomas.</td>
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*A majority of the Panel voted that a threshold of ≥20% was indicative of ‘high’ Ki-67 status. Others, concerned about the high degree of inter-laboratory variation in Ki-67 measurement [25] and the possibility for undertreatment of patients with luminal disease who might benefit from chemotherapy, would use a lower (local laboratory specific) cut-point to define Ki-67 ‘high’ or use multi-gene expression assay results, if available.

This factor was added during Panel deliberations after circulation of the first draft of the manuscript, to reflect a stronger minority view. Although neither the 21-gene RS nor the 70-gene signature was designed to define intrinsic subtypes, a concordance study noted that over 90% of cases with a low RS and almost 80% of those with a 70-gene low-risk signature were classified as Luminal A [95].*
Adjuvant online (www.adjuvantonline.com) and PREDICT (www.predict.nhs.uk) are free web based programs that predict, based on published data, the statistical impact of therapeutic interventions on a patient. These should be used, in conjunction with clinical expertise, to formulate a treatment plan for a patient and advise on prognosis.

Ductal carcinoma in situ (DCIS)

Introduction
- 20 – 30% of malignant disease found at breast screening
- Pre-malignant stage in the development of invasive carcinoma
- May present as a mass, Paget’s disease or nipple discharge but more commonly as soft tissue density or micro calcification on mammography
- Local recurrence associated with size, histology and completeness of excision. 50% of local relapses are invasive not in situ disease.
- Lymph node staging is not normally required, however relative indications include
  - Mastectomy patients
  - Extensive
  - Suspicion of invasive disease

Indications for surgical treatment

Breast conservation alone
- Clear excision margins (greater than 1mm)
- Low and intermediate grade histology
Breast conservation and radiotherapy
- High grade histology

Mastectomy
- Multicentric/extensive multifocal disease proven with core biopsy
- Inadequate (less than 1 mm) margins after repeated local excision
- Immediate reconstruction should be considered
- The axilla may be staged in the case of a mastectomy for DCIS

Lobular Neoplasia
- Not a pre-cancerous lesion
- Usually an incidental finding
- High risk of invasive cancer in both breasts
- Close monitoring advised (annual screening) for 5 years

- There is no indication for adjuvant hormone therapy outside clinical trials

The Management of Malignant Breast Disease

Indications for surgical treatment

The patient’s treatment should have been discussed in the diagnostic MDT. This plan may be modified at the time of surgery according to clinical and patient requirements. All appropriate treatment options, including SLNB, WLE, mastectomy, immediate or delayed reconstruction (etc) should be discussed and be available. If an appropriate option is not locally available the patient should be offered this option in the next closest part of the Network. All units should offer all breast surgical techniques with the exception of specialised reconstructive work (e.g. DIEP flap), in this case a referral pathway should exist.

Surgical technique is to be of the standard set out by the RCS ABS Guidelines.

A single peri-operative dose of antibiotics may be administered (Cochran Collaboration)

Breast conservation

- Patient selection
  - Technically suitable for breast conservation; including those patients that have received primary therapy with chemotherapy or endocrine treatment
  - Agrees to radiotherapy (RT) and no contraindication for RT
  - Consider “Therapeutic Mammoplasty” excision where possible
  - Oncoplastic closure of Surgical cavity where necessary

- Patient management
  - Wide local excision
  - Clips to mark the cavity in all patients (to aid radiotherapy planning)
  - Orientation of specimen is important to delineate complete excision
  - Margins must be assessed using a method acceptable to the local MDT (>1mm)
  - Clearance of margins documented and discussed at MDT
Mastectomy

- Patient selection
  - Multiple lesions or widespread DCIS (see section on DCIS)
  - Inflammatory cancer
  - Size of breast would give unacceptable cosmetic result with conservation surgery
  - Recurrence after breast conservation and RT
  - Patient refuses breast RT
  - Contraindication for RT such as previous RT (mantlefield)
  - Patient choice

Patient management (axilla)

The aim of axillary management is two fold
  - To provide staging information
  - Therapeutic

At the time of diagnostic core the axilla should be examined ultrasonographically and any suspicious nodes (for metastatic involvement) should be assessed by FNAC/Core biopsy. If the FNAC contains malignant cells the axilla should be cleared. If the axilla is clear on US or FNAC a SLNB should be undertaken. This will reduce the need for two procedures. Patients undergoing chemotherapy for downstaging who are clinically node negative are eligible for SN biopsy prior to or after chemotherapy.

- All patients should have staging of the axilla
  1. Sentinel Lymph Node Biopsy is the standard of care for low risk tumours
  2. Indications for sentinel lymph node biopsy
     a. Node negative clinically and on ultrasound examination and US FNA/Core biopsy
  3. Exclusions
     a. Allergy to contrast or imaging media
     b. Pregnancy or Breast Feeding (use isotope alone, not blue dye)
     c. Malignant Cytology from Axillary Lymph nodes preoperatively

- Axillary clearance indications
  1. Positive SLN biopsy (Consider entry into POSNOC)
  2. Positive FNAC following staging ultrasound of the axilla

- After Sentinel Node Biopsy
  1. MDT do not need to offer axillary clearance if only micrometastases in one node.
  2. If the patient has macrometastases and has had a mastectomy or WLE, they need to be offered a clearance, radiotherapy to the axilla or entry into POSNOC.

- Management of the axilla in patients undergoing neoadjuvant chemotherapy
  - All patients should have axilla assessed by USS at the time of diagnostic imaging and any suspicious axillary LNs should have FNA or core biopsy
  - Any patient with positive axillary lymph nodes pre-neoadjuvant chemotherapy should have axillary clearance at the time of surgery (both ACOSOG 71071 and SENTINA trial show unacceptable false negative rate from SLNB in this group of pts even if clinically node negative following neoadjuvant chemotherapy)
  - In clinically node negative patients sentinel node biopsy may be performed either before or after chemotherapy.
  - Patients with negative SLNB prior to neoadjuvant chemotherapy do not require any further axillary surgery
Reconstruction after mastectomy

Immediate reconstruction should be discussed with all women needing mastectomy even if only to say why IBR is not appropriate.

- Stage I/II women undergoing mastectomy should be offered reconstruction – immediate or delayed.
- Oncologically safe
- Skin sparing mastectomy for local small tumours and DCIS
- Pre-reconstruction RT prevents use of implants/tissue expanders without tissue transfer protection
- RT can be given to skin flaps post reconstruction including implants but cosmetic results will deteriorate with time and risk of capsular contraction is higher
- Smokers and medically unfit may not be suitable for tissue transfer

Axillary recurrence

- Best treated by axillary node clearance if this has not already been carried out

Medically unfit patients

- Biopsy is required to confirm diagnosis and establish endocrine responsiveness
- Surgery is best for control of local disease either wide-local excision or mastectomy
- Anaesthetic options may include local or regional
- Management of the axilla is individually determined according to the performance status, stage and patients' wishes
- If inoperable for consideration of:
  - Radiotherapy
  - Systemic therapy
  - Palliative Care
Indications for radiation treatment

The standards and techniques of radiotherapy are held in the Rosemere Cancer Centre. The prescribing clinician must possess the appropriate qualifications and experience. Radiotherapy will be delivered according to the relevant standards.

Timing of radiotherapy and other considerations:

Enough time between surgery and commencement of radiotherapy should be given to allow time for surgical wound healing, reasonable resolution of seroma, and/or resolution of post-operative inflammation/infection. The timing will also help to avoid radiotherapy causing surgical wound breakdown. Delay should be kept to a minimum.

Where adjuvant systemic chemotherapy is indicated, this should be undertaken first, then followed by the radiotherapy.

Radiotherapy is delivered concurrently with Hormone Therapy (HT) in ER+/PR+ disease.

Radiotherapy can be given concurrent with adjuvant Trastuzumab in Her2+ patients.

Patient(s) with a Pace-maker in situ will require assessment of the location of the Pace-maker, dosimetric analysis and liaison with the Cardiology/Pace-maker team before, during and after the course of the radiotherapy.

The Radiotherapy centre is aspiring to deliver breath hold radiotherapy for left sided tumours.

