Manchester Cancer
Breast Pathway Board

BREAST ONCOLOGY GUIDELINES

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1. AIMS OF MANAGEMENT AND PROTOCOL GUIDELINES

- To provide a simple reference manual for the management of breast cancer in the Greater Manchester & Cheshire Network.
- To update the manual as new information becomes available. To this end sections are separated according to subject and can be exchanged easily.
- To provide an up to date list of protocols together with outline information
- To identify good practice guidelines in accordance with *NHS Improving Outcomes in Breast Cancer* and NICE guidance on *Improving Supportive and Palliative Care for Adults with Cancer.*

1.1 GUIDELINES FOR GOOD PRACTICE

1.1.1 Patient-Centred Care

- Acknowledgement that patients want to be treated with dignity and respect, and may want choice in making decisions about their treatment and care.
- That patients should be given the name and contact details of a nurse they may access for communication and support.

1.1.2 Information

- Patients should receive clear, timely information, both verbal and written in keeping with their individual needs.
- Information is given regarding disease, diagnostic procedures, treatment options, effectiveness and side effects.
- Complementary and health professionals respond to patients' desire for timing and amount of information.
- Patients have access to verbal and written information regarding support and practical help i.e. benefits, local support groups and complimentary therapies.

1.1.3 Communication

- Special communication training is required for all health care professionals providing direct care.

- Provision of suitable interpreters for patients whose preferred language is not English.
- Acknowledgement of difficult communication situations and adherence to Breaking Bad News Policy (See Christie Professional website).
- Accurate documentation of key points of consultations in patients notes and swift communication of any treatment changes to all other professionals involved in care.

1.1.4 Supportive and Palliative care

- Access to information about their disease, aspect of management, available services and how to access them. This may for example include local and national patient support networks
- Advice on the practical and financial help
- Emotional and spiritual support, with specialist help for those with difficulties in adjustment and coping.
- An active rehabilitative approach to maximise functional recovery and adaptation to consequences of cancer and its treatment, including information on the effects of the treatments on physical, emotional and sexual functioning.
- A meticulous approach to the relief of pain and other symptoms at any stage. This should lead to early referral to specialist services if management of problems should prove difficult.

2. BASELINE INFORMATION

2.1 Early Breast Cancer

- Histology and grade of the tumour
- Margins, if wide local excision is performed (shavings are advisable in order to determine completeness of excision).
- Oestrogen and progesterone and HER 2 receptor testing are mandatory for all patients where endocrine therapy or herceptin may potentially play a part in their management. Ki67 and EGFR status can also be helpful.
- Nodal status.
- Full blood count and biochemical profile.
- Bone scan (or CT scan with bone windows) and CT scan Thorax/Abdomen should be considered in patients at high risk of disseminated disease (N2 and N3).

2.2 Locally Advanced Disease

- Histology and grade of the tumour
- Oestrogen and progesterone receptor and HER 2 status
- Full blood count and biochemical profile.
- CT Thorax/Abdomen and bone scan to exclude systemic disease are mandatory before local treatment is planned.

2.3 Metastatic Disease

- Histology, desirable if an easily accessible site can be biopsied.
- Oestrogen, progesterone and HER 2 receptors on the biopsy or primary tumour. N.B. The receptor status of the metastatic disease may differ from the primary.
- FBC, profile
- Bone scan
- CT thorax and upper abdomen
- X-rays of long bones if hot spots on the bone scan.

3. SURGERY

3.1 Aims

- Appropriate operation for each patient
- Excellent local control
- Obtain full prognostic information in order to plan systemic treatment.
  Excellent cosmesis (within technical limits)

3.2 Breast conserving surgery (BCS)

- Numerous randomised clinical trials have demonstrated no differences in overall survival in women with operable breast cancer treated with mastectomy compared to those treated with BCS followed by adjuvant radiotherapy [Fisher 1989, Veronesi 1990, Jacobson 1995, Blichert-Toft 1990]
- The aim of BCS is removal of the primary tumour with clear histological margins whilst preserving the breast shape. It is recommended that the margins of excision are examined by the pathologist following "inking" of the specimen and that the specimen is orientated to ensure that the appropriate margin can be identified (if one is involved).
- For screen detected, impalpable lesions (i.e. surgical excision is radiologically guided) it is mandatory to perform a specimen X-ray intraoperatively (NHS Breast Screening Programme recommendation). Due to the recognised difficulty of assessing excision margins, it may be helpful to perform cavity biopsy shavings to assess excision status. Where clear excision margins cannot be achieved, re-excision or mastectomy should be performed as advised by the MDT.
- The size of the tumour that can be excised with adequate cosmesis depends on breast size. For example a 2cm tumour in a small breast may not be suitable for BCS. Conversely, a 4cm tumour in a lady with large breasts may be suitable for a therapeutic mammoplasty. Patients opting for this latter type of surgery should be warned that if the tumour margins are involved then a completion mastectomy may be required.

- Patients with a large tumour but wishing breast conservation may be offered preoperative systemic therapy (see section 5).
- The use of titanium surgical clips to localise the tumour bed facilitates tumour bed boost planning and partial breast radiotherapy. Clips should be positioned at the medial, lateral, superior, inferior cavity edges at the time of surgery.

3.3 Contraindications to breast conserving surgery (BCS)

- Multicentric disease (affecting > 1 quadrant)
- Incomplete wide local excision despite two attempts at breast conserving surgery
- Extensive in-situ component
- Breast cancer recurrence after previous irradiation.
- Pregnancy (1st or 2nd trimester) – relative contraindication to adjuvant radiotherapy
- Patient preference for mastectomy or where patient is unwilling to undergo radiotherapy
- Active scleroderma or active SLE -relative contraindication to adjuvant radiotherapy (discuss urgently with Clinical Oncologist)
- In certain circumstances patients with extensive co-morbidities, may not be offered radiotherapy. Such patients should be discussed with the Clinical Oncologists at the pre-op MDT.

Consideration should also be given to patients where radiotherapy may be technically difficult e.g. limited shoulder movement or cardiac pacemaker in situ.

3.4 Reconstructive surgery

Breast reconstruction can be performed as an immediate procedure at the same time as mastectomy or as a delayed procedure anytime afterwards. The aim is to produce symmetry that satisfies the patients' wishes within the limits of technical feasibility.

Oncological principles are not compromised. Breast reconstruction is often not a single operation to completion; further minor operations will be required which can include nipple and areola complex reconstruction.

Immediate reconstruction may not suitable for the following groups as many of these patients may also require post-operative radiotherapy.

- Patients with primary tumours >4cm
- Node positive tumours (esp if grade 3)
- Locally advanced disease
- Inflammatory cancers (absolute contraindication)
- Large cancers down-staged by neo-adjuvant chemotherapy
- Where there is clear pre-operative evidence of extensive lymphatic/lymphovascular space invasion
- In the presence of severe co-morbidity

Radiotherapy following breast reconstruction may be associated with increased complications including impaired cosmetic outcome, especially when an expander/implant is used. Autologous reconstructions tend to tolerate radiotherapy better.

Patients considering breast reconstruction should have the techniques, limitations, complications and outcomes fully explained by the surgeon. Patients should meet the specialist breast care nurse and be shown photographs of different outcomes to help them make their choices. The potential risk of delaying subsequent adjuvant treatment should be explained to ensure informed consent. All patients undergoing breast reconstruction should have pre-operative and post-operative photographs for the medical records and for medico-legal reasons.

For women where there are local issues in providing breast reconstruction there should be arrangements made by that trust to refer to the most appropriate unit in a timely manner especially when immediate reconstruction is required. Women keen on using abdominal wall tissue for reconstruction can be referred directly to South Manchester for consideration of a free flap e.g. DIEP (deep inferior epigastric perforator).

3.5 Skin-sparing Mastectomy

Skin-sparing mastectomy (SSM) techniques with immediate breast reconstruction can deliver superior cosmetic results. The published literature report equivalent local recurrence rates to those of conventional mastectomy (CM). Most patients in these studies had smaller tumours and the concern is whether patients with larger/higher risk tumours may have a higher local recurrence rate with SSM than CM.

The following should exclude patients from being considered for SSM:

- Primary tumour > 4cm
- Node positive tumours (especially if Grade 3)
- Locally advanced disease
- Inflammatory cancers (absolute contraindication)
- Clear pre-operative evidence of extensive lymphatic/lymphovascular invasion
- Large tumours that are down-staged by neo-adjuvant chemotherapy or endocrine therapy. These should be discussed at the MDT to determine possible adjuvant radiotherapy use (which will affect decisions regarding SSM and reconstruction).
- The presence of severe co-morbidity

The use of SSM in patients at higher risk of local recurrence should be discussed on an individual case basis at the MDT.

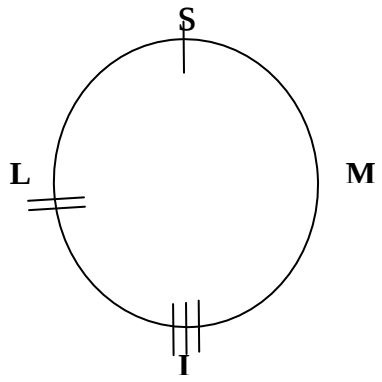
3.6 Impalpable lesions

Ultrasound guided surgery, needle localisation surgery or other techniques such as ROLL (radio-guided occult lesion localisation) can be used to localise impalpable lesions. Intraoperatively the specimen should be radiographed in two perpendicular planes for a radiological assessment of the completeness of excision. A comment on the completeness of excision based on the intraoperative image must be made in the operation note by the surgeon. If the biopsy is undertaken for macrocalcification a comment must be made in the operation note relating to the presence of microcalcification in the X-ray image of the excision specimen. In all cases the specimen must be orientated prior to radiology and pathology assessment - e.g. by

metal clips as shown below (SLIM orientation of right breast lesion). Cavity shavings can be taken from around the adjacent breast tissue in order to confirm an adequate margin of clearance. The shaving may have a ligaclip placed on the biopsy cavity surface to allow the pathologist to orientate the shaving itself.

The operation note should record the specimen weight.

Example



Superior	1 clip
Lateral	2 clips
Inferior	3 clips
Medial	

3.7 Management of ductal carcinoma in situ (DCIS)

- Surgery aims to produce complete excision. If a biopsy is reported as incompletely excised (<1mm circumferential margin), then further wide excision must be offered. Complete excision with clear margins (>1mm and clear cavity shavings) is associated with a low recurrence rate. Radiotherapy is not a substitute for adequate surgical clearance.
- Completeness of excision will depend to some extent on whether the DCIS is unicentric or multicentric. If it is unicentric (<4cm), then the woman may be suitable for BCS. Patients with multicentric disease have widespread field changes in the breast and should be offered a total mastectomy (see below for axillary surgery in these patients). For some individual patients, breast size may allow consideration of oncoplastic breast conserving surgery for tumours greater than 40mm. These cases should be discussed at MDT preoperatively.

- Re-excision is required if only one margin is involved but if several margins are involved, mastectomy should be considered.
- If conservation surgery is successful, the patient has yearly mammograms for the first 5 years to provide early detection of any recurrence.

Patients who are undergoing mastectomy for DCIS should be offered the option of immediate reconstruction.

3.7.1 Sentinel Node Biopsy for DCIS

By definition all axillary nodes should be negative in patients with DCIS and therefore sentinel node biopsy is not necessary. However, in certain circumstances sentinel node biopsy should be considered. These are presented below and such patients should be discussed at MDT level.

1. DCIS > 5cm - 50% of these patients will harbour invasive disease within the area of DCIS
2. DCIS presenting as a mass lesion (either a clinical mass or a radiological mass lesion) should be subject to core biopsy or vacuum assisted biopsy to thoroughly ensure that there are no areas of invasion. If, after thorough biopsies, the diagnosis remains B5a for a mass lesion the MDT may wish to consider a sentinel node biopsy for such patients.
3. DCIS of high grade in premenopausal patients. These patients should be thoroughly assessed as above to ensure, as much as possible, that there are no areas of invasion. If the diagnosis remains B5a the MDT may consider sentinel node biopsy.
4. DCIS of high grade in premenopausal patients
5. Where mastectomy is being performed for DCIS, a sentinel node biopsy is indicated as this may be the only chance to perform this operation which would be required should the mastectomy specimen harbour unexpected invasive disease. In these patients no more than 1 or 2 SLN should be removed.

3.7.2 Adjuvant endocrine therapy for DCIS

- The NSABP B24 trial has indicated additional benefits for Tamoxifen after BCS and XRT, reducing the risk of within-breast recurrence by 60% in patients with ER +ve DCIS, with the greatest benefits seen in women under 50 years of age [Fisher 1999]. In the UKCCR DCIS trial 12 year update the benefit of Tamoxifen was smaller, although ER status was not studied in this trial.

- Patients with ER +ve DCIS and features indicating high risk of recurrence (eg. high grade, young age, extensive disease) may be considered.

3.8 Surgical management of the axilla

- The intention of axillary surgery is to provide control of disease within the axilla and to provide prognostic information for the patient which may be of importance in planning subsequent treatment. Axillary lymph node status remains the most powerful prognostic indicator for early breast cancer.
- Axillary surgery is indicated for all patients with invasive breast cancer, but is not routinely indicated for patients with pure DCIS unless a mastectomy is being performed (see above).
- There are two principle surgical approaches:
    - **Sentinel node biopsy** in which the sentinel node is identified and excised. It is not appropriate if palpable axillary nodes are present.
    - **Level III axillary node clearance (ANC)** in which all lymph nodes up to the apex of the axilla are removed.

3.8.1 Sentinel node biopsy

- This technique should be considered for patients in whom there is no palpable axillary lymphadenopathy.

- The axilla should be assessed using a " triple assessment" approach i.e. clinical examination followed by ultrasound scan and FNA/core biopsy of nodes with an abnormal appearance on ultrasonic assessment. Following such an assessment those patients with cytologically proven axillary node metastases should proceed directly to level 3 ANC. Those patients with no palpable axillary nodes and normal ultrasound appearances of the axillary node architecture can proceed to sentinel lymph node biopsy.

- Both radioisotope and blue dye localisation should be performed. Patients need to be informed of the very rare but potentially serious side effect of anaphylaxis. If the sentinel node biopsy is positive, either axillary radiotherapy or ANC will be necessary.

3.8.1.1 SLNBx & the Significance of Metastases

Macrometastases (tumour deposits>2mm) in 1 or 2 sentinel nodes

a) Tumour size < 50mm radiologically

multifocality is not an exclusion to this protocol - take size of largest focus

extracapsular spread is not a contra-indication to entry into POSNOC

ER negative or any ER *and* HER2 positive tumours

consider entry into POSNOC
if chemotherapy indicated, MDT to consider adjuvant chemotherapy prior to further surgery, then
- proceed to POSNOC outcome
- completion ANC if patient not in POSNOC

ER positive tumours

consider entry into POSNOC
if patient declines POSNOC completion ANC is indicated

b) Tumour size > 50mm radiologically

Patient is recommended to undergo ANC

ER negative or any ER *and* HER2 positive tumours

consider chemotherapy then completion clearance

ER positive patients

consider completion clearance and then MDT discussion re chemotherapy or not

Macrometastases (tumour deposits>2mm) in 3 or more sentinel nodes

patient advised to undergo ANC

ER negative or any ER *and* HER2 positive tumours

consider chemotherapy then completion clearance

ER positive patients

consider completion clearance and then MDT discussion re chemotherapy or not

Micrometastases (tumour deposits >0.2mm - 2mm) or isolated tumour cells

The American Z0011 study showed no negative effect of the presence of micrometastases on overall survival in the same group of patients.

Patients should *not* undergo further axillary surgery.

Preoperative diagnosis of sentinel node involvement

Core biopsy shows:

macrometastases	-recommend ANC
micrometastases	-discuss at MDT whether patient should proceed to sentinel node biopsy or ANC

FNA shows malignant cells: - recommend to ANC

3.8.1.2 SLNBx and Neoadjuvant chemotherapy

SNB after neo-adjuvant chemotherapy should not be performed unless the patient has had a complete clinical and radiological response in the breast. Each case should be discussed at the MDT. Results from the ACOSOG Z1071 trial suggest that the false negative rate is higher for cases which were clinically node positive at presentation and 2 or fewer sentinel nodes are removed (Boughey 2013). Similar results have been found in the SENTINA trial (Kuehn 2013). A recent meta-analysis has shown a large variation in false negative rates (Fu 2014) and the most recent

ASCO guidelines urge caution in the use of sentinel node biopsy following neoadjuvant chemotherapy (Lyman 2014).

3.8.1.3 SLNBx and Pregnancy

The use of blue dye is contraindicated in pregnancy. The use of radio-labelled colloid appears to be safe. However there is limited evidence of the use of SLNBx in pregnancy-associated cancers. The current thinking is that SLNBx should not be performed prior to 30 weeks gestation [Filippakis 2007, Pandit-Taskar 2006, Carlson 2011]. After this time, each case should be discussed individually at the MDT.

3.8.1.4 SLNBx and Previous surgery

Previous surgery to the breast does not alter the success or the accuracy of SLNBx [Luini 2005, Haigh 2000]. SLNBx after previous axillary surgery is more controversial and cannot be recommended. However, individual circumstances may permit such an option following discussion at the MDT [Port 2002, Intra 2005]

3.8.1.5 SLNBx and Mulitfocal/multicentric cancers

Although there are conflicting reports, on the whole the data supports SLNBx in patients with more than one focus of caner within the same breast. Therefore these patients should be offered SLNBx in line with other guidelines [Gentilini 2011, Giard 2010, Lyman 2005].

