Breast Cancer Clinical Guidelines

Title: NECN Breast Cancer Clinical Guidelines
Authors: Breast NSSG members
Circulation List: Breast NSSG
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Date: April 2015 Version: V2.5 Review Date: May 2016

Document Control

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<th>Version</th>
<th>Date</th>
<th>Summary</th>
<th>Review Date</th>
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<tr>
<td>2.5</td>
<td>22.04.15</td>
<td>Pages 20-27 age changed from 40 to 35</td>
<td>May 2016</td>
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<tr>
<td>V2.4</td>
<td>06.04.15</td>
<td>Family History section re-written Oncotype DX mentioned as desirable Biopsy of metastases Checking menopausal status before endocrine therapy SLNB section updated and ABS document</td>
<td>May 2016</td>
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<td>V2.3</td>
<td>29.11.13</td>
<td>Resection margin changed from 3mm to 1mm on page 39 and 41.</td>
<td>May 2014</td>
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<td>Position</td>
<td>Name</td>
<td>Organisation</td>
<td>Date Agreed</td>
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</tr>
<tr>
<td>Breast NSSG Chair</td>
<td>Mr M Carr</td>
<td>Northumbria Healthcare NHS FT</td>
<td>06.04.15</td>
</tr>
<tr>
<td>Breast NSSG Vice-Chair</td>
<td>Dr M Verrill</td>
<td>Newcastle Hospitals NHS FT</td>
<td>13.05.15</td>
</tr>
<tr>
<td>Medical Director</td>
<td>Dr M Prentice</td>
<td>Cumbria, Northumberland, Tyne and Wear Area Team</td>
<td>13.05.15</td>
</tr>
<tr>
<td>Chemotherapy Network Group Chair for:</td>
<td>Mr S Williamson</td>
<td>Northumbria Healthcare NHS FT</td>
<td>13.05.15</td>
</tr>
<tr>
<td>CYPCG Chair for:</td>
<td>Sue Cornick, Head of Specialised Commissioning</td>
<td>Cumbria, Northumberland, Tyne and Wear Area Team</td>
<td>13.05.15</td>
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NSSG members agreed the Guidelines on:
**Date Agreed:** circulated 13.05.2015 for endorsement at the July Meeting
**Review Date:** May 2016
INTRODUCTION

Terms of Reference

This document provides regional guidelines for the management of breast cancer and is designed to complement existing national guidelines e.g. National Institute for Health and Care Excellence (NICE) and Association of Breast Surgery (ABS). This guideline does not override the individual responsibility of healthcare professionals in making decisions appropriate to the circumstances of the individual patient. It is not anticipated that the guidelines will cover all clinical situations in all patients, but where unusual circumstances exist, it is expected that such treatments would be discussed in the appropriate MDT.

These guidelines take into account NICE clinical guidelines, CG80 (NICE February 2009, April 2012) CG81 (June 2014) and CG164 (June 2013), and have been reviewed and revised, following TSSG discussion, in April 2015.

The guidelines will be reviewed on an annual basis. Where new treatments are introduced between revisions they will be added as an addendum to the current guideline.

Facts and Figures

- More than 40,000 breast cancers are diagnosed each year in the UK (1)
- Breast cancer causes around 13,000 deaths per annum the UK (1)
- One woman in 9 will develop breast cancer at some time during her lifetime.
- Eight of ten breast cancers occur after the menopause.
- Screening may reduce the chance of dying from breast cancer. It provides women with more choices in the planning of their surgical treatment.
- Nine out of ten breast lumps are not cancer.
- The number of deaths from breast cancer in England peaked in the late 1980’s and since then has been falling faster than in any other country (2)
- Between five and ten per cent of women with breast cancer have an inherited predisposition.

Public Health and Prevention

Environmental factors including obesity (BMI>32), moderate amounts of alcohol, nulliparity, and hormone replacement therapy have been associated with an increased risk of developing breast cancer. Caffeine, dairy products and smoking are not known to cause breast cancer. In 88,000 women in the Nurses’ Health Study, there was an inverse association between breast cancer risk and the intake of low-fat dairy products. A healthy lifestyle involving regular physical activity, avoidance of high calorie diets and promotion of breastfeeding can lead to prevention of some cases of breast cancer.
SCREENING

General Population Screening

The National Breast Screening programme is well established. The aim of the screening programme is to produce a 30% reduction in mortality from breast cancer. The screening programme has an independent national quality assurance programme, run regionally by the Quality Assurance Reference Centre (QARC).

- All women aged 50 to 70 are currently invited for three yearly mammographic screening. The programme is being expand to the age group 47 to 73 over the next few years
- Women over 70 are informed that they may request mammography although they are not routinely invited in the national screening programme.(Some age 71-73 will be called as part of the expansion)
- The chance of finding a cancer by mammography screening is 1 in 200 as outlined below:

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Screened</td>
<td>200</td>
</tr>
<tr>
<td>All clear</td>
<td>186</td>
</tr>
<tr>
<td>Recall for assessment</td>
<td>14</td>
</tr>
<tr>
<td>Needle biopsy</td>
<td>5</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
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</table>

There are separate screening recommendations for women previously treated with radiotherapy for Hodgkin’s Disease
Management of Patients with a Family History indicating increased risk of Breast Cancer

http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.html

http://www.nice.org.uk/guidance/CG164/chapter/Introduction

NICE guidance on familial breast cancer stratifies women into three groups: near population risk, raised risk and high risk.

Patients with a Family History of Breast Cancer will be managed in accordance with guidelines issued by NICE and by the NHSBSP.

<table>
<thead>
<tr>
<th>Breast cancer risk category</th>
<th>Near population risk</th>
<th>Moderate risk</th>
<th>High risk¹</th>
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<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lifetime from age 20</td>
<td>Less than 17%</td>
<td>Greater than 17% but less than 30%</td>
<td>30% or greater</td>
</tr>
<tr>
<td>Between ages 40 and 50</td>
<td>Less than 3%</td>
<td>3–8%</td>
<td>Greater than 8%</td>
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<td><strong>Site of Management</strong></td>
<td>In Primary Care Reassurance, advice on avoiding risk factors.</td>
<td>In Secondary Care Breast Unit</td>
<td>In Tertiary Care Specialist Genetics Referral</td>
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</table>

¹ This group includes known BRCA1, BRCA2 and TP53 mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11), Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).