(Techniques are referred to in document as being located in radiotherapy dept)

Adjuvant therapy

- Aims of treatment
  - Reduce incidence of local recurrence following breast conserving surgery
  - Reduce incidence of local recurrence of DCIS (see section on the management of DCIS)
  - Reduce incidence of local recurrence in selected patients following mastectomy
  - Increase overall survival (8-9%)

- Treatment Techniques
  - The protocols for radiotherapy administration are located in the Radiotherapy Department
  - These include treatment guidelines, Quality Assurance and mechanistic protocols

- Patient selection: breast conservation

  All patients with the possible exception of Grade I tumours, <1 cm diameter or tubular histology. All patients with exception of those less than 3cm G1 or G2, ER+/HER-2 –ve (as per the PRIME2 trial)

- Patient selection: mastectomy

  Radiotherapy following mastectomy is directly indicated using any of the major criteria, however an number of minor criteria may lead to a decision to irradiate if the MDT feels that there is a high risk of relapse

Chest wall RT: major criteria

- T3-T4 tumours
- Tumours within 1 mm of the deep resection margin
- Tumours invading muscle or skin
- Axillary clearance with 4 or more nodes positive
- Following neo-adjuvant chemotherapy for tumour size >5cms or inflammatory carcinomas
Chest wall RT: minor criteria

- 1-3 nodes positive
- Extensive lymphovascular invasion
- Grade 3 tumours
- Multi focal disease

Nodal irradiation

- The potential morbidity of combined surgical clearance and nodal radiotherapy should be balanced against the risk of loco-regional relapse
- Post mastectomy, if the nodes are to be irradiated, chest wall radiotherapy is usually administered as nodal involvement is considered to represent a high risk of loco-regional relapse.
- Post mastectomy chest wall and nodal radiotherapy is the subject of the Supremo trial (results awaited)

Supraclavicular fossa only

Between 4-9 involved lymph nodes

Supraclavicular fossa and axillary RT

- Axillary staging positive (unless a surgical clearance has been carried out)
- Extensive peri-nodal disease
- 10 or more nodes are involved or >50% of total cleared
- High risk group (T2-T4, Grade 3, clinically node positive) if axillary surgery cannot be done

Patient management: breast conservation

- RT to whole breast
- Maximum depth of lung irradiation < 2 cm
- Exclude cardiac apex if possible
- Standard dose is normally 40 Gy in 15 fractions over three weeks
- Boost to tumour bed if tumour is within 1 mm of resection margin and cannot be improved surgically
- Boost to patients <40 years old (some benefit between 40-50, discuss with each patient)
- Boost dose is 10Gy in 5 fractions to follow on directly from the whole breast radiotherapy
- Involvement in radiotherapy trials is recommended, including FAST, IMPORT and Prime

Patient management: mastectomy

- RT to chest wall to cover site of mastectomy
- Lung depth 2cm
- Exclude cardiac apex if possible
- Standard dose is normally 40 Gy in 15 fractions over three weeks
- RT to supraclavicular fossa (and axilla for selected patients)
- Consider local radiotherapy trials

Locally recurrent breast cancer

- Exclude distant metastases.
- Resect if possible, consider initial with hormonal therapy if endocrine responsive, chemotherapy if not, if initially unresectable.
- Post-operative radiotherapy if surgical margins close and if previous radiotherapy has not exceeded a tolerance dose.
- To treat fungating breast cancer.
- To reduce bleeding in a fungating lesion.
**Metastatic breast cancer**
- Painful bone metastases
- Spinal cord compression
- Troublesome tumour deposits (e.g., skin, nodes, choroids, for fractionation see Radiotherapy Dept Protocols)
- Brain metastases consider referral for stereotactic radiotherapy

**Adjuvant Chemotherapy**
- **Aims of treatment**
  - Eliminate systemic micro-metastases that may be present
  - Increase cure rate
  - The absolute benefit of chemotherapy is multifactorial based on histological features as well as comorbidities. Any patient who may be eligible for neo-adjuvant or adjuvant chemotherapy must be discussed at a breast MDT with a medical or clinical oncologist present. See section on patient selection.

- **Background**
  - Meta-analysis (Oxford Overview 2005) shows statistically significant reductions in disease free recurrence and survival times in all patients below 70 years (Early Breast Cancer Trialists' Collaborative Group, Lancet 2005;365:1687-1717)
  - The benefits of chemotherapy and hormone therapy (in ER/PR positive tumours) are nearly additive. In ER positive tumours in pre-menopausal women, ovarian ablation (e.g., Goserelin) may be equivalent to standard CMF therapy.
  - No survival benefit has been shown with high dose regimens
  - Taxanes add a further 4% absolute benefit in overall survival (TAX316, PACS 01). Adjuvant taxane trials largely in node positive patients. Latest Laporte metaanalysis also shows benefit in node negative disease with improved DFS
  - Taxane benefit is greatest with either docetaxel 3 weekly, or paclitaxel given on a weekly schedule (SWOG E1199) (EBCC)
  - HER 2 positivity is associated with a worse prognosis. The adjuvant use of herceptin should be considered along with adjuvant chemotherapy in all patients with HER2+ve breast cancer (either 3+ on IHC, or positive on FISH analysis). Herceptin improves both DFS and OS in these patients (NSABP B31, NCCTG N9831, HERA, BCIRG 006)

- **Patient Management**
  - Patients should be involved in the treatment decision, and have sufficient information regarding benefits and potential toxicities (as well as written information) to make an informed choice
  - Standard chemotherapy options are as follows
    - For node positive and high risk node negative FEC $^{100}$T
    - Consideration to be given to FEC $^{100}$T in HER2+ve breast cancer given superiority of concurrent Herceptin treatment
    - FEC $^{100}$ weekly paclitaxel as alternative for patients in whom 3 weekly docetaxel unlikely to be tolerated
    - FEC $^{100}$ 4-6 cycles for low risk node negative (and if contraindication to taxanes)
    - Consider FEC $^{60}$ 4-6 cycles in patients with borderline performance status
    - 4 cycles of TC (taxotere and cyclophosphamide) is an alternative particularly for patients with cardiac risk factors (USO 9735)
    - Dose intensity is important and primary prophylaxis with neulasta should be considered for all patients
• If Her 2 +ve then Herceptin should be given (in either intravenous or subcutaneous preparation)
  - Standard treatment is 3 weekly for 12 months (duration trials such as Persephone and SOLD are currently in process)
  - Herceptin should not be given concurrently with anthracyclines, but should be given concurrently with the taxane component of chemotherapy where appropriate
  - An alternative Herceptin containing regimen in patients who either need to avoid anthracyclines or in whom it is thought to be important to start Herceptin earlier is TCH (Taxotere, Carboplatin and Herceptin) which has significantly less cardiac risk compared with anthracycline regimens (BCIRG 006)
  - All patients starting Herceptin should have cardiac assessment at baseline including blood pressure and must have LVEF >50%
  - Assessment of LVEF should be pre-chemotherapy, then pre-herceptin and then 4 monthly whilst on treatment
  - See appendix on cardiac monitoring for Herceptin for monitoring and management of cardiac compromise – Appendix II

• Women with T1/N0/HER-2+ cancers, should be considered for 12 weeks weekly Taxol and Herceptin as an alternative to standard regimes.

• Pre-menopausal ER/PR positive patients who continue to have regular periods after chemotherapy can be considered for ovarian ablation (eg Goserelin, or laproscopic oophorectomy). Discuss on individual basis, not NICE guidance

• Pre-menopausal ER positive patients in the intermediate risk category may be offered Goserelin for 2 years as an alternative to chemotherapy

• All ER/PR positive patients should be offered endocrine therapy following chemotherapy. See section on hormonal therapy

• The patient should be considered for cuffed central line if venous access inadequate on the opposite side to the breast cancer

Treatment induced sub-fertility and infertility and menopause

• Chemotherapy may induce an early menopause, the frequency increases according to the age of the patient and the chemotherapy regimen

• Hormonal therapy with zoladex induces temporary menopause

• Attention to the management of iatrogenic menopause should form part of routine follow-up

• Departmental guidance exists that suggest urgent referral to St. Mary’s is considered for any premenopausal patient who has not had children (at present, Dr Cheryl Fitzgerald).

• Any intervention may delay primary treatment and therefore may adversely affect prognosis.

• Risk and benefit analysis should be presented to the patient in advance

• Potential options include
  - IVF and embryo freezing (most successful and preferred)
  - Oocyte extraction and freezing
  - Ovarian tissue biopsy and freezing

• Minimum duration of IVF is of the order of 4 weeks.

Chemotherapy, its administration and side effect management

• Departmental protocols exist describing the indications and administration for all chemotherapy protocols

• Network wide prescriptions are in use and all chemotherapy is prescribed electronically. New regimes should have a protocol drawn up as soon as possible and should be approved by the Breast Cancer Lead Clinician

• All protocols should state the anti-emetic protocol. These are agreed centrally and if alternatives employed the reason should be stated in the notes

• All patients should be reviewed between chemotherapy cycles by an oncologist (or appropriate nurse specialist) and toxicities assessed
Neo-adjuvant (preoperative) systemic therapy

- **Indications**
  - Initially inoperable cancer
  - Reduce size of large tumours in order to perform breast conserving surgery

- **Aims of treatment**
  - Reduce size of tumour to increase the chance of operability with clear margins
  - Reduce size of tumour to allow breast conserving surgery to be performed
  - Eliminate systemic micro-metastases that may be present and therefore increase cure rate
  - Obtain information about chemo sensitivity of the tumour (theoretical advantage)
  - May be considered for patients with node involvement, inflammatory cancer or rapidly growing cancer.