3.8.2 Axillary Clearance

The extent of axillary dissection is defined with reference to the pectoralis minor muscle:

- Level I - lower axilla up to the lower lateral border of the pectoralis minor.
- Level II - axillary contents up to the medial border of the pectoralis minor.
- Level III - axillary contents extending to the apex of the axilla.

Level III ANC is relatively indicated for the following patients and should be discussed at MDT level on a case by case basis

- patients with previous axillary surgery and current ipsilateral breast cancer diagnosis
- patients with inflammatory breast cancer
- patients receiving neoadjuvant chemotherapy for large/locally advanced breast cancer
- patients wishing to completely eliminate the possible need for a second axillary operation if a sentinel node procedure yields a positive node (could have axillary irradiation).

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4. SPECIAL CLINCAL SITUATIONS

There are a number of special situations encountered in patients with breast cancer that need individualised management.

4.1 Lymphoedema

Lymphoedema may develop as a result of metastatic disease in the axilla or as treatment related either from surgery or radiotherapy. Disease may not be palpable in the axilla and MR imaging can provide useful information as the most likely cause of lymphoedema. When lymphoedema is disease related the use of radiotherapy or drug therapy should be considered. Patients who develop lymphoedema should be referred to the lymphoedema specialist for appropriate management which may involve massage, exercises, simple lymphatic drainage or manual lymph drainage, support/compression with graduated compression hosiery or multi-layer bandaging, and skin care. All women undergoing axillary node clearance should have their arm circumference measured with a tape or perometer at 4 cm intervals, prior to surgery, in line with national guidelines

The Christie Lymphoedema Service accepts Christie Hospital Patients with lymphoedema as a result of Cancer and its treatment. However, as lymphoedema is a condition that requires long-term management, whenever possible patients are referred to the service closest to their home. (see also section 11)

4.2 Brachial plexus neuropathy

Radiation induced brachial plexus neuropathy is seen here only extremely rarely, as result of the radiotherapy techniques the Christie uses. The RAGE group was formed in the 1990' s by patients suffering injury following treatment at some other units and there is a specific RCR report and guidance on this. Patients with brachial plexus damage may be referred to the Breast Radiotherapy Injury Rehabilitation Service at the Christie. This is a multi-disciplinary clinic with a pain specialist, lymphoedema

practitioner, occupational therapist, physiotherapist, oncologist rheumatologist and respiratory physician.

Whatever the aetiology, affected patients usually have difficult neuropathic pain, progressive loss of function and may also develop lymphoedema. Consider referral to the local pain clinic or specialist palliative care (the latter may prove easier to access) for advice with pain management. Hospices often provide lymphoedema care also. Occupational therapy assessment should be requested as early as possible for consideration of splints, practical advice and aids to help adaptation to disability.

4.3 Pregnancy associated breast cancer

- Patients who present in the first trimester of pregnancy should be considered for therapeutic termination since radiotherapy and the majority of cytotoxic drugs are potentially damaging to the foetus.

- Patients presenting later in pregnancy should be treated by means of mastectomy and delivered as early as considered feasible by the Obstetrician (usually 32-34 weeks).

- The use of chemotherapy during the 2nd and 3rd trimester has been shown in small studies to be relatively safe to both the mother and the foetus [Ring 2005, Giacalone 1999, Berry 1999]. However, long-term effects on the unborn child are not yet known and its use should be approached with caution.

- Chemotherapy can usually be safely commenced around 2 weeks following delivery as long as there are no post-operative wound complications.

- Patients should be advised not to breast-feed while on chemotherapy.

- Thereafter the patient should be treated in the same manner as a non-pregnant patient. High risk patients are advised not to become pregnant

for at least 2 years after completing treatment, as this is the time of highest risk of recurrence. Population-based studies have shown that pregnancy following a diagnosis of breast cancer is not detrimental to survival [Velentgas 1999, Sankila 1994].

4.4 Female fertility preservation

Adjuvant chemotherapy in pre-menopausal women risks premature ovarian failure and infertility. Women who are under 40 at the time of their diagnosis and who have not yet completed their family are entitled to a referral to the GMCCN female fertility service to discuss fertility options which include ovarian stimulation and embryo storage prior to adjuvant chemotherapy. Such women should be referred to the fertility service **at the time of their diagnosis in order to allow sufficient time for fertility preservation techniques** even if the need for adjuvant chemotherapy is uncertain at the time.

Whilst all premenopausal women are entitled to have the option of discussing fertility issues and options, fertility treatment will only be funded within current NHS guidelines, for example, women under 40 years. Women older than 40 years may still be referred for a consultation, however, if they decide to pursue fertility preservation options, private care will be recommended.

To refer a patient for a consultation, please download and complete **' URGENT REFERRAL FOR FERTILITY CONSULTATION' form** from the Greater Manchester and Cheshire Cancer Network website and fax directly to Dr Cheryl Fitzgerald on 0161 224 0957. Patients will be contacted within an appointment and seen within 7 working days.

Women with concerns about fertility preservation may also be referred for a consultation to one of two breast oncologists to discuss the oncological aspects of fertility preservation. For patients in North Manchester area: Dr Juliette Loncaster. For patients in South Manchester area: Dr Anne Armstrong. The referral can be for consultation only or for breast cancer treatment and ongoing care, and should be sent off at the same time as the referral to St.Marys, at the time of diagnosis.

Adjuvant rather than neoadjuvant chemotherapy may be more appropriate for many women who are concerned about fertility preservation.

4.5 Menopausal symptoms

Breast cancer treatments are known to both induce and exacerbate menopausal symptoms (Anderson, 2011), resulting in significant related morbidities, regardless of age. Reasons for this include iatrogenic ablation of ovarian function with chemotherapy or with the use of Luteinising Hormone Releasing Hormone (LHRH), oopherectomy as a prophylactic treatment option for BRCA patients, endocrine treatments or as a consequence of stopping HRT abruptly when diagnosed with breast cancer (Blaes et al, 2011). Women already postmenopausal at diagnosis are also more likely to develop further menopausal symptoms as a result of treatment and symptoms are more likely to be intense (Carpenter et al, 1998) and experienced for prolonged periods (Harris et al, 2002). Hot flushes and night sweats are the most commonly reported vasomotor symptoms (Dinnerstein et al, 2000) and can exert a profound effect on quality of life (Savard et al, 2001).

4.5.1 Treatments options

The European Menopause Association advocate a personalised approach according to individual needs (Neves-e-Castro et al, 2015). Women with a history of breast cancer are likely to benefit from maintaining a healthy weight, being physically active, limiting alcohol consumption and stopping smoking are some of the lifestyle interventions which may also impact on vasomotor symptoms. Patients often request advice regarding complementary medicine and alternative therapies including the use of sage, evening primrose and vitamin E although research evidence does not demonstrate a consistent benefit with their use in comparison to placebo (for a comprehensive review see Borrelli, F. and Ernst, E, 2010). Some studies have shown benefit over control procedures for acupuncture for the relief of hot flushes, although a recent systematic review failed to find sufficient evidence to either support or refute its use for this indication (Garcia et al, 2015). Small studies have shown a benefit for cognitive behavioural therapy (Chilcot et al, 2014).

Prescribed medications which may be considered include clonidine, gabapentin, paroxetine and venlaflaxine, which are all endorsed and recommended by EMAS and NAMS. Clonidine has been found in a systematic review and meta-analysis to show a significant benefit over placebo (Nelson et al, 2006). However, this drug can enhance the effects of antihypertensives, anxiolytics and alcohol.

Gabapentin has shown some activity as a treatment for menopausal hot flushes. In placebo controlled trials followed by a meta- analysis confirm that, compared to placebo, gabapentin reduced the frequency and severity of hot flushes by 20-30% (Toulis et al, 2009), comparable to improvements seen with SSRI' s and SNRI' s.

4.5.2 Interactions between SSRIs and Tamoxifen

The cytochrome P450 enzyme, CYP2D6 is the rate-limiting step in the conversion of tamoxifen to its most active metabolite, endoxifen. In some retrospective studies, drugs that are known to inhibit the enzyme activity of CYP2D6, such as the antidepressants fluoxetine and paroxetine, had been shown to result in an increase in the relapse rate in patients on adjuvant tamoxifen. However, retrospective analysis of large scale randomised phase III trials (ATC and BIG 1-98) did not substantiate these findings. The co-prescription of such drugs is no longer felt to be contraindicated, so any patient who is already established on fluoxetine or paroxetine should not have their antidepressant medication changed when they commence tamoxifen.

4.5.3 Urogenital Symptoms

Urogenital symptoms due to oestrogen deprivation are a common consequence of systemic therapy for breast cancer. Symptoms can include vaginal dryness and dyspareunia and result from thinning of the epithelial cells of the vulvovaginal area.

Cigarette smoking may accelerate vaginal atrophy and smoking cessation should be advised. Scented hygiene products should be avoided.

A wide range of vaginal moisturisers are available including Replens, Sylk and Yes. Few studies have investigated the safety or otherwise of topical oestrogens as

treatment for urogenital atrophy in women with a history of breast cancer, but these preparations should be used with caution in women treated with AI' s.

4.5.4 HRT

The use of HRT after a breast cancer diagnosis is not recommended as there is no evidence from randomised controlled trials that this is safe. Oestrogen based HRT is reserved for patients with very severe symptoms despite use of other remedies. In these situations the patient must be counselled as to the potential safety concerns. It is reassuring if the primary tumour is both oestrogen and progesterone receptor negative.

4.6 Male breast cancer

Less than 1% of breast cancer occurs in men, usually in the 6th or 7th decade. Presentation is with a mass usually below the areola but there is often fixation to the underlying muscle. Following histological or cytological confirmation treatment is normally by mastectomy and axillary surgery. Post-operative radiotherapy to the chest wall is often needed as many of these tumours will involve the muscle and skin. Adjuvant Tamoxifen is also recommended. The prognosis is the same as for age and stage matched female patients.

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5. ADJUVANT RADIOTHERAPY

Radiotherapy is used in a number of situations in the management of breast cancer

1. Adjuvant radiotherapy after surgery for early breast cancer (see below)
2. Combined with systemic therapy and surgery for treatment of locally advanced cancer, including inflammatory breast cancer
3. Treatment for loco-regional recurrence
4. In combination with systemic therapy for the treatment of metastatic disease

(For details of 2, 3 and 4 see the relevant section in these guidelines)

Following breast conserving surgery the patient's risk of local recurrence should be assessed.

The majority will be referred for standard whole breast radiotherapy (section 1). Selected patients at low risk of recurrence may benefit from partial breast radiotherapy (section 2) or follow up only with hormone treatment (section 3). Careful selection will allow patients to be treated with a low risk of cancer recurrence and minimise morbidity from treatment.

5.1 Radiotherapy following breast conserving surgery for invasive breast cancer

In selected patients, whole breast radiotherapy following breast conserving surgery gives equivalent survival and control of local disease to mastectomy [Fisher 2002, Veronesi 2002].

A systematic overview by the Early Breast Cancer Collaborative Group has shown that adjuvant radiotherapy reduces 5 year local recurrence rates from 26% to 7% and reduces 15 year breast cancer mortality from 35.9% to 30.5%. [EBCTCG 2011].

In a series of 2299 patients treated at the Christie between 1989 and 1992, the breast local relapse rate was 6.3 % at 5 years [McBain 2003]. Approximately 50% of these

recurrent patients were salvaged by subsequent surgery, usually a mastectomy. For NHSBSP screen detected cancers the breast recurrence rate was only 4 %.

The 10 year results from the START trial show a 4-5% breast relapse rate at 10 years [Haviland JS. START Trialists' Group, 2013]

The patient must wish to preserve her breast; she must be medically fit enough, and willing to undertake a course of radiotherapy.

5.1.1 Partial breast external beam radiotherapy

The use of partial breast radiotherapy delivered using intensity modulated techniques following complete tumour excision in women with low risk early stage breast cancer has recently been evaluated in the UK IMPORT LOW trial, and the results are awaited. Criteria have been published to define patients where partial breast radiotherapy can be considered [Smith, 2009]

External beam techniques for partial breast radiotherapy give an increased safety margin compared to intra-operative methods. Pending the results of randomised trials using external beam treatments, partial breast radiotherapy could be considered for patients who fit the criteria outlined by the IMPORT LOW trial:

- > 50 years
- Tumour size $\leq$ 3.0 cm
- Node negative
- Invasive adenocarcinoma [excluding lobular] unifocal disease, microscopic margins $\geq$ 2 mm
- Tumour bed is easily identifiable with surgical clips or a seroma visible on CT scan.

It is useful to consider for patients with very large breasts and a small primary cancer to reduce radiation morbidity.

5.1.2 Intra-operative Radiotherapy (IORT)

A randomised trial of intra-operative radiotherapy (Targit-A) has shown local recurrence rates of 3.3% at 5 yrs compared to 1.3% for external beam whole breast

radiotherapy, p=0.042. [Vaidya 2013]. Additional external beam radiotherapy was necessary in 15% of patients because of unexpected pathology results.

Very careful selection is advised as this treatment approach is decided on pre-operatively. The decision must be made in consultation with a clinical oncologist.

If IORT methods become available the following patients could be considered for this approach:

- > 60 years
- Screen-detected
- ≤15mm
- G1 or 2
- ER positive
- Node negative on US

5.1.3 Selective avoidance of radiotherapy following breast conserving surgery

A group of patients can be identified where the risk of local recurrence without XRT is low. One trial in patients over 70, T1 N0 ER positive, has reported a 9% relapse rate with surgery and tamoxifen versus 2% with surgery, tamoxifen and radiotherapy [Hughes 2010]. Survival was identical. The UK PRIME II study has given similar results in good risk patients over age 65: 1.3% vs 4.1% breast recurrence at 5 years, with a 96.4% and 97% overall survival in respectively. (Kunkler 2013). Giving XRT for such low risk patients will benefit a minority, but clearly gives inconvenience, discomfort and a small risk of serious morbidity to the majority. Omitting XRT will not prejudice the patient's chance of survival. Careful follow-up will allow most recurrences to be detected early and further breast-conserving surgery to be used at the time of relapse.

Avoiding radiotherapy after breast conserving surgery is an option which can be considered in certain selected patients, in consultation with a clinical oncologist.

- Age 70 or over
- G1 or 2 IDC
- ER-positive and to receive adjuvant endocrine therapy
- Path node negative

- Tumour size ≤ 15mm
- Clear margins

5.2 Radiotherapy following mastectomy

A systematic overview has shown that post-mastectomy radiotherapy reduces 10 year local recurrence rates from 26% to 8% in node positive women and breast cancer mortality from 54% to 48%. [EBCTCG 2014].

Radiotherapy to the chest wall is advised after mastectomy when there is a high risk of local recurrence.

- Large primary tumours > 5 cm.
- Tumours incompletely excised e.g. tumour at the deep resection margin, or invading muscle or skin.
- N2 and N3 disease.
- Chest wall irradiation may be considered for some patients who do not fulfil the above criteria but where there is a combination of adverse histological features e.g. Grade 3 invasive ductal carcinoma, extensive lymphovascular invasion, involved margins or N1 disease. (Cambridge post-mastectomy index, Mukesh 2014)

- SUPREMO trial. The SUPREMO trial was designed to evaluate the benefit of post-mastectomy chest wall radiotherapy in patients who have an intermediate local recurrence risk, and do not fulfil the criteria above. These include patients with 1-3 involved axillary nodes or grade 3 tumours. The study closed in 2013 and the results are awaited.

5.3 Indications for nodal radiotherapy

5.3.1 Radiotherapy to the supraclavicular fossa

- N2 disease following axillary node clearance

5.3.2 Radiotherapy to include the axilla and supraclavicular fossa en bloc

- Inoperable axillary disease.

- Positive sentinel biopsy (although an axillary node clearance is usually performed)

- N3 disease following axillary node clearance, especially where there is extensive extra-capsular spread. Note of caution: Axillary nodal radiotherapy after a level III axillary dissection increases the risk of arm oedema from less than 10% to 30-40%; this has to be balanced against the risk of uncontrolled axillary recurrence. The patient should be so advised and consent sought.

In cases where nodal irradiation is indicated it is usual practice to also irradiate the chest wall.

5.3.3 Radiotherapy to Internal Mammary Nodes

- Sentinel lymph nodes studies indicate that only a very small proportion of patients have sentinel nodes in the IMN chain.

- Clinical recurrence in the IMN chain is relatively rare, even without IMN radiation.

- Randomised trials have shown some benefits from regional nodal irradiation, including the IMN chain, but it is difficult to assess the specific contribution of IMN irradiation. (Poortmans et al 2015, Whelan et al 2015, Budach et al 2013).

- Long term toxicity data (e.g. cardiovascular effects) are required in the setting of modern radiotherapy techniques and adjuvant systemic therapies.

- Routine RNI to include the internal mammary chain along with ipsilateral axilla and SCF is currently not considered the standard of care for patients as it is uncertain if the improved DFS was due to irradiation of the Axilla/SCF or the IM chain and the uncertainty of the long term effects of such irradiation as well as lack of international consensus.