Chemoprophylaxis for Women at High Risk of Breast Cancer

NICE (CG184) states that postmenopausal women with a uterus with no personal history, but at high risk of breast cancer women due to a family history, should be offered either tamoxifen or raloxifene for 5 years to unless they have a past history of, or may be at increased risk of, thromboembolic disease or endometrial cancer.

However, these guidelines also acknowledge that neither agent currently has a UK marketing authorisation for this indication and that prescribers should follow relevant professional guidance, taking full responsibility for the decision and that informed consent should be obtained and documented.
Pathway(s) for High Risk Women – in the North East and North Cumbria

Referral from oncology (supra-diaphragmatic RXT under 30)

Referral from primary care and other sources for ? family history

New referrals to secondary or tertiary genetics assessment

Low risk
High Risk New referrals
High risk Already known to genetics, but under age (genetics will refer when of age)
Moderate Risk

Breast Screening Programme
Enter on to NBSS IT system at local NHSBSP

Screening
MRI only (NUTH/NTH)
MRI (NUTH/NTH) & Mammo
Mammo only (Local BSP)

Assessment
MRI Mammo & needle biopsy, U/S & results (NUTH / NTH)
MRI guided needle biopsy
Mammo & needle biopsy U/S & results (local BSP)

Management as standard population
Some women will opt out of screening at any stage and return to standard population

High & Moderate risk
Family history Women already referred by Genetics and under care of different breast units around the NE & North Cumbria

High risk
Moderate risk

Symptomatic breast services (local arrangements)
Some women will opt for bilateral Mx at any stage

Referral for treatment comes under symptomatic service

Diagnostic surgical biopsy
# Protocols for the surveillance of women at higher risk of developing breast cancer

<table>
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<th>Risk</th>
<th>Ages</th>
<th>Surveillance Protocol</th>
<th>Frequency</th>
<th>Notes</th>
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<tr>
<td>BRCA1 or BRCA2 carrier or Not tested, equivalent high risk</td>
<td>20-29</td>
<td>n/a</td>
<td>Annual</td>
<td>Review MRI annually on basis of background density</td>
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<tr>
<td></td>
<td>30-39</td>
<td>MRI</td>
<td>Annual</td>
<td></td>
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<tr>
<td></td>
<td>40-49</td>
<td>MRI + Mammography</td>
<td>Annual</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50+</td>
<td>Mammography ± MRI</td>
<td>Annual</td>
<td></td>
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<tr>
<td>TP53 Li-Fraumeni</td>
<td>20+</td>
<td>MRI</td>
<td>Annual</td>
<td>No mammography</td>
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<tr>
<td>A-T Homozygotes</td>
<td>25+</td>
<td>MRI</td>
<td>Annual</td>
<td>No mammography</td>
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<tr>
<td>A-T Heterozygotes</td>
<td>40-49</td>
<td>Mammography</td>
<td>18 monthly</td>
<td>Routine screening from 50</td>
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<tr>
<td></td>
<td>50+</td>
<td>Mammography</td>
<td>Routine screening (3 yearly)</td>
<td></td>
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<tr>
<td>Supradiaphagmatic radiotherapy: irradiated below age 30</td>
<td>30-39</td>
<td>MRI</td>
<td>Annual</td>
<td>Surveillance commences at 30, or 8 years after first irradiation, whichever is the later. Review MRI annually on basis of background density. Confirmation of history of radiotherapy must be obtained</td>
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<tr>
<td></td>
<td>40-49</td>
<td>MRI ± Mammography</td>
<td>Annual</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50+</td>
<td>Mammography ± MRI</td>
<td>Annual</td>
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Taken from: NHSBSP Publication No 74

**Proforma for Referral of Patients to Clinical Genetics Service**

![Proforma Image]

**The Newcastle upon Tyne Hospitals NHS Foundation Trust Institute of Human Genetics**

**FAMILY HISTORY BREAST SCREENING REFERRAL**

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<tr>
<td>Address</td>
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<td>Telephone Number</td>
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| Genetics Reference no:                |

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Risk assessment and any relevant family history

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<th>Has patient had breast cancer</th>
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<td>If yes give details</td>
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<table>
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<tr>
<th>Has patient had oophorectomy</th>
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<td>Supradiaphragmatic radiotherapy irradiated</td>
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<td>MRI Annually</td>
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<td>Below age 30</td>
<td>40-49</td>
<td>MRI + mammography annually</td>
<td></td>
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<tr>
<td>BRCA1/2 or not tested equivalent risk</td>
<td>40-49</td>
<td>MRI + mammography annually</td>
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<tr>
<td>Known TP 53 (Li Fraumeni)</td>
<td>50-70</td>
<td>MRI annually</td>
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<td>&gt;30% probability of TP53 carrier</td>
<td>50-70</td>
<td>3 yearly - NHSESP</td>
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<td>A-T Homozygote</td>
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<td>MRI</td>
<td></td>
</tr>
<tr>
<td>AT Heterozygote</td>
<td>50-70</td>
<td>3 yearly - NHSESP</td>
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<tr>
<td>High Risk: Non BSP</td>
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<td>MRI + mammography annually</td>
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<tr>
<td>Moderate Risk</td>
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<td>3 yearly - NHSESP</td>
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<tr>
<th>Section C: To be completed by Screening service</th>
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Referral accepted for high risk screening  □  Referral rejected for high risk screening □
Reason for rejection
Form not completed  □  Does not meet criteria □
Radiologist signature  Date

* Surveillance protocols based on agreed guidelines – May 2014*
Pathway for patients with suspected Breast Cancer

**Triple assessment - One Stop - Breast Clinic**

1. Clinical Examination Imaging +/- Biopsies
   - Is cancer confirmed or still suspected?
     - No: Results discussed with patient
   - Ye: Further diagnostics?
     - No: Histology results available
     - Ye: Further investigations carried out
   - Ye: Initial MDT discussion of investigation results, treatment & rehabilitation plan plus consideration for clinical trials

2. Decision to treat date
   - Ye: Early Clinical Assessment Date (ECAD) for commencement of subsequent treatment
   - No: First Treatment

3. First Treatment
   - Ye: Early Clinical Assessment Date (ECAD) for commencement of subsequent treatment
   - No: Best time in

4. Relevant verbal and written information provided
   - Provide ongoing psychological support & assessment
   - Allocate Breast Care Nurse/Key Worker