- **Patient selection**
  - All patients for consideration of neo-adjuvant chemotherapy should be discussed in the breast MDT
  - Pathology from core biopsy including ER/PR and HER2 status should be available at MDT to make decision regarding neo-adjuvant treatment
  - Large tumours (>3 cm) that would normally require mastectomy but where breast conservation would be a preferred treatment option
  - Tumours that are deemed inoperable at the outset
  - Patients with high grade and particularly ER/PR –ve or HER2+ve cancers are most likely to respond favourably to neo-adjuvant chemotherapy and should largely form the subset of patients in whom this approach is offered

- **Patient management**
  - Patients must understand that breast conserving surgery may not be possible
  - Radiologically inserted clip for tumour localisation strongly recommended prior to commencing chemotherapy
  - Record tumour dimensions at each visit (ultrasound and mammography may be necessary)
  - Continue treatment unless there is a measured increase in the dimensions of the tumour
  - Surgery 4-6 weeks after the last cycle of chemotherapy

- **Standard therapy** (unless contraindicated)
  - FEC₁₀₀-T chemotherapy
  - Alternative chemotherapy regimens such as 6 cycles of FEC₁₀₀ may be considered if performance status or other co-morbidities preclude the standard regime.
  - Add in Herceptin in HER2+ve cancers. To start after anthracycline component of chemotherapy (ideally concurrent with taxane) and continue through surgical period until patient has received 12 months
  - TCH can be considered as an alternative.
  - If minimal response consider individualised management (operate to try to obtain local control and improve symptoms)

- **Management of the axilla in patients undergoing neoadjuvant chemotherapy**
  - All patients should have axilla assessed by USS at the time of diagnostic imaging and any suspicious axillary LNs should have FNA or core biopsy
  - Any patient with positive axillary lymph nodes pre-neoadjuvant chemotherapy should have axillary clearance at the time of surgery (both ACOSOG 71071 and SENTINA trial show unacceptable false negative rate from SLNB in this group of pts even if clinically node negative following neo-adjuvant chemotherapy)
  - In clinically node negative patients sentinel node biopsy may be performed either before or after chemotherapy
  - Patients with negative SLNB prior to neoadjuvant chemotherapy do not require any further axillary surgery
Primary Hormone Therapy

- Primary hormone therapy is indicated for hormone responsive tumours where either the tumour is inoperable at the outset or the patient is unfit for an operation.
- Can also be used in patients with low grade, strongly ER/PR +ve cancers who require a mastectomy at the outset in an attempt to shrink to allow breast conserving surgery.
- Use letrozole 2.5mg daily for at least 3 months (continue in the adjuvant setting as per guidelines ie 5 years).
- Tamoxifen should be used in pre-menopausal women.
- For non-compliant patients faslodex can be considered as an alternative.
- Patients should have their tumour assessed on a regular basis on treatment.
- If no response consider surgery (or chemotherapy and then surgery).
Guidance on the Endocrine Treatment of Breast Cancer in the adjuvant setting

Treatment choice will depend on risk assessment and side effect profile. All endocrine responsive patients should be offered hormonal therapy following chemotherapy.

Optimal duration and sequencing of therapy is not known: nor if any further risk stratification on receptor subtype is indicated.

Trials are divided into 4 groups, substitution, switching, sequencing and duration.

Substitution trials include ATAC and BIG 1-98, switching trials include IES, ABCSG 8/ARNO and ITA (small numbers), sequencing trials include BIG 1-98 and TEAM and extended adjuvant include MA-17 and ABSCG 6a. Data from extended use of tamoxifen is available from ATLAS and aTTom trials.

**ATAC** (arimidex, tamoxifen, alone or in combination), n= 9366, post-menopausal women in a prospective double blind randomised trial comparing 5 years arimidex, 5 years tamoxifen, and 5 years anastrozole plus tamoxifen. Median age 64yrs, 35% node +ve and 25% received chemotherapy. The combined arm was not superior and is not considered further. At 68 months there is an absolute benefit of 4% (hazard ratio of 0.83) in disease free survival in favour of anastrozole, there is no survival benefit. Flushes (35% vs 40%), endometrial carcinomas (3 vs 15 patients), deep venous embolism (1.5% vs 5%), cerebral ischaemia (1.1% vs 3.3%) and hysterectomy rate (1.5% vs 5%) in favour of anastrozole. However, bone fractures (7.1% vs 4.4%) and musculoskeletal disorders (30.3% vs 27%) in favour of tamoxifen.

**BIG 1-98** trial randomised 8010 postmenopausal endocrine responsive patients to 1 of 4 arms: letrozole for 5 yrs, tamoxifen for 5yrs, tamoxifen for 2yrs and letrozole for 3yrs, letrozole for 2yrs and tamoxifen for 3yrs. At a median follow-up of 8·7 years from randomisation letrozole monotherapy was significantly better than tamoxifen: intention-to-treat disease-free survival HR 0·86 [0·78—0·96], overall survival HR 0·87 [0·77—0·999]. At a median follow-up of 8·0 years from randomisation for the comparison of the sequential groups with letrozole monotherapy, there were no statistically significant differences in any of the four endpoints (including disease free survival and overall survival) for either sequence. Thromboembolic episodes (grade 3-5) were more common on tamoxifen whilst patients on letrozole had more fractures.

**The Intergroup Tamoxifen Anastrozole** randomised 426 endocrine responsive or endocrine unknown breast cancer patients to 5 yrs of tamoxifen or to switch to arimidex at any point after 2 yrs of tamoxifen continuing therapy for a total of 5 yrs. At 36 month median follow up hazard ratio for relapse is 0.36, p= 0.006, and for death is 0.18, p= 0.7, in favour of the switching arm.³

**Intergroup Exemestane** study randomised 4742 postmenopausal endocrine responsive or endocrine unknown patients who had received 2-3yrs of tamoxifen to be given tamoxifen or exemestane for a total of 5 years. At 30.6months median follow up disease free survival was absolutely improved in the switching arm by 4.7% (hazard ratio 0.68 p=0.000 5) although there is no change in overall survival. In those taking exemestane arthralgias, fractures (not significant) and diarrhoea were more common and vaginal symptoms and thromboembolic events less common.⁴

**ABCSG-8 / ARNO95** trial randomised 3224 patients to 5 yrs of tamoxifen or 2-3 yrs of tamoxifen and 3-2yrs of anastrozole up to a total of 5 yrs. At median follow up of 28 months event free survival was 96% in the switched group (vs 93% in the control group) with a hazard ratio of 0.60 p<0.001. The switched group suffered more fractures (2.4% vs 1.2% p=0.015) and less thromboses (p=0.034).⁵

**In MA17** postmenopausal women with hormone receptor-positive breast cancer (N = 5,187) were randomized to letrozole 2.5 mg or placebo once daily for 5 years following completion of 5 years of tamoxifen therapy. At a median follow-up of 30 months, letrozole significantly improved disease-free survival (DFS; $P < 0.001$), the primary end point, compared with placebo (hazard ratio [HR] for recurrence or contralateral breast cancer 0.58; 95% confidence interval [CI] 0.45, 0.76) $P < 0.001$). Furthermore, letrozole significantly improved distant DFS (HR = 0.60; 95% CI 0.43, 0.84; $P = 0.002$) and, in women with node-positive tumors, overall survival (HR = 0.61; 95% CI 0.38, 0.98; $P = 0.04$).
Clinical benefits, including an overall survival advantage, were also seen in women who crossed over from placebo to letrozole after unblinding, indicating that tumours remain sensitive to hormone therapy despite a prolonged period since discontinuation of tamoxifen. Hot flushes, arthralgia, myalgias and osteoporosis were more frequent in those taking placebo.

The ATLAS trial was a worldwide study which recruited 12 894 women with early breast cancer who had completed 5 years of tamoxifen and randomised them to continue tamoxifen to 10 years or stop. 90% of patients were post menopausal, 50% node negative. Among women with ER-positive disease (n=6843) allocation to continue TAM reduced: risk of breast cancer recurrence (617 recurrences in 3428 women on TAM vs 711 in 3418 controls, p=0·002), breast cancer mortality (331 deaths vs 397 deaths, p=0·01) and overall mortality (639 deaths vs 722 deaths, p=0·01). The reductions in adverse breast cancer outcomes increased after year 10 recurrence rate ratio (presumably due to the known benefit of tamoxifen continuing until year 10) [RR] 0·90 [95% CI 0·79–1·02] during years 5–9 and 0·75 [0·62–0·90] in later years breast cancer mortality, RR 0·97 [0·79–1·18] during years 5–9 and 0·71 [0·58–0·88] in later years). The cumulative risk of recurrence during years 5–14 was 21·4% for women allocated to continue versus 25·1% for controls. Breast cancer mortality during years 5–14 was 12·2% for women allocated to continue versus 15·0% for controls (absolute mortality reduction 2·8%). Treatment had no effect on breast cancer outcome women with ER-negative disease (1248), and an intermediate effect among women with unknown ER status (4800). Among all 12 894 women, mortality without recurrence from causes other than breast cancer was little affected (691 deaths without recurrence in 6454 women allocated to continue versus 679 deaths in 6440 controls; RR 0·99 [0·89–1·10]; p=0·84). For the incidence (hospitalisation or death) rates of specific diseases, RRs were as follows: pulmonary embolus 1·87 (95% CI 1·13–3·07, p=0·01 [including 0·2% mortality in both treatment groups]), stroke 1·06 (0·83–1·36), ischaemic heart disease 0·76 (0·60–0·95, p=0·02), and endometrial cancer 1·74 (1·30–2·34, p=0·0002). The cumulative risk of endometrial cancer during years 5–14 was 3·1% (mortality 0·4%) for women allocated to continue versus 1·6% (mortality 0·2%) for controls (absolute mortality increase 0·2%).