- If internal mammary nodes are known to be positive (e.g. after sentinel node biopsy) an individualised CT planned treatment to include the IMN chain is advised

5.4 Adjuvant radiotherapy for DCIS

- Whole breast radiotherapy reduces the risk of ipsilateral breast relapse after complete excision of DCIS. Randomised trials indicate adjuvant radiotherapy approximately halves the risk of recurrent DCIS and invasive disease [EBCTCG 2010].

- Radiotherapy should be considered in all patients at an increased risk of recurrence and this essentially constitutes all women with > 10 mm high-grade DCIS or > 20mm intermediate grade DCIS. Radiotherapy may also be considered for smaller tumours with other risk factors for recurrence such as young age, close margins and presence of comedo necrosis [Silverstein 2010].

- In practice radiotherapy is often omitted in patients considered at low risk of recurrence (see www.sloaneproject.co.uk)

- Normally adjuvant radiotherapy is not required for women who have undergone mastectomy for DCIS.

5.5 Radiotherapy techniques

5.5.1 Whole breast radiotherapy after breast conserving surgery.

- A megavoltage tangential pair of fields is used to encompass the breast. Skin bolus is not used routinely. The field arrangement is imaged by CT scanning and electronic portal imaging to ensure that the maximum depth of lung being irradiated does not exceed 2 cm, and the cardiac apex is excluded in the majority of patients. IMRT planning is used as it improves dose homogeneity and facilitates cardiac shielding when needed.

- A mid-plane dose of 40 Gy in 15 fractions over 3 weeks is used.

- Occasionally shorter course regimens may be used, particularly in patients with poor performance status and significant co-morbidities. 30 Gy in 8/10 daily fractions or 30Gy in 5 weekly fractions.

5.5.2 Tumour bed boost

Boost radiotherapy to the tumour bed has been demonstrated to reduce local recurrence rates following breast-conserving surgery. The greatest benefit is seen in patients under 40 years of age and a moderate benefit is seen in women between 40 and 50 years of age. Less benefit is seen in women over 50 years of age [Bartelink 2001]. In view of these findings we recommend that boosts are given at least to the following groups:

- Women under 40 years of age
- Women between 40 and 50 years of age who are at high risk of local recurrence (grade III, extensive lymphovascular invasion)
- Women of any age with involved surgical margins (< 1 mm)

The boost is planned using information from the pathology report, surgical notes, pre-op mammograms, the presence of surgical clips in the tumour bed, and surgical changes e.g. post seroma, visible on the radiotherapy planning scan.

5.5.3 Radiotherapy after mastectomy.

- Chest wall irradiation is undertaken using a tangential pair of photon fields designed to treat the chest wall thickness, minimising lung and heart irradiation.
- There is no evidence that the use of bolus reduces the risk of chest wall recurrence (Graham 2011), although bolus should be considered when there has been tumour involvement of the skin.
- A prescribed dose of 40 Gy in 15 fractions in 3 weeks is used.

5.5.4 Regional nodal radiotherapy.

- A supraclavicular fossa field, with lateral margins just medial to the glenoid cavity, and medial margins at the midline, may be used if axillary irradiation is not required, particularly after a full level 3 clearance, as this is associated with a lower incidence of lymphoedema. Indications would include involvement of 4 or more axillary nodes after a level 3 clearance.
- Irradiation of a target volume including the full axilla and supraclavicular fossa en bloc may be indicated (a) after a positive axillary sampling procedure, (b)

where there is inoperable axillary disease, or (c) in cases where there is very heavy axillary nodal involvement following a level 3 axillary clearance (e.g. > 10 positive nodes and/or extensive extracapsular spread). Radiotherapy to the supraclavicular fossa and axilla may be considered, if the risks of axillary recurrence are thought to outweigh the risks of treatment toxicity, in particular lymphoedema.

- A single anterior megavoltage is used (6MV). Christie practice is to specify a dose near the anterior surface and accept that the dose in the mid-axilla is lower than this (e.g. 85% of the prescribed dose at 5cm deep for a 6MV beam).
- Other centres may use posterior axillary boost fields to increase the dose in the mid-axilla; this can lead to “hot spots” (and increases the risk of radiation induced brachial plexopathy).
- Accurate matching of nodal radiotherapy fields to adjacent fields irradiating the breast or post-mastectomy chest wall is critical to avoid overlap (a common cause of brachial plexopathy). The patient’s position is not changed between fields and methods such as asymmetric collimation are used to ensure accurate delivery of treatment. The incidence of brachial plexopathy at the Christie using the described techniques is extremely low, less than 1% (Livsey 2000).

5.6 Integrating chemotherapy/radiotherapy

There are few prospective data available on the optimum sequence of chemotherapy and radiotherapy. Simultaneous chemotherapy and radiotherapy is avoided. The preferred option is to give radiotherapy after chemotherapy is completed (essential if anthracyclines are used).

5.7 Radiotherapy for patients treated by mastectomy and immediate reconstruction

- Patients treated by means of mastectomy and immediate reconstruction should normally have small tumours with good prognosis and, therefore, radiotherapy will not be required.

- In patients where pre-operative assessment reveals clinical features indicating the possible need for post-operative radiotherapy, immediate reconstruction may not be appropriate.

- However, there will be situations where mastectomy and immediate reconstruction is carried out and the patient is found to have higher risk disease where post mastectomy radiotherapy would normally be advised. When required on clinical grounds, there is no absolute contraindication to radiotherapy in a patient with a breast prosthesis in situ or with a myo-cutaneous flap. However, the tissues around the prosthesis may, on occasion, shrink following radiotherapy and cause pain, requiring removal of the prosthesis. The patient should be advised that radiotherapy may impair the cosmetic and functional result.

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6. PREOPERATIVE (NEO-ADJUVANT) THERAPY

6.1 Aims of treatment

- To reduce the size of large tumours in order to perform breast conserving therapy
- To eliminate systemic micro-metastases if present (as in postoperative therapy)
- To obtain prognostic information (tumour response)
- To obtain biological (predictive) information for research purposes

6.2 Rationale

- **Locally advanced.** Neo-adjuvant therapy is currently the standard of care in locally advanced breast cancer to facilitate potentially curative surgery. Partial or complete tumour responses occur in the majority (~80%) of such tumours during combination chemotherapy. However, significant differences in histo-pathological response rates are observed for tumours of different pathological phenotypes.

- **T2 and T3 tumours.** Neo-adjuvant chemotherapy increases breast conservation rates but no survival advantage has consistently been demonstrated over post-operative chemotherapy [Fisher 1998, Van der Hage 2001, Scholl 1994].

6.3 Patient selection

- Inoperable, locally advanced breast cancers.
-
- Large tumours that would normally require mastectomy but who wish to have breast conservation.

- Tumours would normally be greater than 3 cm in size. However patients with smaller tumours in small breasts may also require pre-operative chemotherapy for conservation.

- Neo-adjuvant cytotoxic therapy is generally not advisable for grade 1 ER and PgR expressing breast cancer.

6.4 Chemotherapy

- The best pre-operative chemotherapy regimen has not been identified. However pathological complete response (pCR) has been identified as an excellent prognostic factor [Fisher 1998] and new regimens are tested in neo-adjuvant trials with pCR as the primary endpoint. These indicate that regimens containing anthracyclines +/- taxanes have highest pCR rates.

- The NSABP B-27 trial demonstrated the superiority of 4AC followed by 4 Taxotere pre-operatively compared to 4AC alone pre-operatively and 4AC preoperatively with 4Taxotere given post-operatively in terms of improved pCR rates, although no difference in DFS or OS was found [Bear 2006].

- Phase II trials (von Minckwitz 2014, Sikov 2015) have shown an improvement in pCR rates when neo-adjuvant platinum-containing regimens are used in triple negative breast cancer (TNBC), although this is at the expense of increased toxicity. Platinum-containing regimens may be considered for use in young patients with high risk TNBC and good performance status. Otherwise EC-Paclitaxel should be used.

Suggested regimens for neo-adjuvant chemotherapy

- EC x 3-4 followed by Docetaxel 100mg/m^2 x 3-4 or Paclitaxel (weekly) for 9-12 weeks
- Carboplatin (3 weekly or weekly) and Paclitaxel (weekly) followed by 3 EC for selected TNBC.
- TCarboH may be considered for HER2 over-expressing tumours

6.5 Trastuzumab (Herceptin)

- The addition of concurrent trastuzumab to neo-adjuvant taxane containing chemotherapy in women with HER2 over-expressing tumours increases the pCR rate, but has no significant impact on survival [Budzar 2005]. Cardiac toxicity may become an issue with combination epirubicin and trastuzumab and, as such, remains a regimen for clinical trials. Combination of

trastuzumab with docetaxel (either FEC – TH or TCH regimens) should be considered for HER-2 over-expressing tumours.

6.6 Endocrine Therapy

- Hormone receptor positive tumours respond relatively less well to neo-adjuvant chemotherapy than receptor negative tumours [Von Minckwitz 2005, Untch 2002, Kuerer 199, Colleoni 2001].

- Primary endocrine therapy with anastrozole has been shown to be as effective as four cycles of AT in patients with ER positive breast cancer [Semiglazov 2007].

- Postmenopausal women with locally advanced tumours expressing high levels of ER and PgR could be considered for neo-adjuvant endocrine therapy, particularly in the presence of co-morbid conditions and poor performance status.

- AIs have demonstrated superiority over tamoxifen in terms of response rates and facilitation of breast conserving surgery in post-menopausal women [Smith 2005, Ellis 2001].

- The optimum duration of neo-adjuvant endocrine therapy is not known. In the absence of progression treatment should continue for 4 months. If no objective response is seen at this point treatment should be discontinued. If response is seen then treatment should continue for up to 12 months or when BCS becomes feasible or the first suggestion of disease progression – whichever comes sooner.

6.7 Procedure

- A core biopsy must confirm invasive carcinoma

- A full explanation of the procedure should be given to the patients including information that breast conservation may not necessarily be possible even after chemotherapy.

- Tumour size should be estimated by clinical measurement, mammography and ultrasound before treatment begins (baseline). Clinical measurements should be repeated each visit and mammography and ultrasound half way through and at the end of treatment (pre surgery).

- If the response to treatment is good and breast conserving surgery is anticipated the patient should be referred back to her surgeon for consideration of placement of a clip in the tumour to aid in the surgical excision of the tumour bed and in histological assessment.

- Treatment should continue as long as there is no increase in tumour size. Clinical stability can represent pathological response and late responses occur with a switch in class of chemotherapy.

- Conservation surgery should be by quadrantectomy or wide excision. It is important to take shavings of the tumour bed. If a small area of micro-calcification was present in the original tumour complete excision of the area must be confirmed by specimen x-ray. Surgery is advised 3-4 weeks after the final chemotherapy injection and when blood counts have recovered.

- Complete axillary dissection is advised to prevent recurrence, reduce the need for axillary radiation, and to give prognostic information. There is limited data on the role of sentinel node biopsy after primary medical therapy and this is not recommended.

- Post mastectomy radiotherapy should be based on the initial tumour and lymph node characteristics. Even after cPR and mastectomy the local recurrence rates are high if the original tumour was large or heavy lymph node involvement was present.

- For information regarding clinical trials please refer to the Christie Hospital Clinical trials website.

6.8 References

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7. ADJUVANT CHEMOTHERAPY

7.1 Aims of Management

- To select patients who require adjuvant therapy
- To select appropriate adjuvant therapies
- To enter patients into clinical trials since the benefits of current therapy are modest.

7.2 Assessment of Risk

There are a number of major risk factors for the development of metastases. Nodal status remains the most important prognostic factor, followed by tumour size. However factors other than stage alone are also predictive of poor prognosis. Such factors include histological grade, with grade III tumours having a worse prognosis than grade I tumours; young age (<35 years) HER2 over-expression, lymphovascular invasion and high proliferation rates (Ki-67). Estrogen and Progesterone receptor (ER) expression are associated with a better prognosis and ER expression is predictive of a response to endocrine therapy [EBCTCG 2005].

A number of tools are available to clinicians to allow an estimation of a patient' s prognosis from the above prognostic factors:

7.2.1 The Nottingham Prognostic Index (NPI) [Haybrittle 1982].

The NPI estimates prognosis in early breast cancer following surgery and radiotherapy but without systemic therapy:

NPI= tumour grade (1-3) + lymph node stage (1-3) + 0.2 x tumour size in centimetres.

An NPI of < 2.4 is associated with an excellent prognosis, similar to that of the normal population; 2.4-3.4 gives a good prognosis with an 80% 10 year survival; 3.4-5.4 gives an intermediate prognosis and a 50-60% 10 year survival and an NPI of > 5.4 is associated with a poor prognosis and a 10 year survival of less than 20%.

The NPI does not take into account many other prognostic factors including Her2 and ER/PR.

7.2.2 St Gallen Risk Categories [Goldhirsch 2007]

LOW		INTERMEDIATE		HIGH
≤ 2 cm *and* Grade 1 *and* Node – ve *and* ER and/or PR positive *and* Her2/neu not over-expressed or amplified *and* Age ≥ 35 *and* Absence of extensive peri-tumoural vascular invasion		Node – ve *and at least one of:* • > 2cm • Grade 2-3 • Extensive peri-tumoural vascular invasion • ER and PR negative • Her2/neu over-expressed or amplified • Age < 35 1-3 Nodes *and* • ER/PR positive *and* • Her2/neu not over-expressed or amplified		1-3 Nodes *and* • Her2/neu over-expressed or amplified *or* • ER/PR negative 4+ Nodes

7.2.3 Adjuvant! Online (www.adjuvantonline.com) [Ravdin 1996]

Adjuvant! Online gives estimates of 10 year breast cancer specific and overall survival rates for untreated patients based on rates observed in the SEER registry for women diagnosed between 1988 and 1992 and gives estimates of adjuvant treatment efficacy based on data from the EBCTCG meta-analyses as well as single trial data and unlike the NPI allows ER status and the patients age and co-morbidities to be factored in. Adjuvant! does not, however, take into account the implications of HER2 over-expression nor the presence or absence of lympho-vascular invasion though the user can add an allowance for increased risk. The accuracy of the tool is less for the very young and the elderly patient with breast cancer. Recent data suggests that Adjuvant! Online may over-estimate overall survival in the UK by about 5% and may therefore underestimate gains from adjuvant systemic therapy (Campbell, Taylor et al. 2009).

Adjuvant!Online allows the clinician to have an estimation of the absolute benefits of adjuvant treatment for any given patient. The absolute benefits for any patient are therefore dependent on that patient' s risk of recurrence ie their prognosis. For example if a treatment is associated with a 25% reduction in the relative risk of death at 10 years (a hazard function of 0.75) then a patient whose risk of recurrence at 10 years is 10% will have an absolute benefit of 2.5% from that treatment (ie if 100 patients are given that treatment 2-3 lives will be saved). If the patient' s risk of recurrence at 10 years is 40% then the absolute benefit of that same treatment is 10%. Tools such as Adjuvant! can be useful as decision aids to allow patients to have a more informed decision about the potential benefits or otherwise of chemotherapy and allow them a better understanding of the risk: benefit ratio.

' Predict' is an alternative predictive programme (www.predict.nhs.uk)

7.2.4 Proliferation markers and multi-gene signatures

One area of rapid progress is in the distinction between endocrine sensitive but chemotherapy resistant tumours of luminal A subtype from those of luminal B, which are relatively endocrine resistant and chemo-sensitive. Ki-67 may be a useful factor in differentiating between the luminal subtypes although cut off values to define high vs low subgroups vary significantly between published studies (3.5-34%) [Yerushalmi 2010]. Use of the median Ki67 value to define this cut point has been adopted in the majority of such studies although significant heterogeneity in the median values exists (3.5-28%) [de Azambuja 2007]. In Manchester the median Ki67 value for grade II breast tumours assessed at the Christie Hospital 2006-2010 with strong ER and PR expression (QS 7-8) was 18%.

Furthermore proliferation is the most important part of multi-gene signatures and has led to a better understanding of the biology of Elston grade 2 tumours. Grade 2 cancers can be dichotomised into low grade (two thirds of cases) and high grade (one third) tumours by assessing their proliferative or ' genomic grade' signatures [Ivshina 2006, Loi 2007, Wirapati 2008]. Screen detected cancers demonstrate reduced proliferative rates compared to stage matched symptomatic tumours and should be treated according to measured biological factors rather than by method of detection alone. This is an evolving field of research. Although an un-validated approach at the time of writing, it may in future be possible to input quantitative

ER/PR, Ki67 and Her2 into a novel algorithm termed IHC4 which has demonstrated similar capacity to predict relapse free survival as the well validated Oncotype DX assay.

7.2.4.1 Oncotype Dx

This test was given NICE approval in September 2013 for guiding adjuvant chemotherapy decisions in early breast cancer management (www.nice.org.uk/DG10).

The reason for the test must be within the criteria of the NICE recommendations:

Oncotype DX is recommended as an option for guiding adjuvant chemotherapy decisions for people with estrogen receptor positive (ER+), lymph node negative (LN−) and human epidermal growth factor receptor 2 negative (HER2−) early breast cancer if:

- the person is assessed as being at intermediate risk **and**
- information on the biological features of the cancer provided by Oncotype DX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy **and**
- the manufacturer provides Oncotype DX to NHS organisations according to the confidential arrangement agreed with NICE.

For a Recurrence score (RS) indicating low risk (< 18) then chemotherapy would not be recommended.