5. See TYA
   - Inform patient's GP of Serious Diagnosis
   - See Breast Rehabilitation Care Pathway liaise & involve healthcare professionals as required

6. Early Clinical Assessment Date (ECAD) for commencement of subsequent treatment
   - Ye: Further investigations as required
   - No: Appropriate After Care

**First Treatment**

- Primary Endocrine Therap
  - Patient assessed
  - MDT discussion to review histology & staging results also consider for clinical trials
  - Further investigation required?
    - Ye: Early Clinical Assessment Date (ECAD) for commencement of subsequent treatment
    - No: Further investigations required?
      - Ye: Appropriate After Care
      - No: Chemotherap

**Further Investigation**

- Endocrine Therapy
- Radiotherapy
- Biological Agent

**Supportive Palliative Care**

**Further investigations**

- Chemotherap
- Surgery +/- reconstruction
- Supportive Palliative Care
CRITERIA FOR URGENT BREAST CLINIC REFERRAL (UNDER 2 WEEK RULE)

Symptoms and warning signs that are suspicious and warrant urgent investigation:

- **Lump**
  - any new discrete lump
  - new lump in pre-existing nodularity
  - asymmetrical nodularity that persists at review after menstruation

- **Pain**
  - if associated with a lump
  - unilateral persistent pain in post-menopausal women

- **Other potential signs of cancer**
  - ulceration
  - skin nodule
  - skin distortion
  - breast abscess or inflammation not settling after one course of antibiotics
  - nipple discharge especially if age >50, or bloodstained
  - nipple eczema unresponsive to topical steroids
  - recent (<3month) nipple inversion

- **Physical Examination**
  - An appropriate examination should be performed prior to referral
  - The aspiration of a lump in a patient with a history of multiple cysts should only be performed by a General Practitioner who has the necessary skills. Aspiration of solid lumps should not be attempted as it may affect imaging and delay diagnosis or even lead to mis-diagnosis.

Priority for Referral

Following the Government's Health Service Circular (HSC 242/98), all patients with symptoms deemed to be suspicious by their GP will, if the letter is faxed or e-mailed, be seen within 14 days of the decision for referral (3). The guidance for the GPs determining which symptoms are suspicious is outlined in the booklet by Austoker et al (4). Such referrals must be considered as urgent and offered the next available appointment by the local breast clinic. The guidance for GPs should be directed by the Hospital and must be clear and easy to follow; an example of the recommended guidance is listed in Appendix 1.

Two weeks for all breast clinic referrals

In line with new targets all referrals to symptomatic breast clinics will be seen within 2 weeks from the end of 2009.
## Referral Pathways

<table>
<thead>
<tr>
<th>CCG Referral Pathways</th>
<th>Trust</th>
<th>Designated MDT</th>
<th>Named MDT Lead/Contact/Tel/Fax</th>
<th>Screening Centres</th>
</tr>
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<tbody>
<tr>
<td>South Tees</td>
<td>South Tees Hospitals</td>
<td>James Cook</td>
<td>Dr A Humphreys T: 01642 854353 Fax: 01642 854940</td>
<td>Yes</td>
</tr>
<tr>
<td>Hambleton, Richmondshire &amp; Whitby</td>
<td>South Tees Hospitals</td>
<td>James Cook</td>
<td>Dr A Humphreys T: 01642 854353 Fax: 01642 854940</td>
<td>Yes</td>
</tr>
<tr>
<td>Hartlepool &amp; Stockton</td>
<td>North Tees &amp; Hartlepool</td>
<td>University Hospital of</td>
<td>Mr V Kurup T: 01642 617617 F: 01642 624957</td>
<td>Yes</td>
</tr>
<tr>
<td>Newcastle West</td>
<td>Newcastle Upon Tyne</td>
<td>Royal Victoria</td>
<td>S Nicholson T: 0191 2823748 F: 0191 2325278</td>
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<tr>
<td>Northumberland</td>
<td>Northumbria Health Care</td>
<td>Wansbeck General joint with North Tynside General Hospital</td>
<td>Mr M Carr T: 01670 529209 F: 01670 529220</td>
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</tr>
<tr>
<td>Gateshead</td>
<td>Gateshead Health NHS FT</td>
<td>Queen Elizabeth</td>
<td>Ms T Fasih T: 0191 4820000 F: 0191 4820360</td>
<td>Yes</td>
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<tr>
<td>Sunderland Easington</td>
<td>City Hospitals Sunderland</td>
<td>Sunderland Royal</td>
<td>Dr J Connor T: 0191 5656266 Ext 42933 F: 0191 5410515</td>
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<tr>
<td>North Durham</td>
<td>County Durham and</td>
<td>University Hospital of</td>
<td>Mr A Bhatti 0191 3332333 F:0191 594406</td>
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<tr>
<td>Durham Dales, Easington &amp; Sedgefield (excl Easington)</td>
<td>Darlington Memorial Hospital</td>
<td>Darlington Royal</td>
<td>Mr L Barthelmas T:01228 523444 F:01228 634001</td>
<td>Yes</td>
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</tbody>
</table>

Source - Mid-2013 Population Estimates for Clinical Commissioning Groups (CCGs) in England - ONS.gov.uk
NSSG Guidelines for Teenage and Young Adults

Teenage and Young Adults Peer Review Measures Topic (Functions of the Network Site Specific Groups for TYA)

1. Teenage and Young Adult Pathway for initial Management

The NSSG has received the document named ‘NECN Teenage and Young Adult Cancer Pathway Guidance Paper’ and agrees to follow the generic TYA Pathway with any site specific variations to be documented. Please see Appendix 1 for pathway.

2. Teenage and Young Adult Pathway for Follow up on completion of first line treatment

Patients aged 19-24 years will adopt the site specific adult follow up pathway on completion of first line treatment. It is acknowledged by both the CYPCG and NSSGs across NECN that further work is required to develop these pathways for this age group and partly in response a TYA working group has been established to take this work forward.

If advice is required regarding the follow up care of a 19-24 year old patient, then the Lead TYA Clinician at the designated hospital or PTC should be contacted. Please see Appendix 2 for contact details.