The aTToM is the UK counterpart to ATLAS and updated results were presented at ASCO 2013. 6953 women were randomised to continue Tamoxifen for further 5 year vs observation after completing 5 years of adjuvant Tamoxifen. ER+ 40%, 60% unknown, estimated 75% of these will be ER+ therefore overall population estimated to be 85% ER+. Reduction in breast cancer recurrence 32% vs 28% (RR 0.85, p=0.003). The benefit was only seen after 5yr follow up presumed due to continued benefit of Tam in yrs 5-10 for those patients who discontinued at yr 5. HR years 5-6 1.1; years 7-9 0.79; years10-14 0.78; years 15+ 0.66. Reduction in Breast cancer mortality 24% vs 21% (RR 0.88, p=0.06). Again benefit only after 5 yr follow up: HR year 5-6 1.17; years 7-9 0.99; years 10-14 0.79; years 15+ 0.75. Increased incidence endometrial cancer 2.9 vs 1.3%, endometrial cancer death 1.1% vs 0.6% ie 0.5% absolute increase in endometrial cancer death. Overall survival: 50% deaths non breast cancer related. Overall all cause mortality appeared less in Tamoxifen group 35% vs 34%, overall survival 26.1% vs 24.5%.

Comment

Aromatase inhibitors are better than tamoxifen in the post-menopausal setting, however the absolute benefit for disease free survival is <10% with some studies failing to show an overall survival benefit. ASCO recommendations support incorporation of an AI into the adjuvant treatment of postmenopausal women.

Planned switch from tam to AI (exemstane or anastrozole) results in selection bias, those patients that do not relapse are switched (selects good prognosis group). This strategy may permit a small number of relapses in comparison to upfront usage of an AI. This strategy was not superior to 5 yrs of letrozole or tamoxifen alone in BIG 1-98.

Planned switching should be considered for peri or pre menopausal patients in whom AI are not effective as initial therapies. Menopausal status means no periods for 12 months and biochemically menopausal. Data is not available to determine the optimal time to switch but should be considered after 2-3 yrs of tamoxifen and again at year 5.

Tamoxifen is satisfactory for low risk patients and pre-menopausal patients. Patients who are not low risk may have their endocrine therapy extended on an individual basis for up to 10yrs.
Tamoxifen use may be extended to 10 years however the benefits of extended tamoxifen use are not seen until year 10 post diagnosis.

**Recommendations**

- Choices and length of adjuvant hormonal treatment should be based on menopausal status, risk of disease relapse and side effects of therapy.
- Patients with low risk tumours (NPI < 2.4) may be offered tamoxifen for 5 yrs.
- Premenopausal patients should be offered tamoxifen as adjuvant hormonal therapy.
- Tamoxifen for 10yrs should be recommended to premenopausal patients who remain premenopausal at year 5 follow up. The risks/benefits of continuing treatment should be discussed taking into account individual risks of recurrence and side effects of treatment.
- Pre-menopausal patients should be offered tamoxifen until menopause has been biochemically confirmed.
- If at year 5 a previously premenopausal patient is postmenopausal there are 2 options:
  1. Data from ATLAS/aTTom have demonstrated benefit for 10yr TAM
  2. Data from MA17 has shown benefit for letrozole.

  We do NOT know which of these 2 options are superior. Practically if a lady is tolerating Tamoxifen well she may wish to continue rather than risk SEs of an AI. Decisions needs to be made again on individual risk and side effects, remember could also switch back to Tamoxifen if not tolerating the AI.
- Peri-menopausal patients can be offered planned switching (when menopausal) (using exemestane or anastrozole). However, this would mean they only have 5 year adjuvant treatment rather than potentially 10yr if they hadn’t switched which seems counterintuitive.
- Patients who are postmenopausal at diagnosis should be offered an AI upfront (letrozole or anastrozole) (efficacy and cost are very similar; hence clinician preference). Normal duration is 5 years.
- There is currently no evidence that more than 5 years treatment with an AI is beneficial and the safety profile of more than 5 year AI is not determined. However, this should be discussed on an individual patient basis in cases of high risk of relapse (Supported by St Gallen).
- Side effect management; at the time of starting an AI a DEXA scan should be undertaken and the need for calcium /vitamin D supplement be assessed. The scan should be repeated according to local and national guidance once the BMD has been determined.
- Tamoxifen is a suitable alternative for those patients with contraindications/intolerance to AIs.
- Ovarian oblation following chemotherapy - results of SOFT trial awaited. Current evidence is inconclusive. Can be considered if patient can’t have tamoxifen or young high risk patient
## Summary adjuvant hormone therapy guidelines 2016

### Premenopausal Patients

<table>
<thead>
<tr>
<th>Notes</th>
<th>1-5 years</th>
<th>6-10 years</th>
<th>1-5 years</th>
<th>6-10 years</th>
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</thead>
</table>
| Tamoxifen | Tamoxifen or AI (if has become post-menopausal) | - All patients should have an endocrine review at end of year 5  
- The risks/benefits of continuing treatment should be discussed taking into account individual risks of recurrence and side effects of treatment.  
- Pre-menopausal patients should be offered tamoxifen until menopause has been biochemically confirmed, noting the unreliability of biochemical testing in patients on or recently taking tamoxifen  
OFS Consider Ovarian Suppression if high risk – see notes  
Tamoxifen, or AI (if has become post-menopausal)  
- All patients should have an endocrine review at end of year 5  
- The risks/benefits of continuing treatment should be discussed taking into account individual risks of recurrence and side effects of treatment.  
- Pre-menopausal patients should be offered tamoxifen until menopause has been biochemically confirmed, noting the unreliability of biochemical testing in patients on or recently taking tamoxifen  
OFS Consider Ovarian Suppression in patients at higher risk of recurrence ie remaining Premenopausal post chemotherapy, lymph node positive or <35 yrs (?Grade 3)  
Women >40 with low grade, node negative cancers are unlikely to benefit and may experience more side effects  
Tamoxifen vs Exemestane Exe/OFS combination may be considered in selected patients <35 yrs or 4+ lymph nodes and at high risk of recurrence but has no proven survival benefit |
<table>
<thead>
<tr>
<th>Notes</th>
<th>1-5 years</th>
<th>6-10 years</th>
<th>1-5 years</th>
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### Postmenopausal Patients

#### Node-Positive

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<th>6-10 years</th>
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<tbody>
<tr>
<td>AI vs Tamoxifen</td>
<td>Low risk – node negative, low grade, HER2 negative, Strong ER expression – additional AI benefit likely small and side-effect profile/patient preference is crucial</td>
<td>Low risk – node negative, low grade, HER2 negative, Strong ER expression – additional AI benefit likely small and side-effect profile/patient preference is crucial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk – Larger, node positive, adverse molecular features – relative AI gains may be more important so include at some point</td>
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<td></td>
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<tr>
<td>5yrs or 10yrs</td>
<td>All patients should have an endocrine review at end of year 5. The risks/benefits of continuing treatment should be discussed taking into account individual risks of recurrence and side effects of treatment. If considering additional AI beyond 5 yrs repeat dexametasone scan</td>
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#### Node-Negative

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<tr>
<th>Notes</th>
<th>1-5 years</th>
<th>6-10 years</th>
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</thead>
<tbody>
<tr>
<td>AI or Tamoxifen or Sequence</td>
<td>AI or Tamoxifen</td>
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</tbody>
</table>

Note - A 20-year perspective is needed on ER+ disease. Distant recurrences continue steadily into years 5–20 when stopping endocrine therapy after 5 years. Without further endocrine therapy, distant recurrence risk in years 5–20 is around 14% for T1N0 and much greater for T2N0 or N+ disease (see graph below from EBCTCG data (ASCO 2016)
Long-term recurrence risks after use of endocrine therapy for only 5 years: Relevance of breast tumour characteristics (EBCTCG ASCO 2016)
Endocrine treatment for advanced breast cancer

Efforts should be made to obtain biopsy of relapsed disease for ER, PR and Her2 status, as discordance in tumour phenotype between primary breast tumour and recurrence is common\textsuperscript{1,2}.

**Endocrine treatment in hormone receptor positive Her2 negative postmenopausal women**

Endocrine treatment (ET) is preferred to chemotherapy especially in patients with bone disease only or with other non-visceral metastases. It is also appropriate to use ET as first line systemic therapy in patients with visceral metastases, and the decision whether to use upfront ET or chemotherapy should be based on the extent of visceral disease, patient’s symptoms, adjuvant treatment and disease free interval, patient’s age, co-morbidities, performance status (PS) and patient’s preferences.

**First line**

In patients who had no prior adjuvant ET or who received tamoxifen in the adjuvant setting, a non-steroidal aromatase inhibitor (AI, either anastrozole or letrozole) is the treatment of choice. This is supported by results from phase III randomized clinical trials\textsuperscript{3-6}, which showed superiority of AI to tamoxifen in terms of time to progression (TTP) but not overall survival (OS) in ET naive patients. The phase II data of the selective ER down regulator fulvestrant 500 mg monthly versus anastrozole in the first-line metastatic setting showed a significant TTP advantage for fulvestrant and fulvestrant should be considered as a therapeutic option especially if there is a contraindication or intolerance to AIs\textsuperscript{7,8}. Faslodex not approved by NICE as first line treatment.

With non-steroidal AIs being widely used in the adjuvant setting, the choice of a different endocrine agent for first-line advanced disease has to be considered. If discontinued for > 12 months, AIs still remain an option. In the absence of other RCT data, fulvestrant 500 mg would appear to be the best evidence based choice for patients with prior AI exposure\textsuperscript{10}.