For a RS indicating intermediate risk (18-30) the option of chemotherapy would be discussed with the patient.

For a RS indicating high risk (> 30) then chemotherapy would be recommended.

7.3 Referral for Adjuvant Chemotherapy

Clinical trials and the Oxford Overview analysis have clearly demonstrated the benefit of adjuvant adjuvant chemotherapy using a combination of drugs over a prolonged course (4-6 months) [EBCTCG 2005]. The benefits of chemotherapy are greatest in young women under 50 and in women with ER negative or Her-2 positive breast cancer. For example anthracycline-based chemotherapy reduces the annual death

rate from breast cancer by 38% in the under 50s and by 20% in women aged 50-69 years. The threshold for the use or otherwise of cytotoxic chemotherapy is however difficult to define and is dependent on likely benefits from treatment, co-morbidities that may make optimal chemotherapy administration difficult and patients' wishes. All patients with a breast cancer should be discussed with the oncologists at the MDT who will advise on which patients should be seen by a Christie oncologist for a discussion of adjuvant chemotherapy. Such patients include those with:

- **Triple Negative Cancers** (>0.5cm)

- **Her2 positive Cancers** (>0.5cm)

Over- expression of Her2 is an independent poor prognostic factor. The pivotal trials of adjuvant trastuzumab demonstrated a clear benefit of adjuvant trastuzumab in addition to adjuvant chemotherapy for relatively high risk breast cancers (Piccart-Gebhart 2005, Slamon 2006). There is however increasing evidence from several, albeit retrospective, studies that even sub-centimetre Her2 over-expressing breast cancers are associated with recurrence rates of 15-30% (Curigliano et al JCO27 5693-99 2009, Gonzalez-Angulo et al., JCO 2009 27 5700-6, Tovey et al., BJC 2009 100 680-3). There is no direct evidence that adjuvant chemotherapy and trastuzumab will decrease the recurrence rates among small Her2 positive cancers, but, magnitude of benefit in the adjuvant trastuzumab trials was similar across all subgroups defined by size or nodal status (Untch et al Annals Oncology 2009). Given the large magnitude of benefit of adjuvant trastuzumab plus chemotherapy (a relative risk reduction of at least 50%) chemotherapy plus trastuzumab should be considered for patients with T1b (> 0.5cm) cancers. Few women in the retrospective studies had T1a cancers and it is therefore difficult to recommend potentially toxic adjuvant therapies to women with very small Her2 positive cancers.

- **ER-Positive, Her2-negative Cancers**

It remains difficult to define which patients with ER-positive Her2-negative should be treated with chemo-endocrine therapy. Patients who are highly endocrine sensitive may gain little from the addition of chemotherapy; such patients cannot however be easily identified and at the present time patients with an intermediate or high risk endocrine receptor positive cancer should be considered for chemotherapy. The 2009 St Gallen International Expert Consensus [Goldhirsch 2009] made the following suggestions:

	Relative Indications for Chemo-endocrine Therapy	Factors Not Useful	Relative Indications for endocrine therapy alone
ER/PgR	< 50% of tumour cells for either receptor		High ER/PgR
Histological Grade	III	II	I
Proliferation	High (>30%)	Intermediate (16-30%)	Low (<15%)
Nodes	4 or more	1-3 nodes	Node negative
LVI	Present		
Tumour size	>5cm	2-5cm	2cm
Patient Preference	Use of all options		Avoidance of side-effects

All patients, therefore, with relative indications for chemo-endocrine therapy should be considered, in the absence of significant co-morbidities, for adjuvant chemotherapy and be referred through to oncologists at The Christie for a discussion about the potential benefits and potential risks of treatment. Patients with an estimated chemotherapy benefit of greater than 4-5% for overall survival at 10 years are generally recommended adjuvant chemotherapy; patients with a potential benefit of 2-4% should be referred for a discussion though not all patients would decide to have chemotherapy for these benefits. It is important, then, that patients are informed that the referral is to discuss adjuvant chemotherapy NOT that they are being referred to have adjuvant chemotherapy.

7.4 Adjuvant Chemotherapy regimens

7.4.1 Christie Breast DG approved regimens

Standard

- EC-T (3 cycles Epirubicin 90 mg/m2/Cyclophosphamide 600 mg/m2 then 3 cycles Taxotere 80-100 mg/m2)
- EC-P (3 cycles Epirubicin 90 mg/m2/Cyclophosphamide 600 mg/m2 then 3-4 cycles weekly Paclitaxel 80 mg/m2)

Selected patients

- AC (4 cycles Adriamycin 60 mg/m2/Cyclophosphamide 600 mg/m2)
- TC (4 cycles Taxotere 75 mg/m2/Cyclophosphamide 600 mg/m2)
- TCH (Taxotere 75 mg/m2/Carboplatin AUC=6/Trastuzumab)
- PC-EC (3 cycles weekly Paclitaxel 80mg/m2/weekly Carboplatin AUC=1.5 then 3 cycles Epirubicin 90 mg/m2/Cyclophosphamide 600 mg/m2)

7.4.2 General principles

Taxane-containing regimens have been extensively trialled in the adjuvant setting and been shown to provide a modest improvement in DFS and OS in some trials compared with non-taxane containing regimens [Martin 2005, Roche 2004].

All patients should have a clinical review after one cycle of Docetaxel to assess toxicities. Any patient with grade 3 or multiple grade 2 toxicities should have a dose reduction or be switched to weekly Paclitaxel.

Docetaxel can be poorly tolerated in the elderly. For patients over 65 years old or with significant co-morbidities, it is recommended that weekly paclitaxel replaces docetaxel. Data from the E1199 study demonstrates the safety and efficacy of this approach [Sparano 2008]. In patients with significant co-morbidities, or of Asian origin or aged 60-65 80mg/m2 Docetaxel should be used for cycle 1, with a view to dose escalation after clinical review ONLY in the absence of significant toxicities.

Given the potentially serious and unpredictable nature of anthracycline-induced cardiotoxicity, it is good practice to formally assess cardiac status prior to commencement of treatment, or as soon as practicably possible.

The addition of 5FU to EC does not improve efficacy [Cognetti 2014].

6 cycles of anthracycline containing chemotherapy (AC/EC) is not superior to 4 cycles of the same or similar regimen. A maximum of 4 cycles of AC, EC or single agent Epirubicin should be used to avoid long term toxicity without improved efficacy.

7.4.3 Triple negative cancers

Fit patients should receive EC-P not EC-T regardless of age (Sparano et al.)

4 cycles of Paclitaxel can be used as an alternative to EC-P in patients with significant co-morbidities.
Paclitaxel Carboplatin followed by Epirubicin Cyclophosphamide (PC-EC) may be considered for **triple negative breast cancer**, especially in patients with **BRCA mutations (**or fulfil the NICE criteria for BRCA testing). However, this regimen is associated with significant toxicities and should only be used in patients < 60 years with PS 0/1 and no co-morbidities.The EC-PC regimen of choice uses weekly carboplatin with GCSF support.

If BRCA testing to be performed urgently refer to Gareth Evans at St Mary' s. EC can be commenced and decision whether to add carboplatin to paclitaxel made with the results.

7.4.4 HER2 over-expressing cancers

ALL patients should receive a concurrent taxane-trastuzumab regimen as standard

Fit patients for whom an anthracycline is contraindicated can be offered TCarboH

Patients with significant co-morbidties can be offered 4 cycles Paclitaxel with Trastuzumab.

Patients with T1NO tumours can also be considered for 4 cycles Paclitaxel with Trastuzumab (Taloney et al).

7.4.5 Patients with Cardiac History

Where anthracycline containing regimens are not considered appropriate (patients with a **cardiac history** or previously treated with anthracyclines) then 4 cycles of $Docetaxel_{75}$ plus $Cyclophosphamide_{600}$ or 4 cycles of weekly Paclitaxel may be considered.

7.4.6 Elderly/Poor performance status patients

In **elderly** patients with poor performance status but no significant cardiac history, first generation regimens such as 4AC or 4EC may be considered.

7.5 G-CSF prophylaxis

Primary prophylaxis may be considered in

- selected patients in whom there are co-morbid factors which significantly increase their risk of, and from, developing a neutropenic event.

- regimens associated with moderate or high rates of neutropenic events (≥20%) eg. $FEC_{100,}$ $EC_{90,}$ $Taxotere_{100.}$.

The following G-CSF regimen can be used for primary prophylaxis

- Filgrastim (neupogen)300 mcg (<70kg) or 480 mcg (>70kg) sc daily for 5-7 days

Note that Pegfilgrastim (neulasta) 6 mg sc single dose administered 24 hours after chemotherapy may now only be used in exceptional circumstances.

Secondary prophylaxis is indicated for any chemotherapy regimen where patients have experienced a neutropenic event from a prior cycle of chemotherapy.

7.6 Antiemetic Guidelines

The antiemetic guidelines are based on the emetic potential of the drug or drug combination used. Whilst the individual emetic potential of drugs is well documents, the effect of these in combination is less well clear; is the effect additive or supra-additive? The Multinational Association of Supportive Care in Cancer-MASCC/ESMO guidelines published in 2011 following a consensus conference give a list of cytotoxic drugs according to their emetogenic potential.

The commonly used breast cancer chemotherapy drugs are classified thus:

1. **High Emetogenic Potential (>90% risk of emesis)**
    a. IV Anthracycline and cyclophophosphamide combination

2. **Moderate Emetogenic Potential (30-90% risk of emesis)**
    a. IV Administration
        i. Epirubicin
        ii. Doxorubicin
        iii. Cyclophosphamide (< 1500mg/m^2)
        iv. Carboplatin
    b. Oral
        i. Vinorelbine
        ii. Cyclophosphamide

3. **Low Emetogenic Potential (10-30% risk of emesis)**
    a. IV Administration
        i. Paclitaxel
        ii. Docetaxel
        iii. Gemcitabine
        iv. Liposomal doxorubicin
        v. 5-Fluorouracil
        vi. Methotrexate
    b. Oral
        i. Capecitabine
        ii. Lapatinib

4. **Minimal Emetogenic Potential (<10% risk of emesis)**
    a. IV Administration

i. Vinorelbine

b. Oral

i. Methotrexate

The aim of antiemetic treatment is 2-fold:

1. To prevent acute and delayed emesis
2. Rescue of failed preventative treatment

Drugs recommended for prevention of emesis are:

1. **Acute Emesis**
   a. Dexamethasone IV or oral
   b. 5-HT3 antagonists (Ondansetron/Palonosetron)
   c. NK_1 Antagonist (Aprepitant)
2. **Delayed Emesis**
   a. Dexamethasone oral
   b. NK_1 Antagonist (Aprepitant)

There is some evidence that palonosetron may have some NK_1 antagonistic activity and hence may contribute towards the reduction in delayed emesis

Based on the MASCC/ESMO 2011 guidelines, the following stepwise approach to antiemetic treatment is recommended:

Risk	Type of Emesis	Prevention	Following failure of preventative regimen
High	Acute	1. IV Dexamethasone D1 2. IV Ondansetron D1 3. Oral Ondansetron D2-3	1. IV Palonosetron D1 And/Or 2. Oral Aprepitant 125mg D1
	Delayed	1. Oral Dexamethasone D2-3	1. Oral Aprepitant 80mg D2-3 [Also consider adding Palonosetron IV D1]
Moderate	Acute	1. IV Dexamethasone D1 2. IV Ondansetron D1 3. Oral Ondansetron D2-3	1. IV Palonosetron D1 OR 2. Oral Aprepitant 125mg D1
	Delayed	1. Oral Dexamethasone D2-3	1. Oral Aprepitant 80mg D2-3 [Also consider adding Palonosetron IV D1]
Low	Any	1. IV Dexamethasone D1	1. 5-HT3 antagonist OR 2. Metoclopramide

Minimal	Any	No routine medication	Oral Metoclopramide

7.7 Chemotherapy Toxicities

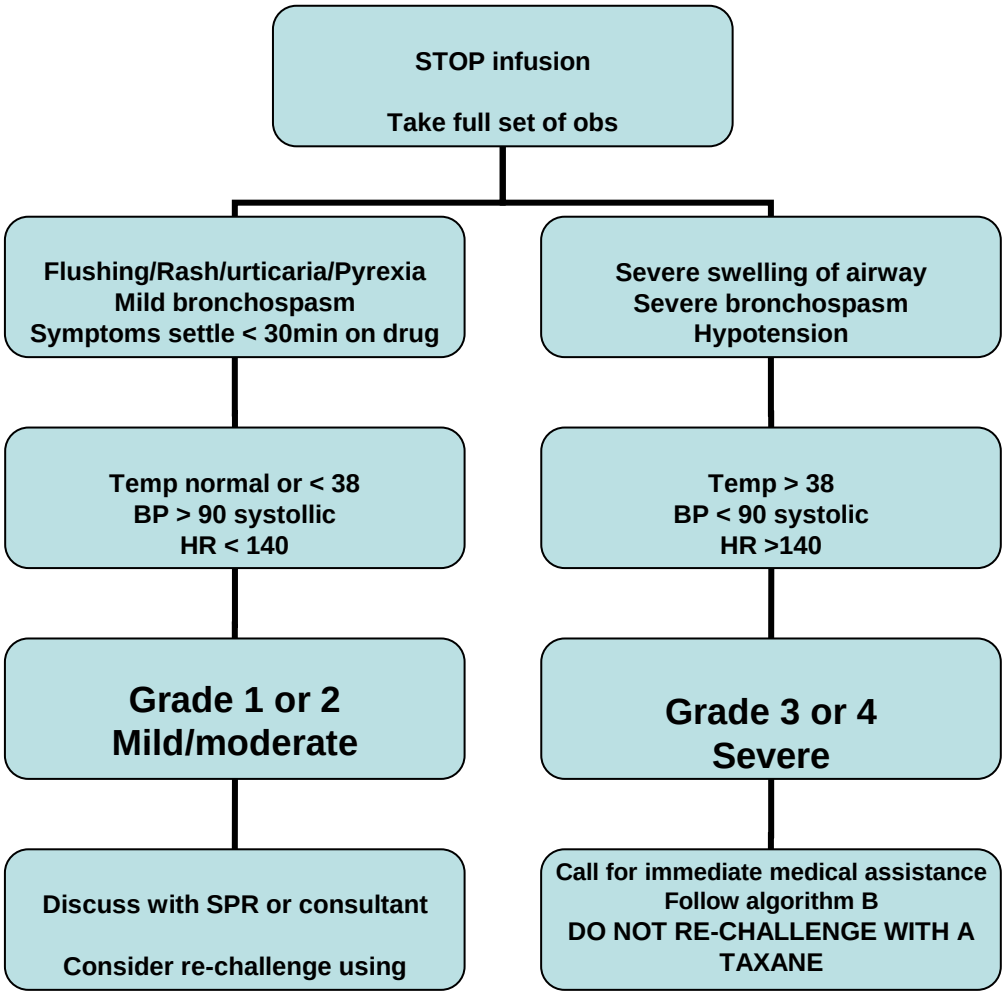
The most important short term toxicity is myelosupression with the risk of potentially fatal neutropenic sepsis. All patients who commence on chemotherapy are told to contact the Christie Hospital Hotline (0161 446 3568) as a matter of urgency if they develop symptoms of infection. Prompt treatment with broad spectrum intravenous antibiotics is indicated for febrile neutropenic patients who, untreated, are at risk of overwhelming sepsis.

Other side effects of chemotherapy include hair loss, nausea and vomiting, diarrhoea and constipation, mucositis and lethargy. Taxane based regimens tend to be more toxic with additional toxicities including myalgia and arthralgia, fluid retention, peripheral neuropathy and nail dystrophy. There is a small excess risk of cardiac toxicity and second cancers for patients who have received adjuvant chemotherapy compared to age-matched controls.

7.7.1 Taxane hypersensitivity reactions

Both commonly-used taxanes, (Docetaxel and Paclitaxel) are known to induce hypersensitivity reactions (HSR). The introduction of prophylactic premedication regimens for both agents has led to significant reduction in the incidence of HSR although severe HSR are seen in 1-2% of patients treated with paclitaxel despite premedication with glucocorticoids and antihistamines (H1 and H2). Nearly 80% of such reactions occur with the first dose administered and almost all within the first 10 minutes of infusion, with as little as 1mg of the drug delivered.

Given that short course premedication is always given before Paclitaxel treatment re-challenge is generally not recommended unless the reaction is mild and settles quickly and spontaneously when the infusion is stopped. In this case algorithm A (below) can be followed and subsequent treatment with paclitaxel or another taxane can be considered. In patients who experience a severe reaction, nab-Paclitaxel (Abraxane) may be considered. Otherwise further treatment with any taxane is not recommended. For reactions to Docetaxel the algorithms below should be followed.



ALGORITHM A: GRADE 1 and 2 REACTIONS

Give 10mg Chlorphenarimine IV Give Hydrocortisone 100mg IV
Restart infusion at 1/4 rate once symptoms have fully resolved
If symptoms do not reoccur after 15 mins increase to 1/2 rate
If symptoms do not reoccur after 15 mins give the remainder of the infusion at normal rate
The next cycle of docetaxel should be given with antihistamine premedication and at the reduced rate described above. If no reaction is seen then subsequent doses can be delivered at the normal rate but with antihistamine premedication.