Patients age 16-18 years will continue to adopt the paediatric and adolescent follow up protocol of the PTC and all advice should be sought direct from the On Call Paediatric Oncologist at Royal Victoria Infirmary 0191 2336161. Paediatric Follow Up Protocols can be found on the CCLG website (2005 second edition) with the exception of trial specific protocols which can be requested via the Children’s Trial Co-ordinator based at the RVI.

3. Pathways for cases involving Specialised NHS services (Only Gynae and Sarcoma)

The Gynae NSSG and SAG reviewed and agreed the Specialised NHS Service pathway for patient’s age 16-24 years. This is attached in Appendix 3.
Appendix 1 – Teenage and Young Adult Pathway for initial Management

Teenage and Young Adult Cancer Pathway – 19 to 24 years old

Urgent referral made by OP/GDP/Screening
Emergency Admission
Other source of referral (screening/genetics clinic)

Assess as per local Tumour Site Specific protocol:
- Site specific diagnostic investigations
- May include diagnostic biopsies, but not definitive cancer surgery

Cancer diagnosed or highly suspicious
Patient informed of joint MDT review and place of care options
NB: MDT discussion should take place in tumour site specific MDT within PTC/TVAs designated hospital AND TVA MDT

Review at TYAMDT
Communication & Liaison between MDTs

Joint treatment planning decision agreed, including:
- Diagnosis and treatment modalities/routine
- Place of treatment delivery, depending on patient age:
  - 16-18 years - PTC facility only (Paediatric & Adolescent Oncology, RVI, Newcastle)
  - 19-24 years - choice of PTC facility (Adult Oncology, FH, Newcastle) or TVA designated hospital
- Named consultant in charge of each treatment modality
- The arrangements/transfer to provide age appropriate support if the treatment is delivered outside the PTC facility
- The results of the discussion of fertility issues
- Consider entry into clinical trials
- Consider palliative & supportive care needs
- Identify patients’ key worker

PTC (RVI or Freeman) – treatment and ongoing care (with options for shared care or supportive care)
Designated TVA hospital treatment with option of TYAMDT outreach support 19-24 yr

Haematological/Oncological Treatment (first definitive treatment)
- Surgery
- Chemotherapy
- Biological therapy
- Radiotherapy

Assess response at site specific haematological/oncological/tumour MDT
Consider need for further consolidation treatment

Relapse or recurrent disease
Long term follow up protocol
Further treatment
Palliative care

Abbreviations:
- TYA (Teenage and Young Adults)
- TYA DH (Teenage and Young Adult Designated Hospital)
- PTC (Paediatric Treatment Centre, Newcastle upon Tyne hospitals)

TYA Cancer Ideal Pathway Map version 17
DLTRJ 2017 and acknowledgment to Vessel Cancer Network
## Appendix 2 – Contact Details

<table>
<thead>
<tr>
<th>Name of NHS Trust and designated hospital site</th>
<th>Name of MDT</th>
<th>TYA Lead Clinician</th>
<th>TYA Lead Nurse</th>
<th>Contact Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gateshead Health NHS Foundation Trust - at Queen Elizabeth Hospital</td>
<td>Specialist Gynaeoncology</td>
<td>Ms Christine Ang</td>
<td><a href="mailto:helen.manderville@ghnt.nhs.uk">helen.manderville@ghnt.nhs.uk</a></td>
<td>0191 4456148</td>
</tr>
<tr>
<td>City Hospitals Sunderland NHS Foundation Trust - at Sunderland Royal Hospital</td>
<td>Haematology</td>
<td>Dr Emma Lethbridge</td>
<td>Faye Laverick</td>
<td>0191 5656256</td>
</tr>
<tr>
<td></td>
<td>Specialist Urology (testicular only)</td>
<td>Dr Scott Marshall</td>
<td><a href="mailto:faye.armstrong@chsft.nhs.uk">faye.armstrong@chsft.nhs.uk</a></td>
<td>0191 5656256</td>
</tr>
<tr>
<td>North Tees and Hartlepool NHS Foundation Trust - at University Hospital of North Tees</td>
<td>All MDTs:</td>
<td>Dr Padmaja Lokireddy</td>
<td>Kat Dawson</td>
<td>01642 617617 ext 24697</td>
</tr>
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<td></td>
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<td></td>
<td><a href="mailto:Katherine.Dawson@nuth.nhs.uk">Katherine.Dawson@nuth.nhs.uk</a></td>
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<td>South Tees Hospital NHS Foundation Trust - at James Cook University Hospital</td>
<td>All MDTs:</td>
<td>Dr Dianne Plews</td>
<td>Jill Linton</td>
<td>01642 854381</td>
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<td>Specialist Gynaeoncology</td>
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Appendix 3 – NHS Specialised Services Pathway

NHS Specialised Services - Referral Pathway for Primary Malignant Bone Cancer for patients age 16-24 years within the North of England

Paediatrician → GP → Radiology/Incidental Finding

- Referral to Sarcoma Service at Freeman Hospital Newcastle (FRH)
  See Sarcoma pathway for contact details

- If age 16-18 years refer to PTC paediatric & adolescent MDT at RVI and Bone & Soft Tissue MDT at FRH

- All patients to be discussed at the TYA MDT (see TYA pathway for contact details)

- If age 19-24 years refer to Bone & Soft Tissue MDT at FRH

Necessary to refer to National Ewing's Sarcoma MDT for discussion?

- Yes
  - Submit electronic MDT proforma and link in via WebEx.
  - Please see Bone & Soft tissue site specific pathway and/or paediatric & adolescent pathway for detail

- No
  - Please see Bone & Soft tissue site specific pathway and/or paediatric & adolescent pathway for detail

5 years post treatment for patients age 16-24 years

- Age 16-18 yrs at time of diagnosis refer to long term follow up clinic/MDT
- Age 19-24 yrs at time of diagnosis follow up on adult protocol
NHS Specialised Services
Referral Pathway for Hydatidiform Mole / Gestational Trophoblastic Neoplasm / Choriocarcinoma
Weston Park Hospital, Sheffield

Gynaecologist / Antenatal dept perform U/S or histology from failed pregnancy confirms hydatidiform mole

Post Pregnancy, ectopic pregnancy or miscarriage confirms choriocarcinoma on histology or high clinical suspicion

Patient referred to Weston Park Hospital Sheffield. Histology reviewed and patient registered on national programme