Another option for patients whose disease recurred during or within 12 months after completion of non-steroidal AI, is combination of steroidal AI exemestane with oral mTOR inhibitor everolimus. A phase III RCT BOLERO-2 showed progression-free survival (PFS) advantage for exemestane + everolimus vs. exemestane + placebo (median PFS 10.6 months and 4.1 months, respectively). This advantage was associated with significant increase in toxicity\textsuperscript{11}.

There are non-randomized data suggesting that tumours will respond to other endocrine agents in the post non-steroidal AI setting (e.g. exemestane, tamoxifen).

**Second line**

Patients whose disease progressed on tamoxifen as first-line ET can be offered 2\textsuperscript{nd} line treatment with either AI or fulvestrant. Patients treated with a non-steroidal AI in the first-line setting can receive either fulvestrant or exemestane + everolimus as a 2\textsuperscript{nd} line (this is not approved by NICE). There are non-randomized data suggesting that response to first-line therapy predicts for response to subsequent ET. However there are no data showing that one treatment sequence is preferable to another.

**Third line**

It seems reasonable to start patients on third-line ET assuming they have had responses to prior ET and have not received that particular agent previously. The options include again non-steroidal AI, fulvestrant or exemestane.

Patients with evidence of endocrine resistance should be offered chemotherapy. No recommendation can be made regarding the number of lines of ET before switching to chemotherapy. Factors that need to be taken into account include response to previous ETs and its duration, presence of symptoms, extent of disease, rate of progression, patient’s preference, performance status and estimated tolerability to chemotherapy.
Endocrine treatment in HR positive Her2 positive postmenopausal women

Her2-targeted therapy should be offered early to all Her2 positive metastatic breast cancer patients, combined either with chemotherapy or ET. Data from RCTs suggest that the addition of Her2-targeted therapy increased the efficacy of ET (trastuzumab + anastrozole, lapatinib + letrozole, lapatinib + fulvestrant) by doubling both clinical benefit rate (CBR) and PFS\textsuperscript{12-14}. There are no randomized data comparing the combinations with anti-Her2 therapy alone. As lapatinib is currently not funded in this setting, trastuzumab + AI can be used, mainly in those patients not considered for cytotoxic chemotherapy.

Endocrine treatment in HR positive premenopausal women

If no prior adjuvant tamoxifen or if discontinued for > 12 months, tamoxifen with ovarian suppression (LHRH analogue) or ablation (surgery or radiotherapy) is the preferred option. A meta-analysis of 4 studies (n=506) showed that combination of ovarian suppression with LHRHa with tamoxifen resulted in significantly prolonged PFS and OS relative to either agent alone\textsuperscript{15}. Further treatment lines (after ovarian suppression/ablation) do not differ from those used in postmenopausal patients.

Further comments

There is currently no evidence to support combination of 2 endocrine agents (except tamoxifen + LHRH analogue in premenopausal women).

Other hormonal treatments such as Megace or oestradiol could be considered as 3\textsuperscript{rd} or 4\textsuperscript{th} line treatments in hormone responsive patients.

Concomitant chemo-endocrine therapy should not be used outside clinical trials. The value of maintenance ET after chemotherapy has not been confirmed by randomized clinical studies, but in view of its low toxicity and potential benefits it is a reasonable approach.

Endocrine therapy should be continued until progression of disease or significant toxicity. Response to treatment should be evaluated every 2-4 months. The interval between assessments should be tailored to the clinical needs and to the aggressiveness of the disease and may be prolonged in case of indolent disease and long-lasting responses\textsuperscript{1}.
**ET algorithm for HR positive Her2 negative postmenopausal women**

<table>
<thead>
<tr>
<th>ADJUVANT TREATMENT</th>
<th>FIRST LINE TREATMENT FOR ADVANCED DISEASE</th>
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<tbody>
<tr>
<td>No prior adjuvant treatment</td>
<td>Anastrozole or letrozole</td>
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<tr>
<td>Recurrence on or post adjuvant tamoxifen</td>
<td>Anastrozole or letrozole</td>
</tr>
<tr>
<td>Recurrence on or &lt; 1 year post adjuvant AI</td>
<td>Fulvestrant or exemestane +/- everolimus* or tamoxifen</td>
</tr>
<tr>
<td>Recurrence &gt; 1 year post adjuvant AI</td>
<td>AI** or fulvestrant or tamoxifen</td>
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<tr>
<th>PRIOR TREATMENT</th>
<th>SECOND LINE</th>
<th>THIRD LINE</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>AI</td>
<td>Fulvestrant</td>
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<tr>
<td></td>
<td>Fulvestrant</td>
<td>AI</td>
</tr>
<tr>
<td>Anastrozole or letrozole</td>
<td>Fulvestrant</td>
<td>Exemestane or tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Exemestane +/- everolimus*</td>
<td>Fulvestrant or tamoxifen</td>
</tr>
</tbody>
</table>

*only if no exemestane given in the adjuvant setting and if no more than one line of chemotherapy given for the treatment of advanced breast cancer

**preferably non-steroidal AI after exemestane and vice versa

**References**


USE OF CALCIUM AND VITAMIN D SUPPLEMENTS WHEN PRESCRIBING AN AROMATASE INHIBITOR

Upon Prescribing an AI in the clinic setting;

Request DEXA scan
Blood test for serum Vitamin D levels

Take dietary and lifestyle history

Needs 1200mg Calcium daily
Assess dietary calcium intake (milk and dairy products, sardines, pilchards, pulses, seeds, tofu, green leafy vegetables)

Consider;
- Early Menopause.
- Smoking and Alcohol intake.
- Weight bearing exercise.
- Use of steroids for more than 6 months.

If patient takes 1 pint of milk daily (800mg calcium) plus other Ca2+ rich foods:
NO CALCIUM SUPPLEMENTS REQUIRED
Await Vit.D levels & DEXA scan result and reassess

If patient takes minimal dairy:
Prescribe Adcal D3 Tabs chewable (600mg/400iu) one tab daily (Stocked in Pharmacy) OR Calcichew D3 Forte Tabs chewable or Calcichew D3 Caplets (500mg/400iu) one tab daily
Avoid ADCAL D3 Caplets as Ca2+ dose too high (750mg/200iu)
Await Vit.D levels & DEXA scan result and reassess

If patient actively avoids dairy:
Prescribe Adcal D3 Tabs chewable (600mg/400iu) two tabs daily (Stocked in Pharmacy) OR Calcichew D3 Forte Tabs chewable or Calcichew D3 Caplets (500mg/400iu) two tabs daily
Avoid ADCAL D3 Caplets as Ca2+ dose too high (750mg/200iu)
Await Vit.D levels & DEXA scan result and reassess
### VITAMIN D SUPPLEMENTATION

<table>
<thead>
<tr>
<th>Serum Vitamin D levels</th>
<th>Serum Vit.D levels drop 20-25 nmols/l during winter; Consider this if levels at low end of healthy in the autumn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 nmol/l = healthy</td>
<td></td>
</tr>
<tr>
<td>&gt; 75 nmol/l = optimal</td>
<td>No vitamin D supplement required ( &gt; 125 nmol/l leads to increased risk of renal stones)</td>
</tr>
</tbody>
</table>

Serum Vitamin D levels
25-50 nmol/l = moderate deficiency
If already on Ca²⁺ /Vit D supplement then increase from once daily to BD to give 800u daily.
Prescribe Fultium 800u daily if only needs Vit.D supplement
Ask GP to re-check vitamin D levels in 6 months

Serum Vitamin D levels
< 25nmol/l = severe deficiency
Prescribe ProD3 20,000 u/daily for 15 days then once a week for 3 months
Maintenance = ProD3 20,000 u/month
Ask GP to re-check vitamin D levels in 6 months

If a patient is on a bisphosphonate or is prescribed this in clinic please also prescribe Ca²⁺/Vit D supplement if not already prescribed
Medical management of advanced metastatic breast cancer using chemotherapy and targeted (non-endocrine) therapy

Her 2 amplified

Relapse >12 months after adjuvant trastuzumab complete, follow the left hand column, if not utilise the right hand column. However, TDM-1 is likely to be licensed in this setting i.e. relapse on or <12 months after adjuvant herceptin.

At each step consider role of anti-Her 2 agent and possibility of resistance. At present continue anti-her 2 agent during progression. The use of trastuzumab and alternative chemotherapy remains the backbone of treatment.

OS seen when pertuzumab trastuzumab docetaxel compared to lapatanib and capecitabine. The correct sequence for lapatanib trastuzumab dual blockade is unknown.

* There is no evidence to continue dual blockade on progression.
Chemotherapy in ER + Her 2- ABC

Chemotherapy in this setting is not likely to lead to cure and possible benefits must be balanced against the side effect profile.

Therapeutic options are determined by performance status and co-morbidity including liver and cardiac function plus pre-existing treatment sequelae such as neuropathy or marrow reserve.

In the advanced setting sequential single agent therapy is recommended over a doublet unless the patient requires a greater certainty of response, sometimes termed 'visceral crisis'. Most recent meta-analyses do not demonstrate a clear OS in either case, doublets lead to greater likelihood of response but Q.O.L. data are absent or minimal in reported trials.

Chemotherapy is not recommended for bone only disease.
Below follows the list of therapeutic options, they are often interspersed with periods of anti-endocrine therapy. Duration of treatment depends upon choice of agent (e.g. Anthracyclines are rarely continued beyond 6 cycles whilst oral chemotherapy is continued whilst tolerated and efficacious).