ALGORITHM B: GRADE 3 or 4 REACTIONS

Call team SPR or SHO/SPR on call
If altered GCS, airway compromise or deteriorating call 2222 for crash team and follow ALS algorithm
Administer High flow O2 15L Give 10mg chlophenarimine IV + hypdrocortisone 200mg Give nebulized salbutamol 5mg (continuous with O2) Commence 500mls N.saline IV stat Give paracetamol 1g IV
Consider 1:1000 Adrenalin 500mcg IM repeat every 5 mins if required
DO NOT re-challenge patient with a Taxane

7.8 Adjuvant Trastuzumab (Herceptin®)

There is evidence form large clinical trials that the use of trastuzumab in the adjuvant setting significantly improves disease free and overall survival in women with HER-2 overexpressing tumours [Piccart-Gebhart 2005, Romond 2005]. The majority of studies have studied 1 year of treatment although a small Finnish study demonstrated similarly beneficial hazard ratios in DFS and OS with a nine week course given with chemotherapy [Joensuu 2006]. Adjuvant trastuzumab is indicated for women whose primary breast cancer is larger than 1cm and whose cancer is scored as 3+ by immunohistochemistry or is amplified by FISH/CISH/D-DISH (ratio > 2.0). Trastuzumab is given sequentially to anthracycline-based chemotherapy though appears more effective when given concurrently with taxane-based chemotherapy [Perez 2009]. There is no data to support the administration of adjuvant trastuzumab in the absence of adjuvant chemotherapy.

Subcutaneous (rather than intravenous) delivery of trastuzumab is recommended except where contraindicated due to involvement in a clinical trial, patient preference, in patients receiving pertuzumab, or other medical reasons.

The recommended subcutaneous dose is 600mg (fixed dose) administered 3 weekly to a total of 18 doses.

For intravenous treatment, the recommended loading dose is 8mg/kg over 90 mins, followed by a 3 weekly maintenance dose of 6mg/kg over 30 mins, to a total of 18 doses. Following the loading dose the patient should be monitored for 6 hours for infusion-related reactions. Emergency equipment must be available. Paracetamol and antihistamines may be used to alleviate infusion-related symptoms.

Re-loading is required if there is a gap between consecutive treatments of over 4 weeks.

Where trastuzumab is used with taxane-containing regimens (eg FEC-T), the trastuzumab should be given concurrently with the taxane, rather than on completion of chemotherapy.

7.8.1 Cardiac health and adjuvant therapy (based on NCRI guidelines 2008)

7.8.1.1 Cardiac monitoring for patients receiving adjuvant trastuzumab

A baseline ECG should be performed in all patients.

Blood Pressure must be recorded at Baseline. BP > 140/85 prior to chemotherapy should be monitored by patient' s GP and treatment with an ACE inhibitor initiated as per UKNCRI guidelines.

LVEF should be assessed (by Echo or MUGA) at the following time points:

- Before chemotherapy is initiated, to establish baseline cardiac status.
- Before initiation of trastuzumab therapy, to assess the impact of chemotherapy on cardiac function, and ensure eligibility for treatment.
- After 4 months of trastuzumab therapy.
- After 8 months of trastuzumab therapy, for patients who do not experience significant changes in LVEF.
- An additional assessment should be performed at 12 months for patients who required intervention during treatment.

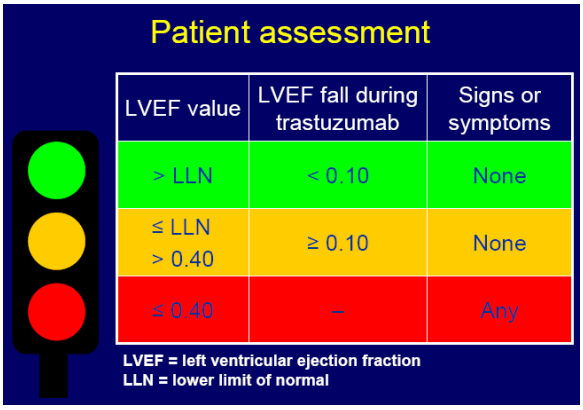
7.8.1.2 Recommendations for initiating, interrupting and discontinuing trastuzumab therapy

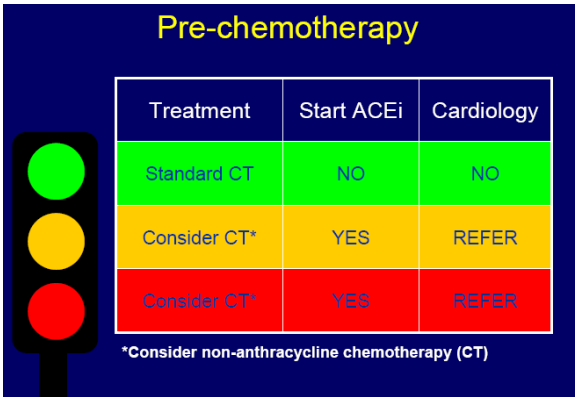
- LVEF should be greater than the local LLN (> 50%) before initiating trastuzumab therapy.

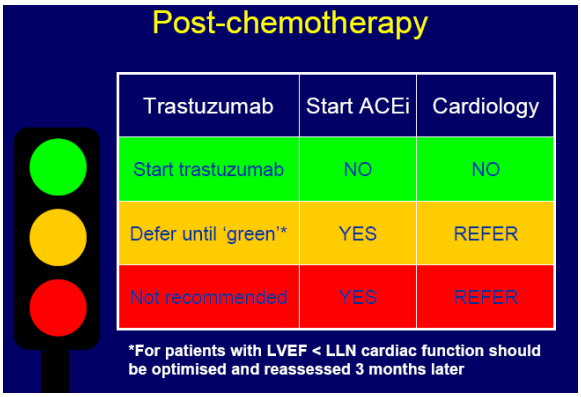
- Intervention with an ACE inhibitor after chemotherapy may be necessary to achieve this. (NB DR Simon Ray (Cardiologist from SMUTH) recommends Ramipril plus Bisoprolol).

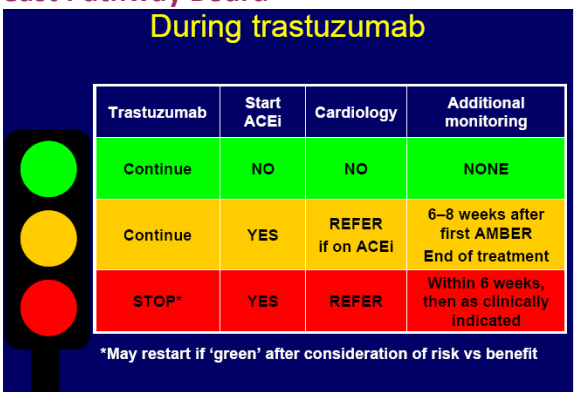
- If LVEF falls by ≥ 0.10 from the pre-trastuzumab LVEF value or to ≤ LLN, initiate ACE inhibitor therapy and re-monitor after 6 weeks.
- If LVEF falls to <0.40 or the patient develops signs or symptoms of heart failure, trastuzumab therapy should be interrupted and they should be referred to a cardiologist.
- If LVEF is restored to > LLN, the patient may be re-challenged with trastuzumab, otherwise discontinue therapy.

Traffic light system to prevent, monitor and manage cardiac events before and after chemotherapy, and during trastuzumab treatment.









7.8.1.3 Recommendations for the management of hypertension in patients with breast cancer receiving trastuzumab

- Patients who are diagnosed with raised blood pressure (>140/85 mmHg) prior to, or during, potentially cardiotoxic chemotherapy, should be initiated on an ACE inhibitor.
- Chemotherapy should not be stopped or delayed.
- Blood pressure and renal function should be monitored and ACE inhibitor dose titrated in primary care along standard guidelines.
- ACE inhibitors should be continued indefinitely, unless a contraindication occurs.
- A cardiologist should be consulted before changing or discontinuing therapy

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8. ADJUVANT ENDOCRINE THERAPY

Endocrine treatments are as important as chemotherapy in premenopausal women and even more so in those who are postmenopausal. Anti-estrogen treatment should be reserved for women with estrogen receptor (ER) positive breast cancer (see below for classification) an considered for rare cases that are ER negative but progesterone receptor (PR) positive. Meta-analyses by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) have demonstrated that 5 years of adjuvant tamoxifen reduces the annual risk of breast cancer death by 31% irrespective of age, chemotherapy use or tumour stage [EBCTCG 2005]. Importantly this improvement in outlook is largely additive to the risk reducing effects of chemotherapy and a middle-aged woman with ER positive breast cancer will have her chances of dying from BC reduced by 50% by the use of anthracycline containing chemotherapy followed by tamoxifen [ECTCG 2005]. Endocrine therapy should not be given concurrently with or prior to cytotoxic chemotherapy unless part of a prospective clinical trial.

8.1 Assessment of ER status

ER and PR status should be measured on all patients with invasive breast cancer at diagnosis to ensure appropriate use of endocrine treatments, which should not be used when both ER and PR are negative. International guidelines suggest endocrine therapy should be considered for any ER staining in the tumour and in practice this equates to 1% or more of cancer cells. Staining intensity is also important and the combination of proportion and intensity are now commonly combined to produce the pathological ‘ quick score’ accordingly:

Proportion	Score	Staining Intensity	Score
0	0	none	0
<1%	1	Weak	1
1-<10%	2	Intermediate	2
10-<33%	3	Strong	3
33-<66%	4		
≥ 66%	5		

Proportion and intensity scores are added to derive a total score from 0-8 (1 is not possible). Tumours with scores of 0 and 2 are considered ER negative but **scores of 3 and above should be considered for endocrine therapy** [Harvey 1999]. Lower ER scores (3-6) make endocrine responsiveness less certain, worsen the prognosis and are a relative indication for chemotherapy [Goldhirsch 2007, Dowsett 2008]. In contrast quick scores of 7 or 8 are a relative indication for endocrine therapy alone.

8.2 Premenopausal women

Tamoxifen remains the mainstay of adjuvant endocrine therapy for premenopausal women and should be given for a period of at least 5 years [EBCTCG 2005, Goldhirsch 2007, Carlson 2009].

There is now evidence of additional benefit from continuation of tamoxifen for an additional 5 years in women who remain premenopausal after completing 5 years of Tamoxifen (Davies 2013, Gray ASCO 2013). The individual relative risks and benefits of this should be discussed with the patient. The benefits are likely to be negligible for very low risk patients (T1N0). Ten years of tamoxifen is recommended for all other pre-menopausal patients requiring adjuvant endocrine therapy.

In women in whom tamoxifen is contraindicated (usually due to a recent history of venous thromboembolism) the combination of a third generation aromatase inhibitor (AI; letrozole, anastrazole or exemestane) and OS should be considered. Such therapy has recently been demonstrated as equivalent to a combination of OS and tamoxifen in a prospective phase III randomised trial [Gnant 2009].

In women with very low risk cancers (NPI VGP group score <2.4) adjuvant endocrine therapy may be withheld after discussion of the risk/benefit ratio with the patient. This is particularly the case for pure tubular cancers which have demonstrated an almost non-existent propensity to relapse or metastasise even in the absence of systemic therapy [Rakha 2010].

8.2.1 Role of Ovarian suppression following adjuvant chemotherapy

Ovarian ablation can be achieved by LHRH analogues. Eg. Goserelin (Zoladex) 3.6 mg s.c. every 4 weeks.

In younger premenopausal women with moderate to high risk tumours who do not develop amenorrhoea with chemotherapy, ovarian suppression (OS) for 5 years should be considered.

The SOFT trial (Francis 2014) demonstrated a 5 year DFS of 82.5% vs 78% in favour of the addition of ovarian suppression to tamoxifen in patients who had received adjuvant chemotherapy. Further improvement was seen with the use of exemstane and ovarian suppression with a 5 year DFS of 85.7%. In women under 35 years, the 5 year DFS was 67.7% for Tamoxifen alone, 78.9% for Tamoxifen plus OS and 83.4% for Exemestane plus OS.

The toxicities of ovarian suppression can be severe and many women who commence combined therapy cannot tolerate it due to the intensity of menopausal symptoms. Any benefit form ovarian suppression also needs to be balanced against potential long term consequences, including hypertension, glucose intolerance, diabetes and osteoporosis. The patient should be fully informed of these potential toxicities. Arrangements for monitoring of bone and cardiovascular health will also need to be made.

Recommended baseline investigations

- HBA1c, fasting glucose
- Fasting lipids
- BP and take cardiac history to including cardiac family history
- Document weight and BMI
- DEXA

Summary Guidance

1. Recommend Tamoxifen plus OS or Exemestane plus OS to women < 35 years who maintain or recover ovarian function after adjuvant chemotherapy

2. Consider Tamoxifen plus OS or Exemestane plus OS to women 35 – 40 years who maintain or recover ovarian function after adjuvant chemotherapy
3. For women 40-50 years who maintain or recover ovarian function after adjuvant chemotherapy it is unlikely there would be significant benefit from giving ovarian suppression, although this may be considered in selected patients who are considered to be at very high risk of recurrence.

8 2.1 Drug interactions thought previously to reduce the effectiveness of tamoxifen

The cytochrome P450 enzyme, CYP2D6 is the rate-limiting step in the conversion of tamoxifen to its most active metabolite, endoxifen. In some retrospective studies, drugs that are known to inhibit the enzyme activity of CYP2D6, such as the antidepressants fluoxetine and paroxetine, had been shown to result in an increase in the relapse rate in patients on adjuvant tamoxifen. However, retrospective analysis of large scale randomised phase III trials (ATAC and BIG 1-98) did not substantiate these findings. These guidelines have thus been changed to reflect this and the co-prescription of such drugs is no longer felt to be contra-indicated.

8.2.3 Women who develop amenorrhoea on chemotherapy (or tamoxifen)

A cautious approach should be adopted in women who develop amenorrhoea during treatment with cytotoxic chemotherapy as residual ovarian function may persist or indeed reappear several years later. The younger the patient, the more likely this is to happen. In addition, amenorrhoea on tamoxifen is not diagnostic of postmenopausal status as tamoxifen suppresses menstruation [Smith 2006, Clemons 2007].

Prior to commencing endocrine therapy blood should be drawn for measurement of serum estradiol and FSH. It is recommended that all such women be commenced on tamoxifen in the first instance and if a sequence strategy is planned with an AI (see below) then bloods should be taken every 3 months for the first year to ensure estradiol and FSH remain in the postmenopausal ranges (high sensitivity estradiol

assays are not available in Manchester). If menstruation resumes or hot flushes abate suddenly then the AI should be stopped and tamoxifen reinstituted.

8.3 Post-menopausal women

8.3.1 Aromatase Inhibitors

Aromatase inhibitors (AIs) block the aromatase enzyme, which converts androgens produced by the adrenal glands to estrogens in abdominal fat, muscle and tumour cells. There are three AIs currently in widespread use; anastrazole (Arimidex), letrozole (Femara) and exemestane (Aromasin) and over 27,000 women have been randomised in adjuvant trials of various designs to test the activity of the AIs against tamoxifen [Baum 2002, Ingle 2005, Jonat 2006, Coombes 2007, Mouridsen 2009].

8.3.2 Choice of endocrine therapy in the post-menopausal woman

Five years of an AI versus tamoxifen has shown improvements in disease free survival by 4% but no significant improvement in breast cancer specific or overall survival [Dowsett 2009] The majority of the benefit appears to be in the first 2-3 years of treatment and the challenge remains to identify the women who would likely benefit most from an AI. To date there is some evidence that certain tumour characteristics (large tumour size, node positivity, lymphovascular invasion and high Ki67) may be associated with increased benefit from an upfront AI treatment strategy as such tumours have a greater peak of relapse during the first 2-3 years of therapy [Mauriac 2007, Viale 2008]. For women who have received 2-3 years of tamoxifen, switching to an AI to complete 5 years of therapy does result in small but statistically significant reductions in overall [Jonat 2006, Coombes 2007] and the sequence strategy has not been demonstrated to be inferior to 5 years of an AI [Mouridsen2009].

Ongoing follow up and other clinical trials may help to define the precise timing, duration, and sequencing of endocrine therapy, in addition to the long-term tolerability profile and the potential differences between anastrozole, letrozole, and exemestane. Uncertainties remain regarding the long-term effect of oestrogen deprivation, particularly with respect to bone and lipid metabolism and these issues should be discussed with the patient.

For the majority of post-menopausal women with newly diagnosed early breast cancer an aromatase inhibitor should form part of their adjuvant management, either

- upfront for 5 years (anastrozole 1mg daily or letrozole 2.5 mg daily) or
- sequentially with 2-3 years of tamoxifen followed by 2-3 years of an aromatase inhibitor to total 5 years. (exemestane 25 mg daily or anastrozole 1 mg daily)

There is no direct evidence from clinical trials to favour one of these approaches over the other in terms of efficacy. However, there is increasing evidence that certain tumour characteristics (grade 3, node positive, >5cm, or ER poor) are associated with a significant risk of recurrence within the first 2.5 years. These patients could be considered for an upfront AI, whereas tumours without these characteristics may be adequately treated by sequential use of tamoxifen and an AI, thus reducing their risk of bone morbidity.