Hydatidiform mole diagnosis confirmed on histology

Patient bloods & urine monitored by Sheffield copies to GP and referring gynaecologist

hCG levels return to normal

Complete follow up protocol

Discharge

hCG levels do not return to normal

Outpatient visit at Sheffield

Staging scan, blood tests, prognosis score, treatment plan at Sheffield

Discuss at Sheffield GTN MDT

Outpatient visit at Sheffield for staging and treatment plan

Choriocarcinoma diagnosis confirmed on histology or further staging needed to confirm

All Treatment delivered at Sheffield

hCG monitoring will be for life via Sheffield. Copies sent to GP and referring gynaecologist

Low risk: methotrexate chemo can be given at local hospital under direction of Sheffield. If age 16-18 years this should be on teenage unit (RVI). If age 19-24 this should be on Young Adult unit at Newcastle (Freeman) or TYA Designated Unit at James Cook, Middlesbrough

Patients age 16-24 yrs having local low risk chemo to be alerted to Newcastle TYA MDT

Patients age 16-24 yrs referred to TYA MDT @ Sheffield

Choriocarcinoma Pathway
Toni Hunt NECN Version 0.4 Aug 2012
HOSPITAL INVESTIGATION AND ASSESSMENT OF BREAST CANCER\textsuperscript{(5,6)}

Triple assessment increases the accuracy and reduces overall cost of diagnosis when compared with selective use of the component tests. The three tests when used in experienced hands can result in a positive predictive value of 99\% (7), thus minimising the need for open biopsy (8). This reduces surgical time and minimises anxiety induced by delay. At least 90\% of women with breast cancer should be diagnosed pre-operatively.

Triple assessment comprising clinical examination, imaging (mammography /ultrasound) and biopsy, is recommended for women with suspected breast cancer at a single visit.

\begin{itemize}
\item Biopsy by needle core biopsy and/or FNA. Needle core biopsy is the investigation of choice where malignancy is suspected.
\item Local anaesthetic may be appropriate for some patients.
\item All facilities and staff needed to provide this service should be in close proximity to the diagnostic clinic.
\item The results of triple assessment should be given to the patient within five working days.
\end{itemize}

The following investigations are recommended for different breast symptoms once clinical examination has taken place:

\begin{description}
\item[Breast Lump:] Triple assessment:
\item[Breast Pain:] Unilateral persistent mastalgia without palpable abnormality: clinical examination only.
\item[Nipple discharge:] clinical examination and imaging as indicated.
\item[Nipple retraction:] clinical examination and imaging as indicated.
\item[Change in skin contour:] triple assessment
\end{description}

When a diagnosis of cancer is made, the only other routine investigations recommended prior to surgery are a chest x-ray, full blood count and biochemistry (bone & liver).

See further information on perioperative staging later.
COMMUNICATING THE DIAGNOSIS

Informing the Patient

- The patient should be informed of the diagnosis by a Consultant or an appropriately experienced member of the MDT [9].
- Facilities should be available for the patient to be informed of the diagnosis during a private uninterrupted consultation.
- A trained breast CNS should be available during the consultation and should be available to provide additional counselling as required [10].
- Opportunity to contact the breast CNS for further counselling, support and information (confidential phone numbers, address and key worker contact cards etc) should be offered and follow up arrangements agreed before the patients leaves.
- Patients should be given time, information and support to make a fully informed decisions about their treatment. This should include discussion with the surgeon, in liaison with the breast CNS, of suitable treatment options. The offered options and the decisions for therapy as indicated by the discussions held at the multi-disciplinary team (MDT) should be recorded in the patient record [11, 12].
- The patients informational needs will be constantly assessed. Details of available therapy should not necessarily be discussed at the diagnostic visit, especially if in the “one-stop” setting. Where necessary, arrangements should be made for a subsequent “treatment planning” visits.
- Patients should be given the opportunity for a close friend or relative to be present during the consultations and the subsequent journey home.
- Written information regarding breast cancer treatments should be available and offered to all patients [13].
- A prognosis should not be offered before adequate staging information is available.

Informing the Primary Care Team

- The GP should be informed of the diagnosis on the same day as the patient or by noon the day following, preferably by fax, using a serious diagnosis proforma.
- The general practitioner should be made aware of the information which has been given to the patient and, if possible, an outline of the planned treatment.
- If the diagnosis is made as in inpatient, the Primary Care Team should be informed prior to discharge from hospital
- Hospital nursing staff should ensure that relevant community nurses are also informed
- Major alterations to the management plan should be communicated to the General Practitioner by telephone, fax or letter within one working day. Similarly, if alterations are made by the general practitioner, these should be communicated to the hospital within two working days. A patient held record, where available, would be a supplementary means of such communication.
CANCER WAITING TIMES TARGETS 2009/10

The cancer standards stipulate a maximum of 31 days from decision to treat to first definitive treatment, and 62 days from 2 week referral to definitive treatment. From December 2009 all referrals to symptomatic breast clinics will be subject to the 2 week rule.

As announced in the Department of Health Cancer Reform Strategy (2007), the 31 day standard has been extended to cover all cancer treatments. This applies to all surgery and drug treatments from December 2008, and to radiotherapy treatments from December 2010.

⇒ Decision to Treat
The decision to treat date is the date of the consultation in which the patient and clinician agree the treatment plan for first treatment. If the first treatment requires an admission (e.g. Surgery) this date is recorded on hospital PAS systems, as the "Date of decision to admit" (used for calculation of waiting list statistics).

⇒ First Definitive Treatment
The first definitive treatment is normally the first intervention which is intended to remove or shrink the tumour. Where there is no definitive anti cancer treatment almost all patients will be offered a palliative intervention (e.g. stenting) or palliative care (e.g. Symptom control) which should be recorded for these purposes.

⇒ Subsequent Treatment
The 31 day standard for subsequent treatment begins at either a second “decision to treat date” or an “earliest clinically appropriate date” (ECAD) for the patient to undergo the next event in their care pathway.

⇒ Breach Reasons
Detailed reports on breaches are recorded and should include how long the patient waited, reason for the breach in the target and action put in place to prevent further breaches.
GUIDELINES FOR SYMPTOMATIC BREAST IMAGING

Based on:

- Association of Breast Clinicians Best Practice Diagnostic Guidelines 2011
- Royal College of Radiologists Breast Imaging Guidelines

General Principles

1. Patients 35 years and over

Mammography is the imaging technique of choice. Target breast ultrasound provides useful additional information and may be used as a primary examination where physical examination suggests a benign process such as a cyst, if the woman has not had mammograms in the past 12 months. Unless there is clinical concern, a mammogram should not need to be repeated within two years. Ultrasound is NOT a suitable screening technique and should not be used in the absence of clinical or mammographic abnormality.