Choice of agent is determined by side effect profile, chance of cross resistance and likelihood of response. Re-challenge with previously effective agents if there is an adequate disease free interval is an option.

Most patients will have been exposed to adjuvant chemotherapy including taxanes and/or anthracyclines. If not previously used one of regimen that contain these drugs should be considered. Beyond that there is no evidence to recommend chemotherapy in any particular order.

One caveat to the above concerns patients who relapse with a solitary site of recurrence, e.g., a loco-regional recurrence. Here, an adjuvant chemotherapy regimen may be offered in the 'pseudo adjuvant setting'.

Consider supportive management of patients receiving chemotherapy with use of relevant anti-emetics and bone marrow support agents which are included in each chemotherapy protocol.

It is necessary to document side effects and benefits clearly in the medical notes; we hope to utilise Medonc to support this.

This section is absolutely not didactic and requires interpretation by the treating clinician. Similarly, the management of ABC and MBC requires multi-modality input and relevant MDT discussion.

Multi drug regimen for chemo naive patients or those who may be pseudo adjuvant

FEC (100 or 75)
TC
FEC
TEC

Multi drug regimen (palliative, greater likelihood of response required) Vin Cap
Gem Carbo
Treo Gem
Single agents
nab paclitaxel
Liposomal
doxorubicin
Vinorelbine
Capecitabine
Gemcitabine
Weekly taxol
Eribulin

Carboplatin
(Cisplatin)
Cyclophosphamid
Weekly
epirubicin

Special circumstances:

**Triple negative disease**: at present treat as 'normal' breast cancer, whilst trials have addressed the role of platins, the results are not yet known. It is reasonable in the metastatic setting to consider using a platinum regime sooner rather than later.

**BRACA gene cancers**: there may be a future role for Parp inhibitors but this is still the subject of clinical trials.

**Role of biopsy in the management of recurrent disease**
ABC 2 guidelines recommend biopsy of newly recurrent disease to confirm diagnosis and review receptor status, if possible.

**Clinical trials**
Recruitment to relevant trials should always be considered.

**Frequency of on-treatment review**
This is flexible given the need to assess response to intervention and patient side effects. Some patients need to be seen every cycle, others on alternate or even less frequently. This should be addressed on an individual basis and the chemotherapy nurses informed.

**Use of long term cannulae**
PICC lines, ports and tunnelled lines should be considered on an individual
Follow-up arrangements

Early Stage Disease (low/intermediate/high risk)

- Asymptomatic breast cancer patients will be followed up by a surgical team (when adjuvant chemotherapy and radiotherapy are completed)

- There is no evidence based guidance regarding the timing or frequency of review visits, so no recommendation is made here. Pragmatically, there should be availability of appointments for patients when problems arise and there should be an appointment for review of endocrine therapy at 5 years.

- Routine follow up may be undertaken by any appropriately skilled professional group surgeon, oncologist, breast care nurse.

- The Surgeon or their deputy in the surgical follow-up clinic, will be responsible for requesting and organising follow-up for imaging surveillance.

- At the end of primary treatment, the patient and specialist should agree a written care plan. Patients should have a contact number for the specialist breast cancer nurse whom they can contact for advice. If following a patient enquiry, it is felt that patient should be referred for an outpatient consultation, the breast cancer nurse will make the appropriate arrangements, either for referral to a nurse-led, surgical or oncology clinic. For advice out of hours, patients are advised to contact their GP or NHS direct.

- NICE guidance enables the patient to choose preferred follow up whether in primary or secondary care.

- Mammographic follow up is annually for 5 years or until reaching screening age if too young for screening at 5 years.

- Following conservation, mastectomy, or following discovery of atypical ductal hyperplasia (ADH) or LCIS/atypical lobular hyperplasia (ALH). Annual mammography for 5 years while under clinical surveillance.

- Local protocols should be agreed for recall arrangements and access to specialist clinics following discharge from clinical surveillance.

Open access should be encouraged

Locally advanced and metastatic disease

- Follow up by medical team (clinical or medical oncology)

- Close co-operation with the palliative care team is often necessary especially for patients with metastatic disease and transfer of care may be appropriate

- Assessment and discussion of patients’ needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis, at commencement, during and at the end of treatment; at relapses; and when death is approaching).
  (NICE guidance September 2013)

- Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of ‘key worker’ for individual patients.
  (NICE guidance September 2013)
• Patients with symptoms of adjustment disorder, anxiety or depression, should be referred for psychological interventions and possibly for psychiatric assessment and treatment.

Patient Led Follow-Up

ELHT have introduced Patient Led Follow Up after discussion and approval with the commissioners.

Patients who are eligible for patient led follow-up, according to the guidelines, will be entered into the programme. They will attend an education day which is then followed by annual mammograms and a questionnaire. In addition there is open access to clinics via the Breast Care Nurses. There is also an appointment made for a Treatment Summary.

Patients who are not suitable for Patient Led Follow-Up are followed up in the traditional ways mentioned above.

Survivorship

There have been significant improvements in breast cancer survival rates in the UK over the past two decades, with over two thirds of women diagnosed now surviving for more than 20 years (CRUK 2014).

As cancer survival rates increase, research has focused on the effect of diagnosis and treatment on individuals’ quality of life after completion of treatment and its ongoing consequences (Sherman et al 2012).

The Cancer Reform Strategy (Department of Health (DH) 2007) and Improving Outcomes in Cancer Strategy (DH 2011) proposed the need to re-consider how care is delivered for individuals living with and beyond the disease.

A number of alternative measures are being or have been developed for patients after treatment for early breast cancer (Tsianakas et al 2012).
Guidelines for patients with a Family History of Breast Cancer

• Each cancer unit should have access to a nurse led breast cancer family history assessment clinic
• On receipt of a referral a questionnaire will be sent out and a clinic appointment arranged unless low risk (these patients may be discharged by letter)
• Assessment will place patients in low, moderate and high risk categories
• High risk patients will be offered referral to a tertiary centre and/or screening locally as per high risk guidelines
• Patients should be offered a written summary of their consultation
• Tyrer Cusick assessment tool is the most comprehensive others do not cover variables such as ADH, LCIS etc. TC is poor for single degree relatives so Claus could be used as well for this group

Referral Guidelines from Primary Care

• One first-degree female relative diagnosed with breast cancer at younger than age 40 years or
• One first-degree male relative diagnosed with breast cancer at any age or
• One first-degree relative with bilateral breast cancer where the first primary was diagnosed at younger than age 50 years or
• Two first-degree relatives, or one first-degree and one second-degree relative, diagnosed with breast cancer at any age or
• One first-degree or second-degree relative diagnosed with breast cancer at any age and one first-degree or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative) or
• Three first-degree or second-degree relatives diagnosed with breast cancer at any age

Guidelines for Secondary Care Patients who do not require referral to a Specialist Genetic Clinic

• One first-degree relative diagnosed with breast cancer at younger than age 40 years or
• Two first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 50 years or
• Three first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 60 years or
• A formal risk assessment (usually carried out in a specialist genetic clinic) or a family history pattern is likely to give risks of greater than 3-8% risk in the next 10 years for women aged 40 years, or a lifetime risk of 17% or greater but less than 30% provided certain other specific are not present (See NICE Guidelines page 23)

Guidelines for Secondary Care Patients who should be offered a referral to Specialist Genetic Clinic

• At least the following female breast cancers only in the family
  o Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative) or
  o Three first-degree or second-degree relatives diagnosed with breast cancer at younger than average age of 60 years (at least one must be a first degree relative) or
  o Four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative) or
• Families containing one relative with ovarian cancer at any age and, on the same side of the family
• One first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years or
• Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years or
• Another ovarian cancer at any age or

• Families affected by bilateral cancer (each breast cancer has the same count value as one relative)
  • One first-degree relative with cancer diagnosed in both breasts at younger than an average age of 50 years or
  • One first-degree relative diagnosed with bilateral cancer and one first or second degree relative diagnosed with breast cancer at younger than an average age of 60 years or

• Families containing male breast cancer at any age and, on the same side of the family, at least
  • One first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years or
  • Two first-degree or second-degree relative diagnosed with breast cancer at younger than an average age of 60 years or

• A formal risk assessment has given risk assessments of
  • A 10% or greater chance of a gene mutation being harboured in the family or
  • A greater than 8% risk of developing breast cancer in the next 10 years or
  • A 30% or greater lifetime risk of developing breast cancer

• Further advice for specific families (as per NICE 2013) from a Specific Genetic Service

Genetic Testing

• Use a carrier probability calculation method (Boadicea – not available yet or Manchester Scoring System) as well as family history to determine who should be offered referral to a specialist genetic clinic
• Offer testing > 10% chance of BRCA1/2 or TP53 mutation in family
• Triple negative breast cancer < 40 years can be tested
• High grade serous ovarian < 60 years can be tested
• Start with testing an affected family member to avoid risk of false negative
• Must offer full mutation testing not partial
• Can now offer to an unaffected individual if no affected relative available
• Offer fast-track genetic testing (within 4 weeks of a diagnosis of breast cancer) only as part of a clinical trial
• All fast track testing to be discussed with a Consultant in cancer genetics and then, if appropriate, with the laboratory. This will generally only be relevant if a woman is having neoadjuvant chemotherapy and the result may help inform treatment decisions (see NICE guidelines 164 for specific advice regarding need for research in this area)

Management

• Advise all women on breast awareness
• Do not routinely offer USS surveillance
• Offer annual mammography for moderate 40-49 years and 40-59 years high risk patients
• Offer annual mammography 40-59 years to women who have not had genetic testing but have a greater than 30% probability of being a BRCA carrier
• Offer annual mammograms aged 40-69 to women with a known BRCA1 or BRCA2 mutation
Consider annual mammogram for:
- Women aged 30-39 at high risk
- Women aged 30-39 years who have not had genetic testing but >than 30% chance of being a BRCA carrier
- Women aged 30-39 with a known BRCA1 and BRCA2
- Consider Aged 50-59 women at moderate risk

MRI Surveillance

- Offer annual MRI to women age 30-49 who have not had genetic testing but have a greater risk than 30% of being a BRCA carrier
- Offer 30-49 years with a known BRCA1 or BRCA2 mutation
- Offer 20-49 years who have not had genetic testing but have a greater than 30% probability of being a TP53 carrier
- Offer 20-49 years with a known TP53 mutation
- Consider annual MRI surveillance for women aged 50-69 years with a known TP53 mutation

Surveillance for women with a personal and family history of breast cancer

- Ensure that all women with breast cancer are offered annual mammography for 5 years in line with NICE guidance 80.