A risk adapted strategy is therefore adopted in postmenopausal patients with ER positive breast cancers:

For women at **high risk** of relapse i.e. a NPI score >4.4 (PPG/MPG2) or women with lymph node node negative cancers with adverse prognostic factors (eg large primary, high grade or Ki67 and LVI+) treatment with upfront AI for five years (anastrozole 1mg daily or letrozole 2.5 mg daily) can be considered [Baum 2002, Mouridsen 2009]. If the AI is not tolerated due to, for example, arthralgia then tamoxifen should be substituted. In patients with high risk disease, the continuation of aromatase inhibition for up to 10 years may be considered, especially if the patient is not experiencing significant toxicities. However, there is no level 1 evidence to confirm a benefit so the individual relative risks and benefits should be discussed with the patient. Ongoing monitoring of bone density is recommended if this approach is used..

For women with **low to moderate risk tumours** i.e. an NPI score of 2.4-4.4 (GPG/MPG1) a sequence strategy with 2 years of tamoxifen follwed by 3 years of an AI, should be considered [Jonat 2006, Coombes 2007].

In women with **very low risk cancers** (NPI VGP group score <2.4 adjuvant endocrine therapy may be withheld completely after discussion of the risk/benefit ratio with the patient. This is particularly the case for pure tubular cancers which have demonstrated an almost non-existent propensity to relapse or metastasise even in the absence of systemic therapy [Rakha 2010]. If treatment is to be given in this group then the incremental benefits with AIs are negligible and in the absence of absolute or relative contraindications such as VTE, thrombotic CVA or obesity, five years of tamoxifen is recommended (NICE 2009).

For women with node-positive breast cancers who have already received between 4.5 and 5 years of tamoxifen, the cross-over to letrozole for a further 3 to 5 years should be considered [Goss 2005]. For node negative women there is less evidence to support the use of endocrine treatment beyond 5 years. The use of extended adjuvant endocrine therapy in this situation should be based on the individual patient risk profile.

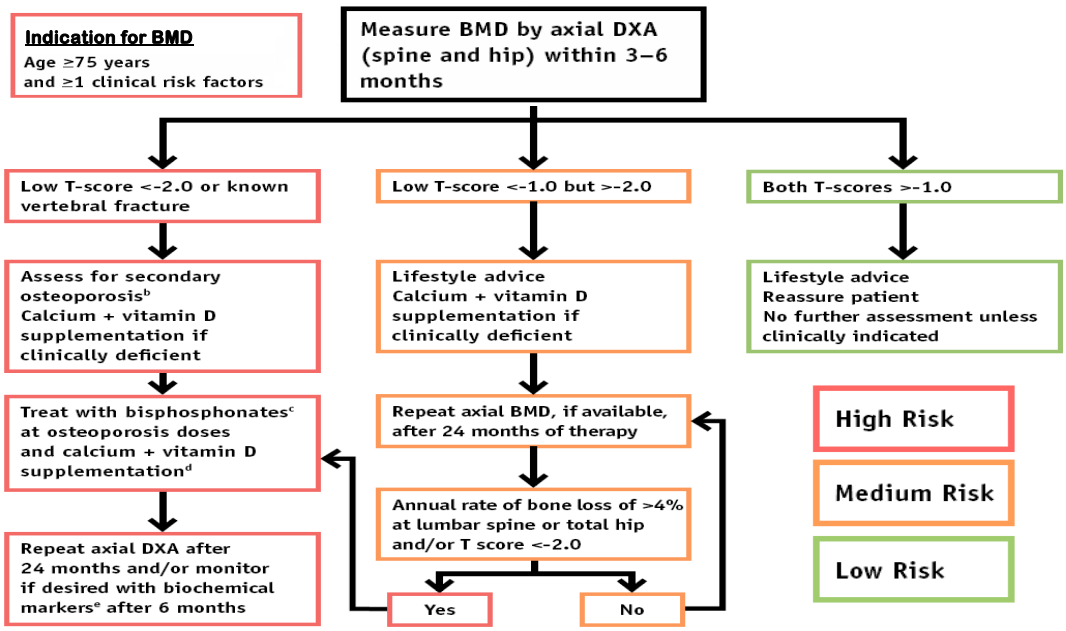
8.3.3 Safety of Aromatase Inhibitors

In general AIs are well tolerated and treatment withdrawal is less frequent than that with tamoxifen. They are associated with reduced gynaecological toxicity including vaginal discharge, vaginal bleeding, hysterectomy rate and endometrial cancer. Venous thrombosis and thrombotic CVA are less common and in some studies hot flushes are less frequent although remain common.

All the aromatase inhibitors are associated with increased bone mineral loss in comparison with tamoxifen. It is accepted that this represents a combination of loss of protective effects seen with tamoxifen and an additional increased loss over baseline as a result of oestrogen deprivation. All patients starting an AI require an assessment of osteoporosis risk factors, calcium intake and baseline bone mineral density scan within three months of initiation. Bone protective therapy and subsequent monitoring should be provided according to UK consensus guidelines summarized below. AIs are also associated with an increased incidence of musculoskeletal complaints, predominately arthralgias which are occasionally severe and may require withdrawal of therapy.

Note that a possible interaction has been cited between thyroxine and calcium supplements that are often used with aromatase inhibitors. Calcium supplements and thyroxine should be administered at least 4 hours apart, as calcium can reduce the absorption of thyroxine.

8.3.4 Bone health and Aromatase Inhibitors (based on NCRI guidelines 2008)



The use of an aromatase inhibitor (steroidal or non-steroidal) is an indication for evaluation of BMD by DEXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DEXA before starting treatment but a baseline assessment should be obtained within 3 months of commencing an aromatase inhibitor.

Monitoring and treatment thereafter depends on the baseline BMD, age, and presence of any major risk factors for osteoporotic fracture. These are defined as:

- previous fragility fracture above the age of 50 years;

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

- For women over the age of 75 years with one or more major risk factors bone protection therapy with a bisphosphonate is recommended irrespective of baseline BMD.

For women aged under 75 years or without major risk factors, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <-2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

- Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m2) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease although intravenous bisphosphonates will usually be appropriate in such patients.
- Repeat DXA after 24 months and/or measurement of a bone resorption marker. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true

non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between -1 and -2, lifestyle advice plus calcium (1 g/day) and vitamin D (400– 800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 ug/L.

- Repeat DXA scan at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <-2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

Low-Risk Group: For those patients with normal BMD (T-score >-1) the risk of developing osteoporosis over a 5-year treatment period is very low. Advice on lifestyle (diet, weight bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

- All patients should be commenced on daily oral calcium (500mg) and vitamin D supplementation (400 I.U.) and given lifestyle advice when aromatase inhibitors are started. For those patients at high risk of osteoporosis (> 75, previous low trauma fracture after age 50, parental history of hip fracture, alcohol intake ≥ 4 units/day, low BMI (<22), diseases associated with secondary osteoporosis, prior corticosteroids for > 6 months) then baseline bone mineral density (BMD) measurements are also recommended.

- The role of routine prophylactic bisphosphonate use in patients on aromatase inhibitors is the subject of ongoing clinical trials.

8.4 Bisphosphonates

Currently bisphosphonates are only indicated, in early breast cancer, for the prevention or treatment of bone mineral density loss secondary to aromatase

inhibition. However, two large randomised studies (ABCSG12 and ZOFAST) have recently demonstrated significant improvements in disease free survival with early vs delayed zometa (given intravenously every 6 months for 3-5 years). The results from several other large adjuvant bisphosphonate studies are awaited, including AZURE, although preliminary results from this study demonstrate a doubling of pCR rates in the neo-adjuvant setting when iv zometa is added to neoadjuvant chemotherapy. Full publication and more mature results are required from these studies to determine whether there will be an overall survival advantage with bisphosphonate therapy and to better define the subgroups most likely to benefit

8.5 Premature ovarian failure and bone health (NCRI guidelines 2008)

- Premature ovarian failure is associated with accelerated bone loss. Tamoxifen in pre-menopausal women may increase bone loss. Women at risk should be given lifestyle guidelines to reduce their risk of developing osteopenia (stop smoking, maintain ideal BMI, regular weight bearing exercise, limit alcohol intake, and healthy diet including adequate calcium intake).

- The development of a treatment-induced menopause or planned ovarian suppression treatment before the age of 45 years are indications for evaluation of BMD by DXA. A baseline assessment should be obtained within 3 months of commencing ovarian suppression therapy or oophorectomy and within 12 months of developing post-chemotherapy amenorrhoea.

- Monitoring and treatment thereafter depends on the baseline BMD and the type of any concomitant endocrine treatment. Due to the very rapid bone loss observed with the use of ovarian suppression therapy plus an aromatase inhibitor, a different threshold for follow-up, monitoring and intervention is recommended.

- Any patient with a documented vertebral fragility fracture or previous low trauma hip fracture should receive prophylactic bisphosphonate treatment irrespective of baseline BMD.

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9. LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER

9.1 Definitions

Locally Advanced

- Patients with inoperable tumours due to skin or chest wall involvement or fixed axillary nodes.
- Metastases limited to ipsilateral supra-clavicular fossa or infra-clavicular region.

Inflammatory

- A clinical diagnosis based on the presence of erythema and peau d' orange of >1/3 of the skin of the breast in a patient with a biopsy proven cancer.
- Inflammatory breast cancers are associated with very poor outcomes.
- Inflammatory carcinomas are usually ER negative and frequently are associated with HER2 over expression and p53 mutations.

9.2 Management

- Staging should be performed to exclude distant metastatic disease.
- Treatment is multi-modality. This involves either endocrine therapy (unlikely in IBC) or primary chemotherapy with anthracyclines +/- taxanes followed by mastectomy and axillary node clearance and post-operative loco-regional radiotherapy plus adjuvant endocrine therapy if ER+ve [Dawood 2010]. Trastuzumab should be incorporated into the pre-operative chemotherapy regimen in HER2 over-expressing tumours [Dawood 2020]. Response to treatment should be monitored radiologically as well as clinically during treatment.
- For information regarding clinical trials in patients with locally advanced and inflammatory breast cancer please refer to the Christie Hospital Clinical trials website.

TREATMENT PLAN: LOCALLY ADVANCED

Diagnostic biopsy for ER, HER 2 & grade
Stage to exclude systemic disease

ER +ve
Endocrine Therapy.
ER-ve
Chemotherapy

RESPONSE → **Mastectomy + XRT**

NO RESPONSE → **Mastectomy (if possible)**
Or
XRT and 2nd line systemic therapy

TREATMENT PLAN: INFLAMMATORY BREAST CANCER

Diagnostic biopsy for ER, HER 2 & grade
Stage to exclude systemic disease

Chemotherapy

RESPONSE → **Mastectomy + XRT +/- Further chemotherapy**

NO RESPONSE → **XRT & second line chemotherapy**

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10. LOCALLY RECURRENT DISEASE

- In the presence of locally recurrent disease, distant metastases should be excluded
- The prognosis depends on the site of local relapse, the extent of relapse and the interval since primary treatment
- Local treatment options with surgery and radiotherapy will depend on the extent of previous treatment
- Local relapse following breast-conserving surgery is managed by a mastectomy in the majority of cases. Relapse within 2 years of primary treatment has a less good prognosis.
- An isolated relapse on the chest wall following mastectomy should be managed by wide local excision and radical radiotherapy (if not previously given). A proportion of these patients will be long-term survivors. Widespread relapse on the chest wall has a poor prognosis. Selected patients may be suitable for chest wall resection. Otherwise widespread chest wall relapse is managed with systemic therapy and palliative radiotherapy.
- Axillary relapse is managed if possible with surgery and/or XRT depending on the nature of treatment used at the time of primary treatment. Extensive inoperable disease has a poor prognosis.
- Supra-clavicular fossa relapse is managed with palliative XRT and systemic therapy
- The selection of systemic therapy is based on the principles set out in Section 9. There is limited data on the effectiveness of systemic therapy, particularly chemotherapy in this situation.
- For information regarding clinical trials in locally recurrent disease please refer to the Christie Hospital Clinical Trials website

11. METASTATIC BREAST CANCER

11.1 Aims

- To palliate symptoms and maintain quality of life.
- To extend life if possible.

11.2 Management points

- Treatment options include specific systemic therapies: Endocrine therapy, chemotherapy and herceptin; supportive therapies, such as bisphosphonates; and specific local therapies; radiotherapy and surgery.
- Receptor status will guide the selection of specific systemic therapy; oestrogen and progesterone receptor estimations, HER 2 status. The receptor status of the metastatic disease can be at variance with the primary tumour in a proportion of cases. Repeat biopsies to ascertain the receptor status of the metastatic disease should be performed where feasible.
- It is usual to start with endocrine therapy in ER or PR +ve patients, particularly with a long disease-free interval, but chemotherapy should be used where there is rapidly progressive lung or liver disease or early relapse on adjuvant hormone therapy.
- Although metastatic breast cancer is not curable with present treatments, specific systemic therapy is of value in the palliation of symptoms with survival advantage for those who respond to treatment.
- Appropriate expertise must be available to deal with the side effects of chemotherapy, which may be life threatening.
- Chemotherapy should be used with extreme care in elderly patients who may have other significant medical problems and cope poorly with common side effects of chemotherapy eg neutropenic sepsis.

- Explanation of the disease process and treatment plans to the patient is highly important.
- All patients with metastatic breast cancer should be discussed in a multidisciplinary team meeting and their management should be supervised by an oncologist.
- Close co-operation between the breast team, the palliative care multi-disciplinary team and the family doctor is needed to provide the best care and support for the patient and her family. Appropriate psychological support is essential.

11.3 Endocrine Therapies

In general endocrine treatment should be offered as the first option to most women with hormone-sensitive metastatic breast cancer, due to the lower toxicity of endocrine therapy and generally longer duration of response compared to cytotoxic therapies. Chemotherapy may be considered when the disease is rapidly progressing and/or life-threatening.

11.3.1 Post-menopausal woman

First line endocrine therapy should be a non-steroidal aromatase inhibitor.

- Non-steroidal aromatase inhibitors): Anastrozole 1 mg OD, or Letrozole 2.5 mg OD.
- Steroidal aromatase inhibitors Exemestane 25 mg OD (Exemestane has some activity in patients who have failed non-steroidal aromatase inhibitors [Lonning 2000]).
- .Selective oestrogen receptor modulators: Tamoxifen 20 mg OD
- Anti-oestrogens: Fulvestrant (Falsodex) administered by monthly i.m. injections. 500mg every 4 weeks, with an additional loading dose on Day 14 of the initial cycle (NB NICE status – rejected. GPs are unlikely to share care).
- Progestogens: Megesterol acetate 160 mg OD.

11.3.2 Pre-menopausal woman

First line endocrine therapy should be Tamoxifen plus ovarian ablation

- Ovarian ablation (in premenopausal patients)
    - LHRH agonists, eg. Goserelin (Zoladex) 3.6 mg every 4 weeks.
    - **Radiotherapy-induced menopause** AP parallel opposed pair ~ 10 x 15 cm centred 3cm above the top of the symphysis pubis. The target volume for XRAM contains the true pelvis. The bony landmarks are the midpoint of the SI joints superiorly, the superior border of the obturator foramina inferiorly and 1 cm beyond the bony pelvic side walls laterally. The dose is 500cGy in 1# for >45yrs old and 1500 cGy in 4# for <45yrs old.
    - oophorectomy.

11.4 Chemotherapy for metastatic disease

- The selection of chemotherapy regimen will depend on the extent and sites of metastatic disease, whether prior adjuvant chemotherapy has been given, and the likely toxicity of the regime.
- The anthracyclines (doxorubicin and epirubicin), and the taxanes (docetaxel and paclitaxel) are the most active agents. Both of these agents must be used with caution in patients with extensive liver disease.
- Patients with primary anthracycline resistance or who relapse after anthracycline-containing adjuvant therapy regimes should be considered for chemotherapy with taxanes, eribulin, capecitabine or vinorelbine as single agents or in combination regimes.
- Consider if the patient is eligible for a clinical trial

11.4.1 Chemotherapy agents/regimes in the metastatic setting

- Anthracyclines: Doxorubicin, Epirubicin, EC or AC. Liposomal doxarubicin (Myocet) may be considered in patients who have previously received anthracycline where there is concern about potential cardiotoxicity.
- Taxanes: Docetaxel and paclitaxel used as single agents or in combination regimes (Docetaxel/Capecitabine or Paclitaxel/Gemcitabine).
    - Nab-paclitaxel (Abraxane) 260 mg/m2 3-weekly has been shown to be equally effective as taxotere 100 mg/m^2 3-weekly, but with reduced toxicity [William 2009]. Nab-paclitaxel can be used in place of docetaxel of paclitaxel in patients with taxane hypersensitivity (only routinely funded indication).
    - Docetaxel 100mg/m^2 is often poorly tolerated in the metastatic setting and appropriate dose reductions (60mg/m^2 or 75mg/m^2) may need to be performed depending on the patient' s age, performance status and co-morbidities.
    - All patients receiving 3-weekly docetaxel require GCSF primary prophylaxis.
- Capecitabine used as single agent or in combination regimes. Patients >70years should be commenced on 1g bd flat dose and dose increased as tolerated.
- Eribulin used as monotherapy
- Vinorelbine (oral or iv) used as single agent or in combination regimes. Note that the recommended oral dosing is 80mg/m^2 weekly following an initial 3 doses at 60mg/m^2.
- Carboplatin or Cisplatin (usually in combination with a taxane or gemcitabine).
- Gemcitabine (usually in combination with a taxane)

11.4.2 Co-trimoxazole prophylaxix against pneumocystis jirovecii (formerly PCP) in patients treated with weekly paclitaxel

All patients with a PS >0 who are due to start weekly paclitaxel with or without trastuzumab for metastatic breast cancer should receive co-trimoxazole 960 mg daily on Mondays Wednesdays Fridays until paclitaxel is discontinued.