2. Patients under 35 years

Many patients attending breast clinics are under 35 years and do NOT require imaging as part of their diagnostic assessment. There is a low incidence of breast cancer in this age group. In patients in this age group with significant focal problems targeted ultrasound is the imaging technique of first choice. Ultrasound is not indicated in the absence of a significant clinical symptom as it is not a screening tool. When malignancy is suspected either clinically or on ultrasound then mammography should be performed.

Symptom-Specific Imaging

Discrete Lump

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<th>Age</th>
<th>Imaging Protocol</th>
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<td>&gt;= 35 years</td>
<td>Mammography + ultrasound</td>
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<tr>
<td>&lt; 35 years</td>
<td>Ultrasound (+ mammography for P4/5 or U4/5 lesions). If P2/3 and U2 a core biopsy should confirm benignity and mammography not needed. If P3 and U1 consider mammography. (Best practice Guidelines P15).</td>
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Criteria for safe avoidance of unnecessary biopsy in females <25 years with solid breast masses

Solid breast masses in young women are a common problem in breast clinics and the majority of these are fibroadenomata. Carcinoma, Phylloides and Papilloma are uncommon under 30 years and rare under 25 years thus the cut-off for targeted biopsy is considered to be 25 years.
If biopsy is NOT being performed then the following criteria should be met:

1. Clinical features:
   - <25 years
   - Mass not rapidly enlarging
   - Smooth discrete mobile mass on palpation
   - No risk factors for malignancy

2. Ultrasound features U2:
   - Homogenous isoechoic or hypoechoic mass < 30mm
   - Ovoid shape and parallel to skin surface
   - Smooth or gently lobulated contour without microlobulations.
   - Thin psuedocapsule
   - No acoustic shadowing or calcifications


**Lumpiness or "Asymmetric Nodularity"**

- **P1/P2 and >= 35 years** Mammography (opportunistic screen)
- **P1/P2 and <35 years** Ultrasound for clinically benign asymmetry (P2). If ultrasound U1 or U2 mammography is not indicated. (Best Practice guidelines p15).
- **P3 and >=35 years** Mammography + ultrasound
- **P3 and <35 years** Ultrasound. Proceed to mammography if indicated on ultrasound (i.e. score U3-U5) (Best Practice guidelines P15)
- **P4/P5 any age** Mammography and ultrasound

**Nipple Discharge – No Lump**

Age appropriate imaging for spontaneous single duct or serosanguinous discharge i.e. under 35 ultrasound; 35 and over mammography + ultrasound

Routine imaging is not indicated in multi-duct or bilateral discharge.

**Breast pain**

Bilateral or cyclical breast pain, ANY AGE, imaging not indicated.
Unilateral breast pain in patients:

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<th>Age Group</th>
<th>Imaging Protocol</th>
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<tr>
<td>&gt;=35 years</td>
<td>Mammography (opportunistic screen)</td>
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<tr>
<td>&lt;35 years</td>
<td>DO NOT REQUIRE ROUTINE IMAGING</td>
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The risk of finding a breast cancer on imaging in a woman with breast pain and normal clinical examination is no greater than the risk of finding breast cancer in an asymptomatic woman having a screening mammogram.

**Suspected Breast Sepsis**

Ultrasound +/- ultrasound guided drainage is indicated in the acute phase. Patients >=35 years should have routine mammography once acute phase has settled. Localised tenderness is a focal clinical sign so should be imaged as appropriate for age i.e. 35 and over mammography, under 35 ultrasound (Best Practice guidelines p19).

**Presumed Fat Necrosis**

If clinically benign (P1/P2) and imaging consistent with fat necrosis U2 (+/-M1/M2) then biopsy is not required. If there is ANY doubt either clinically or radiologically then biopsy should be performed.

**Intracystic Papillary Lesions**

If lesion is clearly seen on ultrasound then biopsy should be carried out and CLIP inserted as biopsy might render lesion difficult to see at a later date.

**Skin Lesions, eg Sebaceous Cysts and Non-Suspicious Nipple Eczema**

Imaging not indicated

**Gynaecomastia**

Gynaecomastia affects one third of all males in their lifetimes and is the commonest cause of a breast “lump” or discrete sub-areolar swelling in a male patient.

Carcinoma of the male breast is very rare and is extremely uncommon in men less than 50 years. It accounts for <1% breast cancers and <0.2% cancers in men.

In clinically suspected gynaecomastia with no suspicious features imaging is not indicated under age 50. If >=50, ultrasound is the imaging of choice.

Unifocal lumps in the male breast should undergo ultrasound of the breast and then guided core biopsy to avoid missing diagnosis of breast cancer or lymphoma. If the biopsy is positive then mammogram and axillary ultrasound is indicated.
**Imaging of the Axilla**

Every patient with suspected breast malignancy should have ultrasound of the ipsilateral axilla.

If an abnormal node is seen (ultrasound criteria) then needle biopsy should be carried out. Positive pre-operative node biopsy identifies those patients unsuitable for SNB.

Ultrasound criteria for lymph node sampling are:

- Cortex>=as per local criteria
- Focal cortical bulge
- Short axis ratio >0.5
- Loss of fatty hilum

i.e. score of N3 or higher

**IF HAEMATOLOGICAL MALIGNANCY IS SUSPECTED FNA IS INAPPROPRIATE. CORE BIOPSY OR EXCISION BIOPSY SHOULD BE CARRIED OUT.**

**Needle Biopsy**

Needle core biopsy is preferred to FNAC for most solid/suspicious lesions and should be performed under image guidance wherever possible to achieve greatest accuracy and reduce the need for repeat procedures.

Free hand biopsy may be appropriate for cases of palpable locally advanced breast cancer and cases where imaging is normal but there is a suspicious localised clinical finding.

**Indications for MRI Scanning**

**To diagnose or exclude breast cancer when triple assessment is inconclusive**

- Clinical/imaging discordance.

- Metastatic carcinoma in axillary lymph nodes with normal mammography and ultrasound.