Risk Management Advice

- Advice on oral contraceptives as per NICE guideline 164
- Breast feed if possible
- HRT as per above guideline
- Alcohol, smoking and weight/physical advice as per above guideline

Chemoprevention for women with no personal history of breast cancer

- Offer Tamoxifen or Raloxifine to pre and post menopausal women at high risk
- Do not offer Tamoxifen or Raloxifine to high risk women who have had bilateral mastectomy
- Consider Tamoxifen or Raloxifine for 5 years for pre and post menopausal women at moderate risk
- Risk and benefits of tamoxifen should be discussed in family history clinics
- Prescription should be done by GP
- Do not continue treatment with Tamoxifen or Raloxifine beyond 5 years
- Inform women that they should stop Tamoxifen at least 2 months before trying to conceive and 6 weeks before elective surgery
- Please see NICE guideline 164 for more specific guidance

Risk-reducing mastectomy/oophrectomy for women with personal history of breast cancer

- Bilateral risk-reducing is appropriate for only a small proportion of women who are high risk
- Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk
- Women considering this surgery should be seen in a Specialist Genetic Clinic to aid decision making, to discuss risk factors and to have appropriate counselling, preparation and support
- Bilateral oophrectomy is appropriate for small numbers of women from high risk families
- The effects of early menopause should be discussed with all women considering this surgery
- Please see NICE guideline 164 for more specific guidance

Summary of surveillance recommendations for women with no personal history of breast cancer (sourced and adapted form NICE 2013)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Moderate risk</th>
<th>High risk</th>
<th>High risk with more than 30% chance of a faulty BRCA gene</th>
<th>High risk with a faulty BRCA1 or BRCA2 gene</th>
<th>High risk with more than 30% chance of a faulty TP53 gene</th>
<th>High risk with a faulty TP53 gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Yearly MRI</td>
<td>Yearly MRI</td>
</tr>
<tr>
<td>30-39</td>
<td>None</td>
<td>You may have a yearly mammogram</td>
<td>Yearly MRI and possibly yearly mammogram</td>
<td>Yearly MRI and possibly yearly mammogram</td>
<td>Yearly MRI</td>
<td>Yearly MRI</td>
</tr>
<tr>
<td>40-49</td>
<td>Yearly mammogram</td>
<td>Yearly mammogram</td>
<td>Yearly mammogram and yearly MRI</td>
<td>Yearly mammogram and yearly MRI</td>
<td>Yearly MRI</td>
<td>Yearly MRI</td>
</tr>
<tr>
<td>50-59</td>
<td>You may have a yearly mammogram</td>
<td>Yearly mammogram</td>
<td>Yearly mammogram and yearly MRI</td>
<td>Yearly mammogram and yearly MRI</td>
<td>Mammogram as part of the population screening programme</td>
<td>MRI if mammogram shows dense breasts. You may have yearly MRI</td>
</tr>
<tr>
<td>60-69</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Yearly mammogram and yearly MRI</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>You may have yearly MRI</td>
</tr>
<tr>
<td>70+</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>Mammogram as part of the NHS screening programme</td>
<td>None</td>
</tr>
</tbody>
</table>
**Cancer-related Lymphoedema**

Also called *secondary lymphoedema*, this is caused by cancer or its treatment and recurrent episodes of infection in the affected area. It can occur if the lymph nodes are blocked with cancer or if they have been removed by surgery. Radiotherapy and chemotherapy can also cause lymphoedema by causing fibrosis within the remaining lymphatic pathways. However the majority of patients who have surgery or radiotherapy to the breast and axilla will not develop lymphoedema.

The patients most at risk are those patients who undergo an axillary node clearance followed by axillary radiotherapy.

The most common areas for lymphoedema to occur after cancer treatment are:

- in the arm or breast after breast cancer treatment to the armpit or breast.
- in the leg if cancer or its treatment affects nodes in the groin area or the pelvis.

The affected area, arm or leg may become swollen, stiff, uncomfortable and awkward to move, making it difficult to do daily activities, such as dressing or washing. Lymphoedema can develop weeks, months or even years after cancer treatment and it is difficult to know who will be affected or how severe the lymphoedema will be. However, most lymphoedema is detected in the early stage with patients noticing mild swelling to the area affected.

Although lymphoedema is usually found in an arm or leg, other parts of the body can become swollen. There may be swelling of the chest or abdomen (trunk) or groin. Swelling of the breast or chest area can sometimes occur after breast-conserving surgery. If the lymph nodes in the neck are affected, the face may swell, but this is rare.

Lymphoedema may cause the following symptoms in the affected area:
- A feeling of fullness, stiffness or heaviness
- Swelling, tightness and stretching of the skin.
- Clothes, shoes or jewelry (rings or watches) may feel tighter than usual.
- Skin changes – the skin in the area may feel tight or stretched and sometimes the texture can feel thicker. Skin may also be dry, flaky, rough or scaly.
- Aching and discomfort with reduced movement of the joints.

The aim of treatment is to reduce the swelling, which in turn will relieve the symptoms associated with it as mentioned above such as discomfort.

There are many treatment modalities, often used in combination but it is a chronic problem. Although the swelling can usually be reduced, there is always a risk of it coming back and may not completely go away. It may take several weeks or months before there is any real improvement, but with treatment the affected part of the body should become less swollen, easier to move and less uncomfortable.

There are different aspects of treatment:

- Skin care and preventing infection
- Self-massage, known as Simple Lymphatic Drainage.
- Limb positioning and movement
- Support using compression garments such as sleeves, stockings and wraps.
- Specific exercises
- Kiniseo taping
- Intensive treatments such as - Low level light laser therapy; Compression pumps, multi-layer bandaging; Manual lymphatic drainage

The therapies may need to be done every day to give the best results. Patients will be shown how to carry them out at home. Many people soon develop a routine that builds their lymphoedema care into their everyday activities.

Good skin care plays a vital part in the treatment of lymphoedema. Lymphoedema can make the skin become dry and itchy and it may crack. Good moisturising can help to prevent this. Suitable creams are available from local chemists or patients can get them on prescription from their general practitioner.

Any break in the skin, however small, may lead to the potential of infection (cellulitis) and the swollen part becomes red, hot and painful. Patients may experience a high temperature, flu-like symptoms, feel generally unwell and lose their appetite. Medical advice should be sought immediately and antibiotics are usually given to treat the infection and should be started straight away and generally taken for two weeks. Patients should be made aware of the symptoms at an early stage and encouraged to see their general practitioner as soon as they suspect they have an infection.

It is important that patients are referred appropriately to a Lymphoedema Service for symptoms which are classed more than mild, for appropriate advice and treatment. There is also a Network Lymphoedema patient leaflet available for patients, which has been developed and explains what lymphoedema is and the symptoms patients might experience.
### Antibiotics for cellulitis in lymphoedema

<table>
<thead>
<tr>
<th>Situation</th>
<th>First-line antibiotics</th>
<th>If allergic to penicillin</th>
<th>Second-line antibiotics</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Acute cellulitis + septicaemia (inpatient admission) | Flucloxacillin IV 2g q6h or benzylpenicillin IV 1200-2400mg q6h + gentamycin IV 5mg/kg o.d. | Clindamycin IV 600mg q6h | Clindamycin IV 600mg q6h (if poor or no response by 48h) | Switch to amoxicillin 500mg q8h when:  
  - Temperature down for 48h  
  - Inflammation much resolved  
  - CRP <30mg/L

| Acute cellulitis (home care)                   | Amoxicillin 500mg q8h + Flucloxacillin 500mg q6h | Erythromycin 500mg q6h or clarithromycin 500mg q12h | If fails to resolve, convert to IV regimen as in row 1, column 2 | Treat for at least 14 days or until signs of inflammation have resolved

| Prophylaxis to prevent recurrent cellulitis (if 2+ attacks p.a.) | Penicillin V 250 mg b.d. (500mg if weight >75kg) | Erythromycin 250mg bd. | Clindamycin 150mg o.d. or clarithromycin 250mg o.d. | After one year, halve dose of penicillin to 250mg o.d. (500mg if weight >75kg)

| Emergency supply of antibiotics “in case of need” (when away from home) | Amoxicillin 500mg q8h | erythromycin 500mg q6h or clarithromycin 500mg q12h | If fails to resolve, or constitutional symptoms develop, convert to IV regimen as in row 1, column 2 above |