11.5 HER 2 Metastatic breast cancer

11.5.1 Trastuzumab

Trastuzumab (Herceptin) is a monoclonal antibody licensed for the treatment of metastatic breast cancer. Patients are only suitable if they strongly over-express the HER 2 protein (approx 25% of patients) and the response rate for single agent trastuzumab is approx 30% [Vogel 2002].

There are 2 broad categories of trastuzumab use in metastatic breast cancer.

1. Trastuzumab monotherapy +/- endocrine therapy .

   (a) Patients with HER2 receptors of 3+ (immunostaining or FISH positive).
   (b) Evaluable metastatic disease.
   (c) Good performance status: WHO $\underline{>}$ 2
   (d) Life expectancy at least 6 months.
   (e) Disease relapsing after treatment with, or not suitable for anthracyclines and taxanes

   .

   (f) Absence of significant cardiac disease (cardiac scan before treatment).

2. Trastuzumab in combination with chemotherapy.

   (a) – (d) as in 1 (a) – 1 (d)
   (e) First relapse with metastatic breast cancer

(f) Can be used in combination with taxanes, vinorelbine, or capecitabine.

(g) Absence of significant cardiac disease.

There is some evidence supporting the use of trastuzumab beyond progression, as a second line therapy [von Minckwitz 2008].

11.5.2 Metastatic Her2 pathway

- 1st line Docetaxel/Pertuzumab/Trastuzumab
- 2nd line TDM-1
- 3rd line Single agent chemo without Trastuzumab

If we lose access to TDM1 then patients should receive 2 lines of trastuzumab-containing regimens only. A line of treatment within a trial (but not on the CDF) does not count as a line of treatment on the NHS.

Patients who relapse within the CNS with stable systemic disease should receive local CNS-directed treatment and continue on their systemic treatment.

11.5.3 Pertuzumab

Pertuzumab (Perjeta)is a monoclonal antibody targeting HER2. Pertuzumab binds to the HER2 receptor and prevents the pairing (dimerisation) of HER2 with other HER family receptors, inhibiting intracellular signalling. It is administered by intravenous infusion.

Indications for use:

- Locally advanced or metastatic breast cancer
- HER2 3+ or FISH positive
- PS 0 or 1
- Any adjuvant HER2 therapy should have been completed more than 12 months prior to metastatic diagnosis
- No prior treatment with chemotherapy or HER2 therapy for metastatic disease

first line treatment in combination with docetaxel and trastuzumab.

Funding is currently through the National Cancer Drugs Fund.

NICE status – awaited.

11.5.4 TDM-1 (Trastuzumab emtansine) (Kadcyla)

TDM-1 is an antibody-drug conjugate. This combines anti-HER activity with targeted intracellular delivery. It is administered via intravenous infusion.

NICE status – rejected.

Currently funded through the National Cancer Drugs Fund for HER2 positive locally advanced or metastatic breast cancer which has previously been treated with a taxane and with trastuzumab in patients with PS 0 or 1 and LVEF ≥ 50%.

11.6 Eribulin

Synthetic analogue of halichondrin B, a naturally-derived compound, first isolated from a marine sponge.

Administered i.v. on D1 and 8 of a 3 weekly cycle.

Indications for use:

- Patients with locally advanced or metastatic breast cancer who have progressed after at least 2 lines of chemotherapy for advanced disease.
- Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Eribulin should be used with caution in patients with cardiac disease, history of arrhythmias, electrolytes disturbances, nutritional deficits and those who are taking medication that can **prolong the QT interval** such as citalopram. See website http://www.crediblemeds.org/pdftemp/pdf/DrugsToAvoidList.pdf An ECG and assessment of K+, Ca++ and Mg++ levels before cycle 1 and 2 is recommended.

Eribulin should be used with caution in patients with **renal impairment** (Creatinine clearance < 50ml/min) and the following dose adjustments are recommended.

Creatinine Clearance (ml/min)	Dose Adjustment
≥ 50ml/min	No dose reduction
49-15ml/min	0.97mg/m^2
<15ml/min	No information available re: dosing discuss with consultant and proceed with caution

Funding currently through the National Cancer Drugs Fund.

NICE status – rejected.

11.7 Everolimus

mTOR inhibitor

Indications for use:

- Post-menopausal metastatic breast cancer
- In combination with exemestane
- Previous non-steroidal aromatase inhibitor
- No previous exemestane
- No more than one previous line of chemotherapy for advanced disease

Funding currently through the National Cancer Drugs Fund.

NICE status – rejected.

Note, there is some literature suggesting that everolimus can have a radiotherapy "recall" effect. Therefore it is recommended that radiotherapy should not be given concurrently with everolimus. Where possible, everolimus should be omitted for 3- 4 weeks prior to radiotherapy.

11.8 Bisphosphonates for patients with bone metastases

Bisphosponates are indicated for use in patients with bone metastases. They have been demonstrated to reduce skeletal related events and symptoms resulting from bone metastases.

The preferred intravenous bisphosphonate is zoledronate (see the information sheet for its use). Oral ibandronate 50 mg daily can be prescribed as an alternative to intravenous zoledronate, and should be considered in patients who are not attending hospital clinics for intravenous chemotherapy. A shared care protocol with GPs has been devised. Oral ibandronate may also be used in patients with impaired creatinine clearance (<30) when a dose reduction to 50 mg once a week is advised.

The use of bisphosphonates has been shown to reduce the incidence of vertebral fracture and radiotherapy requirements in patients with widespread metastatic bone disease.

Rare cases of osteonecrosis (primarily of the mandible) have been reported in patients treated with bisphosphonates. The majority of cases have occurred following tooth extractions. We recommend that patients with dental problems should have any dental surgery performed prior to commencing bisphosphonates. Once treatment has been commenced, any patient requiring dental surgery should be referred to a hospital dental/maxillofacial surgeon.

11.9 Denosumab

Monoclonal antibody that binds to RANKL
Subcutaneous administration

Consider as alternative to bisphosphonates in patients with bone metastases, especially when they are unsuitable for iv bisphosphonates due to significant renal impairment or poor venous access, or in cases of patient/clinician preference.

All patients should have their calcium, phosphate, parathyroid hormone and vitamin D levels checked at baseline and any deficiencies corrected. Patients with a GFR < 50 ml/min should have their calcium rechecked 2 weeks after their first dose and monthly thereafter. Patients with GFR > 50 ml/min should have monthly calcium monitoring for 6 months, and 3 monthly monitoring thereafter.

NICE status – recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer if:

- bisphosphonates would otherwise be prescribed **and**

- the manufacturer provides denosumab with the discount agreed in the patient access scheme.

Denosumab frequency can be de-escalated to 6 weekly to synchronise with chemotherapy regimens. Further de-escalation to q3/12 can be subsequently considered unless drug needed for symptom management (Addison et al.). Markers of bone turnover may help guide frequency decisions.

11.10 Indications for radiotherapy in metastatic diease

- Bone metastases:- pain relief (single fractions of radiotherapy are as effective as prolonged courses); as part of the management of pathological fractures; spinal cord compression.
- If symptoms of pain are widespread it is preferable to give a trial of systemic therapy before radiotherapy. Radiotherapy given to multiple sites compromises the bone marrow and may prevent the patient receiving palliative chemotherapy even when indicated.
- Troublesome tumour deposits e.g. skin or nodal deposits, choroidal metastases.
- Brain metastases:- Palliative cranial XRT can be considered for patients with reasonable performance status, minimal neurological deficit and quiescent systemic disease at other sites.

11.11 Special clinical situations in metastatic breast cancer

11.11.1 Malignant hypercalcaemia

Hypercalcaemia may occur in the presence of bone metastases or due to production of PTH like substances. The diagnosis should be considered in a breast cancer patient who develops thirst, polyuria, nausea, vomiting or mental confusion. Patients should be considered for treatment if Ca^{2+} > 2.8 mmol and/or symptomatic. They should receive i.v. bisphosphonates, after hydration with saline for correction of dehydration. Serum corrected calcium should be checked 5-7 days after treatment

with bisphosphonates. Effective anti-tumour treatment minimises the risk of recurrence and should be deployed where appropriate. However even patients whose disease is refractory to standard systemic therapies can be treated with intravenous bisphosphonates given every two to four weeks to maintain normal serum calcium. Hospices may be able to offer admission for treatment of hypercalcaemic episodes and this option should be considered for those with advanced disease.

11.11.2 Bone fractures

- Prophylactic orthopaedic surgery is recommended to prevent fracture through lytic lesions in the proximal femora and humeri, especially when a lytic lesion involves 50% or more of the cross-sectional diameter.
- Patients with metastatic bone disease may develop pathological bone fracture leading to considerable pain and morbidity. Weight bearing long bones and vertebrae are especially vulnerable and patients at risk of or with established fractures of long bones e.g. neck of femur or head of humerus should be referred
- for orthopaedic assessment. Following surgery post-operative radiotherapy should be given to include the whole length of any prosthesis present. Patients with pathological fractures at other sites such as ribs or pelvis do not require surgical intervention but often benefit from radiotherapy for pain relief and to promote healing.

11.11.3 Liver metastases – local therapy including resection of metastases

Usually liver metastases are treated with systemic therapy. However for very selected patients it may be appropriate to refer for consideration of local liver therapy such as surgical resection, Radiofrequency Ablation, Selective Internal Radiation Therapy, or intra-hepatic chemotherapy:

.

- good performance status

- liver disease is the disease threatening the patient' s longevity
- no radiological evidence of extra-hepatic metastases which would lead to quick progression (e.g. intra-abdominal disease (such as peritoneal or nodal), pleural disease, or brain metastases or uncontrolled local disease). Controlled small volume disease of bone or lungs not complete contra-indication but is relative contra-indication..
- Previous response to chemotherapy/immunotherapy which self-selects patients who are less likely to progress quickly outside the liver or very indolent disease.
- For surgery: predominantly solitary metastases (+/- close daughter lesions), with less than 6/8 of liver affected confirmed by contrast MRI scan
- For Selective Internal Radiation to the Liver (SIRT): peri-operative Oxaliplatin and 5FU (OxMdg) or Irinotecan and 5FU (IrMdg) are commonly used to enhance response and prevent extrahepatic progression."

Suggestion for patient pathway:

1. Patient identified early as liver metastases being the life threatening aspect of patient' s condition. Ideally liver only disease or only small volume disease outside the liver - e.g. small volume lung or bone metastases.

2. Patients discussed at MDT at which a HBP surgeon and a Breast Oncologist are present.
   a. Patient performance status, prognosis and response to chemo/immunotherapy discussed
   b. Is this technically resectable?
   c. Is SIRT or a non surgical approach an option and justified in the clinical context?

3. Contrast enhanced Liver MRI and PET-CT scan performed

4. Patient reviewed by HPB Surgeon/Oncologist and plan made.

5. Medical therapy continues in the meantime

6. Medical therapy continues peri-operatively if possible (e.g. herceptin/hormone therapy or even certain chemotherapies- e.g. capecitabine)

11.11.4 Neurological problems

11.11.4.1 Brain metastases.

- Patients with brain metastases may present with symptoms of raised intracranial pressure, neurological deficit, seizures or mental deterioration. Dexamethasone should be given for raised intracranial pressure pending confirmation of the diagnosis by whole brain CT scan or MRI.

- Seizures can be controlled by anti convulsants. Patients should be considered for palliative radiotherapy taking into account the status of other sites of metastatic involvement. The long term results of treating disease of the central nervous system are disappointing, most patients dying within six months, although some remain free of symptoms for a considerable period of time.

- Selected patients may be suitable for consideration of surgical excision:

    - Solitary metastasis in an accessible site
    - Stable extracranial disease
    - PS 0-1
    - Life expectancy > 6months

- Following surgical excision, whole brain radiotherapy is indicated.

- Stereotactic radiotherapy may be considered in good performance status patients with controlled extra-cranial disease and $\leq$ 3 intra-cranial metastases and for patients with a solitary cranial metastasis which is surgically inaccessible.

- Following stereotactic radiotherapy there is no evidence that whole brain radiotherapy improves survival.

11.11.4.2 Spinal cord compression

- MRI scan is the investigation of choice. It should be requested urgently and within 24 hours of clinical suspicion. CT scan should be requested if MRI scan is not possible (cardiac pacemaker, metal implants, severe claustrophobia).

- Imaging should be performed at the nearest local hospital and scans should accompany the patient when transferred for radiotherapy or surgery.

- High dose steroids should be commenced with clinical suspicion (dexamethasone 16 mgs. i.v/p.o immediately then 16 mgs. daily).

- When imaging confirms clinical diagnosis of cord compression, a senior clinician (specialist registrar or consultant) must refer for urgent treatment. Ideally this should be within 24 hours of onset of neurological symptoms and certainly within 24 hours of confirmation by imaging.

Patients at risk of MSCC should be given information about signs and symptoms of MSCC as per NICE guidance and available here: http://www.christie.nhs.uk/services/i-to-q/metastatic-spinal-cord-compression-mscc/education/mscc-resources/

Also the guide to recognition and early diagnosis is here: http://www.christie.nhs.uk/media/1199/mscc-service_info-for-professionals_guidelines_guide-to-early-recognition-and-rapid-response-primary-care.pdf

And the detailed guidance is here: http://www.christie.nhs.uk/services/i-to-q/metastatic-spinal-cord-compression-mscc/information-for-professionals/guidelines/

11.11.4.2.1 Indications for Radiotherapy:

- Spinal cord compression confirmed by imaging (preferably MRI)
- Following spinal surgery for spinal cord compression unless the patient has had previous radiotherapy to the same level.
- Not suitable for surgery

11.11.4.2.2 Relative contraindications to radiotherapy

- Cord compression is due to vertebral displacement/spinal instability
- Previous radiotherapy to same spinal site
- Poor general condition due to other major and irreversible clinical problems
- Prognosis likely to be less than 1- 2 months

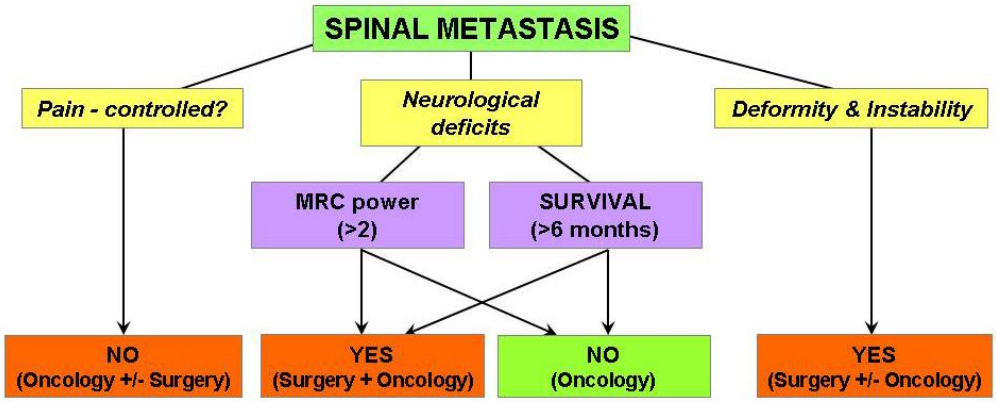
11.11.4.2.3 Situations when surgery should be considered

- generally limited sites of spinal involvement
- cord compression with neurological deficits
- patient is not plegic and is able to move the limb against gravity (MRC grade > 2)
- pain not responding to other measures (eg radiotherapy)
- in cases of spinal instability and/or deformity (including an opinion on spinal stability)
- patient is medically fit (for a general anaesthetic)
- patient has a **life expectancy of at least 6 months**

Early surgery (before severe neurological deficits) produces the best outcome

Surgery is best undertaken prior to radiotherapy (less risk of wound complications)

The **following referral pathway is not absolute** and when in doubt discuss with the relevant Neurosurgical and/or Spinal teams at SRFT.



SURGICAL OPINION:

Contact the on call Neurosurgical SpR (pager – 07623 617892 or via switch board – 01617897373 at SRFT)

For more information and protocols on management of spinal cord compression, see www.christie.nhs.uk/spinal protocols

11.12 Follow up in Metastatic Breast Cancer

11.12.1 Aims

- To give continuous psychological support.
- To monitor treatment.
- To prevent complications (e.g. fractures) or to detect them early (e.g. hypercalcaemia).

11.12.2 Recommendations

- Patients should be seen at least every three months.
- There should be easy access to the clinic in between visits if necessary.
- It is preferable that the patient sees the same team of doctors regularly.
- Patients should be introduced to appropriate other professionals at an early stage e.g. palliative care team, breast care nurse, physiotherapist, lymphoedema therapist, orthopaedic surgeon.

11.13 References

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12. SPECIALIST SERVICES

12.1 Palliative and Supportive care

Specialist Palliative Care Teams are based in community, hospital and hospice settings and work alongside both oncology and primary care teams to support the patient and family. Good communication between all professionals is essential.

12.1.1 When to consider referral to Palliative Care Services:

- There are persistent and troublesome pain and symptom problems
- Additional psychological support would help patient and/or family especially in the final weeks and months
- The patient / carer has complex needs and may benefit from referral to specialist services within the community.
- Patients with advancing disease.
- Help with advance care planning.
- Help with stopping active treatment.
-

Patients with advancing disease should be given opportunities to have contact with specialist palliative / supportive care earlier, thus enabling improved links within the community, smoother transition from active to best supportive care and can prevent crisis intervention.