- Conventional imaging difficult to interpret due to previous treatment or surgery.

**To assess the extent of newly diagnosed breast cancer**

- Clinico/radiological non-correlation of lesion size.

- Lobular carcinoma if conservative surgery planned to affected breast.

- Occult carcinoma to exclude multi-focality and to size accurately if patient wants conservative surgery.
To monitor response to neoadjuvant chemotherapy

- Pre treatment to delineate size and extent of tumour.
- Post 2 cycles of chemotherapy to assess response.
- Post treatment if conservative surgery planned.

Breast implants

Ultrasound examination to be undertaken first. If conclusive of rupture, no further imaging needed.

MRI is indicated when there is a clinical suspicion of rupture and ultrasound is normal. When there is a double lumen implant, MRI is the investigation of choice.

Breast reconstruction

To investigate possible recurrence when mammography and ultrasound unhelpful.

**ALL MRI REQUESTS SHOULD BE DISCUSSED AT THE MDM AND MANAGEMENT DECISION AGREED**
NECN GUIDELINES FOR PATHOLOGY REPORTING

Following the diagnosis of breast cancer a tumour should be staged according to the pT and pN categories of TNM classification (see appendix 1). The breast multidisciplinary team must include a pathologist or pathologists with a special interest and expertise in breast pathology and cytology, with designated time for breast cancer work. The pathology services must be organised according to the NHSBSP guidelines and include the RCPath minimum dataset - link to both sets of guidelines as follows:-

http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html
http://www.cancerscreening.nhs.uk/breastscreen/publications/qa-08.html

Histopathology Standards:

Histopathology procedures and reporting should be as described in the NHSBSP document “Pathology Reporting in Breast Cancer Screening”. The recording of the data for symptomatic patients must be same as that for the screening patients.

Histopathology departments and surgeons must have access to specimen radiography. Specimen radiograph must accompany the specimen.

Histopathology laboratories should work towards nationally defined accreditation standards. It is desirable that Pathologists reporting breast cancer routinely should participate in the EQA National scheme.

It is the responsibility of the operating surgeon to ensure that the specimen is orientated and marked for the pathologist as agreed locally. Ideally nodal levels should be labelled and sent separately. There should be agreement between surgeons and pathologists in each unit on how specimens are oriented and labelled and considering the requirement for a specimen X-ray where appropriate.
REFERRAL GUIDELINES BETWEEN MDTS WITHIN AND OUTSIDE THE NECN

All the constituent MDT’s within the North of England Cancer Network recognise that referral to another MDT, or specialist centre for specific treatment might be required in certain cases. Examples of such referrals are: specialist pathological review in unusual cases, referral to another team if treatment not available locally, i.e., certain types of breast reconstruction or radiosurgery for brain metastases, patient request for relocation of their care.

When a local MDT or cancer team feels that such referral is indicated then the following are agreed:

- The MDT will follow the pathology guidelines regarding specialist MDT referral.
- The MDT or cancer team will provide all data to the receiving MDT including radiology, pathology and clinical information.
- The clinician in charge of the patient or a responsible member of their team will write a formal referral letter to the receiving team.
- The patient and their GP will be informed of the reason for their referral onto another MDT or specialist centre by the referring team.

On return of the patient the specialist MDT team will be expected:

- To provide written information regarding the treatment delivered.
- Indicate the need for any follow up by the referring team, or agreement of continuing shared care.
- To inform patient and their GP of transfer of care back to referring team if appropriate.
SURGICAL TREATMENT OF BREAST CANCER

- Surgical treatment of breast cancer, especially reconstructive surgery, should be carried out by surgeons with a special interest and training in breast disease (see the BASO 1998 guidelines for recommendations for Surgical Training). Breast surgeons must work in Breast Units that provide necessary expertise and facilities for multidisciplinary approach \(^{(14)}\).

- In patients where breast conserving surgery is considered unwise and mastectomy is to be carried out, or where a patient requests mastectomy but with minimal cosmetic disruption, an opportunity should be provided before mastectomy for the patient to discuss the possibilities for breast reconstruction with an oncoplastic surgeon if this is oncologically appropriate. If reconstruction is needed and the MDT concerned do not have the relevant expertise the patient will be referred to another MDT within the Network.

- Multidisciplinary case review and planning (MDM) should be the standard for all patients with newly diagnosed breast cancer \(^{(15)}\). Patients with recurrent or metastatic disease should be discussed where uncontrolled local disease is present, or at the discretion of MDT members.

- Consultants and other core members of the multidisciplinary team within the breast unit should have contractual time for attendance at multidisciplinary meetings in a planned programmed activity.

- The conclusions of the MDM should be recorded in all the patient records, irrespective of the number of hospitals that the patients attend for the management of their breast cancer. This should be supported by the appropriate clerical requirements. The MDM should be minuted with an attendance record; the minutes should be made available to all core members of the MDM.

- The number of therapeutic procedures should be recorded. 90% of patients having conservation surgery should have three or fewer therapeutic operations.

- It is the responsibility of the operating surgeon to ensure that the specimen is orientated and marked for the pathologist as agreed locally. Ideally nodal levels should be labelled and sent separately. As a minimum the apical node should be marked in an axillary clearance specimen. There should be agreement between surgeons and pathologists in each unit on how specimens are oriented and labelled and considering the requirement for a specimen X-ray where appropriate.

- A diagnostic or therapeutic axillary procedure should be performed in all patients with an invasive cancer unless the MDT has specifically advised against this.

- Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle
biopsy. Sentinel lymph node biopsy (SLNB) is the preferred technique. When performing SLNB the aim should be to sample no more than 4 nodes. SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme.

Management of In situ breast cancer

1) Ductal carcinoma in situ (DCIS)
Up to 20% of screen detected cancers fall into this group but nearly 40% of DCIS lesions diagnosed currently in the UK present (often as incidental findings) in symptomatic clinics. DCIS is a direct precursor of invasive breast cancer. Fine needle aspiration is inadequate for distinguishing DCIS from invasive cancer. A core biopsy is necessary for cases with microcalcifications with mammographic appearance of DCIS. Vacuum assisted devices are also available e.g. mammotome which increase accuracy by providing larger volumes of tissue for analysis.