---

a. PO unless stated otherwise  
b. Add if suspect Staphylococcus aureous infection eg folliculitis, pus formation, crusted dermatitis

Reference: British Lymphology Society; Consensus Document on the management of Cellulitis in Lymphoedema. Revised March 2013

Referral of patients from Breast MDT to another MDT

**LOCAL BREAST MDT**

- Treatment intent
  - Specialist MDT input

**CUP MDT**
- Consider referral to CUP MDT
- Indications: CUP metastasis demonstrated on imaging

**Brain/CNS MDT**
- Consider referral to Brain/CNS MDT at LTHT
- Indications: Brain metastasis demonstrated on imaging

**Lung MDT**
- Consider referral to local Lung MDT
- Indications: Lung metastasis/lesion demonstrated on imaging

**Skin MDT**
- Consider referral to Skin MDT at LTHT for Melanomas

**Sarcoma MDT**
- Refer to Sarcoma Diagnostic Clinic at LTHT and if diagnosed refer to Sarcoma MDT at Royal Liverpool.

**Haematology MDT**
- Refer lymphomas

**Specialist Palliative Care Team**
- Refer to local specialist palliative care team
Diagnostic Algorithm for Suspected Metastatic Spinal Cord Compression (MSCC)

Suspected MSCC

Liaise Immediately with MSCC coordinator
(LTHTR Bleep 2664)

1. Start Dexamethasone + Omeprazole
2. If spinal instability suspected
   - Nurse flat
   - VTE prophylaxis
3. Manage acute pain as per guidelines

Clinical diagnosis of MSCC
Very frail
Refer to Palliative care team
(see treatment algorithm)

Urgent MRI at local hospital
- Whole spine
- Within 24 hours of presentation
- If appropriate spinal instability to be commented on in report

Confirmed MSCC

Known prior malignancy

NO –
- Consider Radiotherapy for pain
- Action tissue diagnosis and appropriate treatment
  (if not known to have cancer)

YES –
- Follow treatment algorithm for confirmed MSCC

No history of prior malignancy

Undertake tests to establish cancer diagnosis

Lancashire Teaching Hospitals
main switchboard:
01772 716565
Treatment Algorithm for Metastatic Spinal Cord Compression (MSCC)

Confirmed MSCC

Liaise Immediately with MSCC coordinator (LTHTR Bleep 2664)

Transfer to specialist cancer centre
MSCC coordinator to facilitate discussion between Consultant Spinal Surgeon and Consultant Oncologist within 4 working hours

1. Complete paralysis > 24 hours
2. Frail
3. Poor life expectancy

Single Level, multiple (limited) but otherwise favourable
Good Performance Status
Life expectancy >3/12
Neurological deficit < 24 hours

Single or Multiple levels – surgery deemed unsuitable
Good Performance Status
Severe neurological deficit <24 hours
Or
Mild neurological deficit

YES

NO

YES

NO

YES

NO

Consider Liverpool Care Pathway / Preferred Priorities for care

Refer to Spinal surgeon for decompression and stabilisation

Urgent Radiotherapy

Pain not optimally controlled

Pain well controlled

Consider palliative Radiotherapy

Consider post-op Radiotherapy immediately (administer within 2 weeks)

Refer to appropriate tumour-specific team

Refer for rehabilitation

Lancashire Teaching Hospitals main switchboard:
01772 716565
Chemotherapy Protocols - Breast
Adjuvant & Neoadjuvant

Copies of Chemotherapy Protocols can be obtained from David Barber, Network Pharmacist – david.barber@lthtr.nhs.uk or via the North West Coast SCN website www.nwcscnSenate.nhs.uk

Carboplatin Docetaxel Trastuzumab
CMF
Docetaxel DO
Docetaxel & cyclophosphamide
FEC 60
FEC 100
Trastuzumab
Trastuzumab subcutaneous

Bevacizumab
Capecitabine breast
Capecitabine & vinorelbine
CMF-3 weekly
Docetaxel Breast
Docetaxel & capecitabine
EC 60 & 75
Epirubicin (weekly)
Eribulin
Everolimus
Lapatinib & capecitabine
Nab-paclitaxel (Abraxane)
Paclitaxel
Paclitaxel (weekly)
Paclitaxel & gemcitabine
Pertuzumab, trastuzumab and docetaxel
Trastuzumab
Trastuzumab subcutaneous
Treosulfan & gemcitabine
Vinorelbine IV
Vinorelbine oral
Monitoring of Cardiac Ejection Fraction for Patients with Breast Cancer Receiving Trastuzumab

- All patients require a baseline MUGA or Echo and a cardiovascular assessment
- If a patient’s blood pressure is >145/85 mmHg for a sustained period (>3 measurements over time) then an ACEi should be initiated
- Patients should have assessment of ejection fraction pre herceptin (ie after previous chemotherapy)
- Assessment should be repeated every 4 months on treatment and an additional assessment at 12 months for patients who required intervention during treatment.

### At Baseline

<table>
<thead>
<tr>
<th>Decision to start</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LVEF &gt; LLN</td>
<td>• Start trastuzumab</td>
</tr>
<tr>
<td>• LVEF ≤ LLN but &gt;40%</td>
<td>• Start ACEi followed by beta blocker</td>
</tr>
<tr>
<td>• LVEF ≤ 40%</td>
<td>• Refer to cardiology</td>
</tr>
<tr>
<td></td>
<td>• Hold commencement of trastuzumab</td>
</tr>
<tr>
<td></td>
<td>• Repeat assessment after 6 weeks if &gt; LLN commence trastuzumab</td>
</tr>
<tr>
<td>• Any signs or symptoms of heart failure</td>
<td>• Start ACEi followed by beta blocker</td>
</tr>
<tr>
<td></td>
<td>• Refer to cardiology</td>
</tr>
<tr>
<td></td>
<td>• Hold commencement of trastuzumab</td>
</tr>
<tr>
<td></td>
<td>• Repeat assessment after 6 weeks if &gt; LLN commence trastuzumab</td>
</tr>
</tbody>
</table>

### Monitoring during treatment

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LVEF &gt; LLN or LVEF decrease &lt;10% of baseline assessment</td>
<td>• Continue trastuzumab</td>
</tr>
<tr>
<td>• LVEF ≤ LLN but &gt;40% or LVEF decrease ≥10% of baseline assessment</td>
<td>• Continue trastuzumab</td>
</tr>
<tr>
<td>• LVEF ≤ 40%</td>
<td>• Start ACEi followed by beta blocker</td>
</tr>
<tr>
<td>• Any signs or symptoms of heart failure</td>
<td>• Refer to cardiology if already on an ACEi</td>
</tr>
<tr>
<td></td>
<td>• Repeat assessment after 6-8 weeks</td>
</tr>
<tr>
<td></td>
<td>• Start ACEi followed by beta blocker</td>
</tr>
<tr>
<td></td>
<td>• Refer to cardiology</td>
</tr>
<tr>
<td></td>
<td>• Stop trastuzumab</td>
</tr>
<tr>
<td></td>
<td>• Repeat assessment in 6 weeks if &gt; LLN commence trastuzumab after weighing up risk vs benefit</td>
</tr>
</tbody>
</table>
Starting ACEi and Beta blockers

- Start an ACEi first followed by a Beta blocker a few days after
- Start both at the lowest doses possible then titrate up to target doses (see box)
- Double doses at not less than two weekly intervals

Guidelines on initiation of ACEi treatment

- High risk patients need very close monitoring – these include patients with:
  - Severe heart failure - eg on high dose diuretic therapy which cannot be discontinued, or large doses of vasodilators
  - dehydration
  - hypotension (systolic BP less than 90 mmHg)
  - substantial renal impairment (eg creatinine over 300 micromol/l)

- Monitoring of U&Es is recommended as table:

<table>
<thead>
<tr>
<th>Week</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No monitoring</td>
<td>Check blood and BP at 4 days</td>
</tr>
<tr>
<td>2</td>
<td>Check blood and BP between 7-10 days</td>
<td>Check blood and BP at 10 days</td>
</tr>
<tr>
<td>3</td>
<td>Increase dose if required</td>
<td>Increase dose if required</td>
</tr>
<tr>
<td>4</td>
<td>Check bloods when at full dose of ACEi</td>
<td>Check blood if dose of ACEi increased</td>
</tr>
</tbody>
</table>

Guidelines on initiation of Beta Blocker treatment

- Start 48 hours following ACEi if patient has tolerated the ACEi – if ACEi not initially well tolerated wait 1 week then commence Beta blocker
- Caution using in asthma, patients with heart rate <60 and systolic BP <90, patients with heart block
- Stop diltiazem/verapamil if patient already taking
- Monitor HR, BP
- Check blood biochemistry 1-2 weeks after initiation and 1-2 weeks after final dose titration
- If patient develops fatigue or marked bradycardia <50 beats per min then halve beta blocker

References


This document has been developed and agreed by members of the Lancashire & South Cumbria Breast NSSG (part of the North West Coast SCN).

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