Specialist Palliative care advice to professionals is available out of hours through a helpline at St. Ann' s Hospice 0161 437 8136

12.2 Pain Specialist Teams

These are hospital based and provide out-patient clinic services. Often pain associated with active, progressing cancer is managed by palliative care specialists as there are often multiple co-existent problems; however pain specialists provide valuable advice and help for those with difficult and intractable pain. Referral to a

chronic pain service may be appropriate for those patients who are cured of their cancer but live with difficult pain as a result of treatment or the disease. Often this management requires a multidisciplinary approach in which the focus has moved from the cancer itself to rehabilitation.

12.3 Specialist Psychological Support

- Patients and carers with difficulties in the following areas might benefit from some form of psychological support.
    - Anxiety
    - Depression
    - Personal relationships
    - Psycho-sexual problems
    - Alcohol and substance misuse
    - Past psychotic illness
    - Organic brain disorders
- It is the responsibility of all health care professionals to be aware of psychological concerns and refer on where appropriate.
- In most cases where psychological concerns are identified it is reasonable to initially refer to the breast care nurse/clinical nurse specialist.
- The Breast Care nurse should assess the patient and appropriately refer on for further psychological support, either to the Psycho oncology service at Christie hospital, or possibly to local services, such as primary care or local Macmillan centres or hospices.
- Liaison should be maintained with Mental Health Teams for those patients with co-morbidity.
- (NICE Supportive and Palliative Care Guidance)

12.4 Breast Cancer Nurse Specialists

All patients should have a designated breast care nurse. BCNs can help patients with the following concerns:

- wanting to discuss aspects of their breast cancer, treatment options and side effects
- difficulty coping with the side effects of treatment
- desire for information on the options and desire for breast reconstruction
- symptoms of anxiety or depression and/or having difficulty coping
- problems with their body image
- need for advice on or fitting of bras and/or prosthesis
- need for assistance with social or family-related concerns
- advice re prevention of lymphoedema.

12.4.1 The Christie Breast Care Nursing Service

Any patient having treatment at the Christie who has locally advanced or metastatic breast cancer may be referred to the Macmillan Secondary Breast Care Nurses at the Christie Hospital. Patients being treated for primary breast cancer and patients with advanced disease receiving their car locally will remain under the care of their local BCN team.

All new patients referred to the Christie Hospital should be given the pink leaflet *The Christie Breast care Nursing Service*
To make a referral telephone ext. 3996 and leave a message or bleep 12592 to talk directly to one of the Breast Care Nurses.

12.5 Nurse Clinicians

Nurse clinicians in breast cancer have completed the MSc. in Clinical Nursing, and have a medical role in the management of patients with breast cancer, seeing new patients, those on adjuvant and palliative treatments and routine follow-up.

12.6 Research Nursing team

The Breast Research Nursing team aim to provide equitable access to medical and clinical oncology research breast trials for patients at the Christie and throughout the Greater Manchester and Cheshire Research Network. They have a large trial portfolio which includes phase 1, 2 and 3 clinical research trials.

The dedicated team consists of a Nurse Team Leader, 5 Breast Research Nurses and administrative clinical trial staff. Each Christie Breast clinic is supported by a research nurse who screens all notes prior to the clinic to identify patients eligible for clinical trials. The nurse provides an advisory resource to all members of the MDT as well as caring for patients on clinical trials.

The Team have a SharePoint facility which provides information on all open trials and trials in follow up. Users can access current protocols and information sheets and can also access other useful documents such as RECIST criteria, TNM staging, CTCAE Version 3.0 etc.
To obtain a password new staff should contact Danny Walker Senior Clinical trial administrator on 0161 446 8604.

A Breast group Research meeting is held bi monthly at the Christie hospital. This forum provides a medium to discuss the feasibility of new trials, trials in set up and recruitment issues with current trials. Please contact the team if you wish to be on the mailing list.

12.7 Lymphoedema Services

The Christie offers a comprehensive lymphoedema at both keyworker and Specialist level service to all people with cancer related lymphoedema across Greater Manchester irrespective of whether or not they are a Christie patient.

The service is based at The Christie main site in Withington with 3 satellite clinics, one at Beechwood Cancer Care Centre in Stockport, one at Bolton Hospice and one at Cornerstones in East Manchester.
A keyworker service is also available at The Christie at Oldham and Christie at Salford radiotherapy centres

Referrals are accepted for mild, moderate, severe, complex and palliative lymphoedema of the arm or breast.

Treatments available include advice and education on skin care and preventing infection, exercise, simple lymphatic drainage, provision of compression garments,

manual lymphatic drainage, multilayer lymphoedema bandaging, kinesiotape, deep oscillation therapy, pneumatic compression therapy and provision of a support group.

Referrals are accepted from Consultants, GPs, Specialist Nurses, Lymphoedema Therapists and other Allied Health Care Professionals.

To make a referral please complete the lymphoedema referral form which is available on The Christie intra and internet. We are unable accept referrals via email or telephone or self-referrals from patients.

Out of area services may be found through the British Lymphology Society Website http://www.thebls.com

For further information, please contact Julie Kenyon and Paula Williams, Lymphoedema Specialists on 0161 446 3795

12.8 Physiotherapy

All patients having treatment for breast cancer should have access to physiotherapy at the following stages of the treatment journey:

- Patients undergoing surgery should be taught specifically designed exercises and receive advice regarding lymphoedema prevention.
- Patients should be followed up in post-operative clinics to ensure that full movement is regained and if problems arise, patients should have access to specialist out-patient physiotherapy to prevent chronic problems with pain and dysfunction.
- Patients due to undergo radiotherapy should be invited to attend an exercise class where instructions are given on the appropriate exercises necessary to maintain shoulder movement during and after radiotherapy.
- Patients who present with lymphoedema, impaired shoulder movement and pain, muscle weakness, cording in the arm/axilla, headaches, neck and back pain and postural problems should be referred for specialist out-patient physiotherapy.

- Patients with metastatic disease who develop problems with pain and reduced mobility.

The Christie Physiotherapy Department are able to offer input at the following stages:

- Day 1 post-operative exercises are taught and patients are given an exercise leaflet.
- On commencement of radiotherapy, patients are given a leaflet inviting them to attend an exercise class, which is held in the Rehabilitation Unit (Tues 11am-12pm, and Thurs 1-2pm). To book a place telephone extension 3765.
- Limited out-patient physiotherapy treatment and advice for patients who have problems with pain and reduced shoulder mobility whilst undergoing adjuvant chemotherapy and radiotherapy.

12.9 Complementary Therapies

These services are provided in local settings by voluntary agencies such as Beechwood Cancer Care (Stockport), Neil Cliffe Centre (Wythenshawe Hospital) and many hospices. Information about complementary therapies available to outpatients may be accessed through the Cancer Information Services.

Complementary services are also available at the Christie for inpatients and those coming in daily for treatment. These services are free to the patient and include massage, aromatherapy, chair massage, relaxation techniques and the Snoezelen Room. Smoking cessation advice is also available for patients and carers.

Relaxation classes are held in the Rehabilitation Unit on Tues and Thurs at 6.30-7.15pm.

For further information regarding complementary therapies please contact Peter Mackereth (Complimentary Therapy Co-ordinator) 0161 446 8236.

13. GUIDELINES FOR REFERRAL TO THE BREAST FAMILY HISTORY CLINIC

13.1 Referral criteria to tertiary care (NICE Guideline June 2013)

People who meet the following referral criteria should be offered a referral to a specialist genetic clinic.

- At least the following female breast cancers only in the family:
    - 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**
    - three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative) **or**
    - 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 50 years **or**

- one first-degree or second-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 relatives diagnosed with breast cancer at younger than an average age of 60 years. **or**

- A formal risk assessment has given risk estimates of:
  - a 10% or greater chance of a gene mutation being harboured in the family **[new 2013] 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.

Clinicians should seek further advice from a specialist genetics service for families containing any of the following, in addition to breast cancers:

- triple negative breast cancer under the age of 40 years
- Jewish ancestry
- sarcoma in a relative younger than age 45 years
- glioma or childhood adrenal cortical carcinomas
- complicated patterns of multiple cancers at a young age
- very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father's side of the family).

13.2 Moderate risk referrals

The Family History Clinic accepts moderate risk referrals from the Manchester Health Authority area which consists of:-

1) a single first degree relative under the age of 40.
2) 2 relatives under the age of 60 (referees should be a first degree relative of one of these).
3) 3 relatives at any age on the same side of the family.

Moderate risk referrals from outside the Manchester Health Authority area may be assessed by the local Breast Unit.

13.3 Proposed criteria for discussing prophylactic surgery

- Lifetime risk of 1 in 4 or more
- Two counselling sessions with geneticist/oncologist
- One or more sessions with psychologist/psychiatrist
- One session with plastic/reconstructive surgeon

13.3.1 Risk-reducing Mastectomy MDT Provision

Patients undergoing risk-reducing mastectomy must be discussed at an MDT where members of the genetic and family history team, psychology team, nursing team and surgical team are present. Current provision of this MDT service is at the Nightingale Centre attended by Prof Evans, Prof Howell, Dr Lalloo, Dr Clancy, Dr Rogers, Dr Maurice, Mr Baildam, Mr Barr, Mr Ross, Mr Wilson, Mrs potter and Mrs Affen.

13.4 Mechanics of referral to the family history clinic

- Letter to Prof Gareth Evans or Dr Fiona Lalloo giving as full a family history as possible bearing in mind the criteria for referral.

- Letter will be sent back to you if referral not thought to be appropriate.
- At risk woman sent a family history clinic questionnaire.
- When form returned and clinic appointment is given.
- At visit pedigree checked.
- Subject counselled and offered mammography, genetic testing, prophylactic surgery as appropriate. Entry into clinical trials considered.

13.4.1 Address for referrals

Prof D G R Evans or Dr F Lalloo.
Genetic Medicine,
6th Floor,
St Mary' s Hospital,
CMFT,
Oxford Road.
Manchester
M13 9WL

Prof A Howell or Prof DGR Evans
Family History Clinic
Nightingale Centre & Genesis Prevention Centre,
University Hospital of South Manchester
M23 9LT

14. APPENDICES

14.1 Appendix 1 Pathology Reports

Reports should include the following information in order to plan treatments optimally

- Maximum tumour diameter (where assessable).
- Unicentric or multicentric tumour
- Histological classification of in-situ and invasive tumours
- Histological grade of invasive carcinomas
- Histological grade of DCIS using the NCGBSP recommended method
- Presence or absence of vascular space invasion.
- Completeness of excision with measurement of narrowest margin.
- Total lymph nodes found (when assessable) and total nodes containing metastatic carcinoma in each axillary specimen. Invasion of perinodal fat should be recorded.
- Receptor status (ER, PR, HER 2).

14.2 Appendix 2 - Radiological Approach To Management Of Breast Cancer

The role of radiology in the management of breast cancer is threefold:-

- Staging
- Assessing disease relapse
- Monitoring of response to therapy

Staging

Prior to definitive treatment patients should have bilateral mammography and chest radiography as a baseline investigation. The indications for any additional radiological investigations are outlined below.

Early Stage [Prior to adjuvant therapy]

- Stage pN0: Not indicated
- Stage pN1: Not routinely indicated, but could be considered for high grade disease, T3 disease or HER-2 over expressing tumours
- Stage pN2: Imaging recommended (CT Chest/Abdomen + Isotope bone scan)
- Stage pN3: Imaging recommended (CT Chest/Abdomen + Isotope bone scan)

Locally advanced disease

- Imaging recommended (CT Chest/Abdomen + Isotope bone scan)

- **Assessment of locally recurrent disease**

In patients with either a clinical or mammographic suspicion of locally recurrent disease in the breast special mammographic views and ultrasound should be performed. Confirmation of recurrence requires needle biopsy for histology or fine needle aspiration cytology. If the results are equivocal MRI may be useful for excluding recurrence. If recurrence is confirmed a chest radiograph, liver ultrasound (or CT Thorax/Abdo) and bone scan should be performed. .

- **Assessment of metastatic (and loco-regionally recurrent) disease**
  - CT Chest/Abdomen + Isotope bone scan at presentation of metastatic disease [staging scan]
  - For patients with visceral disease undergoing chemotherapy
    - Baseline scan [same as staging scan]
    - At half way point through chemotherapy to assess response; assuming that the intention is to give 6 cycles, this means scanning after 9 weeks for 3-weekly cycles. For weekly cycles, imaging after 6-9 weeks is recommended
    - At completion of planned chemotherapy to assess response
  - For patients on long term trastuzumab/chemotherapy (e.g. Capecitabine)
    - Baseline scan [same as staging scan]
    - Further scans at 3 monthly intervals to assess response
  - For patients with visceral disease undergoing primary hormonal therapy
    - Baseline scan [same as staging scan]
    - After 9-12 weeks of therapy to assess response
    - No further routine CT scans. Rising tumour marker(s) or clinical suspicion of progression to trigger restaging scan
  - Other indications
    - CT whole brain for patients with clinical suspicion of cranial metastases
    - Pelvic CT for patients with suspicion of pelvic disease

NOTE: Whilst the recommendation is for CT scanning in this group of patients, clinicians may choose to request US abdomen or plain radiographs instead depending on the clinical scenario and the presence of evaluable lesions on US/plain radiograph.

- **Radiological Techniques**

Mammography:

This is the technique of choice for identifying the primary tumour. As interpretation frequently causes difficulty this examination is usually undertaken in centres where appropriate expertise is available.

Chest radiography:

The chest radiograph is the most common method for evaluating thoracic involvement as it is quick, sensitive, inexpensive and easy to repeat for evaluation of treatment and relapse. PA and lateral views will usually show adenopathy, pulmonary metastases, pleural effusions and advanced bone infiltration. Routine chest radiography is not a cost effect method of monitoring asymptomatic patients for pulmonary metastases and should only be used to address a clinical problem relating specifically to the thorax.

Scintigraphy

Skeletal scintigraphy using 99m-technetium labelled diphosphonate is the examination of first choice for the investigation of symptoms suggestive of bone metastases. As stated previously routine use of bone scintigraphy to detect asymptomatic bone metastases is not indicated.

Ultrasound

Despite its many advantages there is no routine role for ultrasound in staging of asymptomatic patients. In patients with abnormal LFTs it is useful both in confirming the presence of metastases and assessing treatment response. It may also be used in the assessment of pleural effusions.

Computed Tomography (CT)

CT is useful in assessing liver disease in patients who are difficult to examine using ultrasound. It also has a role in the diagnosis of lymphangitis and assessment of intra abdominal disease.

Magnetic Resonance Imaging (MRI)

MRI is the technique of choice to evaluate suspected disease affecting the meninges and spinal cord. MRI is also useful in assessment of the axillae and suspected chest wall invasion. Magnetic resonance mammography (MRM) has role in excluding tumour recurrence within the breast and in assessing response of primary tumour to neo-adjuvant therapy.

PET

18FDG-PET has a potential role in differentiating between benign and malignant breast masses, lymph node staging, detecting metastatic disease, detecting local or distant recurrence and assessing response to treatment because of its increased sensitivity and specificity over the other imaging modalities. PET imaging can be considered to exclude metastatic disease prior to curative surgery when other forms of imaging are equivocal.

14.3 Appendix 3 Guide to early recognition and management of spinal cord compression

LOW LEVEL OF CLINICAL SUSPICION	HIGH LEVEL OF CLINICAL SUSPICION	DEFINITE CLINICAL DIAGNOSIS
• Cancer diagnosis • New and persistent, localised back pain • Unilateral nerve root pain (radiates in dermatomal distribution • Pain on movement • No abnormal neurological signs on examination	• Cancer diagnosis with documented bone metastases or myeloma • Bilateral nerve root pain especially band-like • Acute escalation of severe spinal pain • Unsteadiness/heaviness in legs • Tingling or electric shocks in spine with a cough or sneeze • Neurological signs may be equivocal	Unequivocal neurological signs of spinal cord compression • **Weakness in limbs** • **Altered sensation with a sensory level** • **Urinary retention** • **Upper motor neurone signs or sudden flaccid paralysis** • **Saddle anaesthesia and sphincter disturbance (cauda equina lesions)**
ACTION NOW: • Keep possibility of evolving cord compression in mind. • Arrange investigations as appropriate to deal with pain • Arrange early review of patient by yourself or another professional	*ACTION NOW:* • Urgent referral (same day) to hospital for MRI scan (CT scan if MRI contra-indicated) and urgent treatment if diagnosis confirmed • Start dexamethasone 16 mg daily • Refer to Spinal Cord Compression ICP via Christie Hospital website www.christie.nhs.uk	*ACTION NOW:* • Discuss with Consultant Oncologist/team (via Christie) if already involved in this patient's care • Urgent referral to hospital * for MRI scan (CT scan if MRI contra-indicated • Request radiotherapy or surgical decompression as an emergency • *Refer direct to Christie Hospital Consultant if rare tumour (e.g. lymphoma, sarcoma) • Start dexamethasone 16 mg daily • Refer to Spinal Cord Compression ICP via Christie Hospital website www.christie.nhs.uk
REASSESS IF SYMPTOMS WORSEN/PROGRESS	**DO NOT DELAY**	**DO NOT DELAY**