The risk of recurrence following surgery is influenced by grade, size, patient’s age and resection margin. These factors form part of the Van Nuy’s prognostic index which is often used as a guide for the need for radiotherapy after breast conserving surgery despite the fact that it has not been possible to validate this using data from any of the large randomised DCIS trials. While disease at, or very close to, the resection margin is the greatest predictor of recurrence after breast conserving surgery for DCIS once clear margins have been obtained the patient’s age would appear to be the most important factor with young (<35) patients being most at risk.

Surgical management:

- **Multifocal or extensive (>40mm) DCIS**: simple mastectomy. In highly selected patients there may be a role for therapeutic mammaplasty in some larger DCIS lesions. Axillary staging with SLNB should be advised in those patients undergoing mastectomy. Reconstruction should be offered to all patients requiring or chosing mastectomy for DCIS.

- **Small (<40mm), non-central, unifocal lesions**: taking into consideration the patient body habitus and with regard to the resulting cosmetic appearances, the aim is complete local excision.

- **Margins**: remain a contentious issue and there are no clear guidelines available. The Surgical guidelines for the management of breast cancer (Association of Breast Surgery at BASO 2009) state: “Units should have local guidelines regarding acceptable margin width for DCIS and individual cases should be discussed at the treatment MDT meeting. If, after MDT meeting discussion, the margin of excision is deemed to be inadequate then further surgery to obtain clear margins should be recommended”. The international evidence, such as it is, seems to point to a margin of 2mm as being adequate but because margin width is but one variable other factors such as age, DCIS grade and lesion size should be considered by the MDT before recommending repeat excision when the margin is >1mm.

Follow-up specimen radiographs should be carried out to confirm complete excision of all suspicious calcifications, particularly if they are extensive or approach the edge of the surgical specimen.
Adjuvant treatment for DCIS:

- Optimum adjuvant treatment of DCIS is still uncertain. The ultimate goal is to identify lesions that are more likely to recur locally, and thus, might be better treated with further adjuvant therapies. Over treatment of lesions unlikely to recur should be avoided particularly in older (>60) patients with significant co-morbidity. Adjuvant radiotherapy significantly reduces the risk of recurrence following breast conserving surgery for DCIS but has little or no influence on overall survival.

Adjuvant Tamoxifen for DCIS:

- The UKCCCR DCIS trial showed no significant benefit from Tamoxifen\(^\text{(16)}\). The (US) NSABP B24 suggested a small reduction in the risk of recurrence (9.3% vs 6%, absolute benefit 3.3%) although this was in patients without rigorous control of excision margins. No survival advantage was demonstrated.

- The current evidence **does not** support the use of adjuvant endocrine therapy for DCIS outside a clinical trial. However patients who entered the IBISII trial were randomised between tamoxifen and Arimidex (anastrozole). IBIS II has now closed to recruitment.

Lobular carcinoma in situ (LCIS)

This is an uncommon condition, invisible on mammography and often detected coincidentally during histological evaluation of breast tissue. It acts as a marker for increased risk of developing either ductal or lobular breast cancer in the future which is 5-10 times the standard population risk. Invasive cancers may occur either in the ipsilateral or contralateral breast. Invasive cancers are likely to be visible on mammography thus annual mammographic screening for 5 years or until the patient enters the NHS BSP (whichever is later) is recommended.

Recent recommendations point out that **pleomorphic LCIS** should be treated in the same manner as DCIS and clear margins of excision are required.

**Radiotherapy for non-invasive lesions** is discussed in the main Radiotherapy section of this guideline.
**SURGICAL TREATMENT OF INVASIVE BREAST CANCER**

Small unifocal invasive cancers with no palpable nodes.

- Surgery may be wide local excision or total mastectomy, according to patients’ preference, and the size and location of the primary tumour. Co-morbidities may restrict the treatment choices available to the patient and must be considered in treatment planning.

- The maximum size of cancers undergoing breast conserving surgery cannot precisely be regulated, however patient habitus, resulting cosmetic appearances and adequacy of resection margins should be taken into account. For the majority of patients a primary cancer greater than 4cm will probably not be best managed by breast conserving surgery. In those patients undergoing breast conserving surgery the margins must be clearly marked, preferably by a method agreed by the surgeon, radiologist and pathologist.

- There are good data from randomised controlled trials supporting the view that surgical margin status is a strong predictor of long term local recurrence rates\(^{(17)}\), although the trend towards smaller resection margins does not appear to confer a higher local recurrence rate, especially if adjuvant therapy is planned\(^{(18,19)}\).

- Resection margins remain a contentious issue in invasive breast cancer as well as in the treatment of DCIS. The Surgical guidelines for the management of breast cancer (Association of Breast Surgery at BASO 2009) state: For patients undergoing breast conserving surgery “All patients should have their tumours removed with no evidence of disease at the microscopic RADIAL margins and fulfilling the requirements of local guidelines. If, after MDT meeting discussion, the margin of excision is deemed to be inadequate then further surgery to obtain clear margins should be recommended”. The ABS Guidelines also state “Close margins at the chest wall or near the skin may be less important” NICE have previously recommended a minimum radial margin of 2mm, although there are no data to substantiate this. As in the management of DCIS, many other factors need to be considered by the MDT such as patient age and co-morbidity, tumour grade and size and the use of systemic adjuvant therapies which in themselves reduce the risk of local recurrence. Local recurrence risk clearly needs to be stratified – for example a 1mm margin may be perfectly adequate in a 65 year old with a small (<10mm) low grade, ER+ cancer but inadequate in a 35 year old with a larger, high grade ER- cancer

- The indication for diagnostic vs. therapeutic axillary surgery should be discussed in the MDT meeting prior to operation. In rare cases of invasive cancer, there will be a recommendation for no axillary surgery, e.g. in a patient with advanced disease undergoing mastectomy for local control and those >80 with radiologically negative axillae who are fit for surgery but in whom chemotherapy will not be recommended.
Axillary Sentinel Lymph Node Biopsy

All patients with invasive early breast cancer should have a preoperative ultrasound examination of the axilla and subsequent ultrasound guided nodal biopsy when indicated.

Sentinel Lymph Node Biopsy (SLNB) is the standard of care for staging the axilla in patients without pre-operative evidence of nodal disease.

The use and timing of SLNB in patients with locally advanced or inflammatory breast cancer is unclear and requires MDT discussion.

SLNB using radiolabelled nanocolloid is safe in pregnant women as the dose to the uterus is minimal. Blue dye should not, however, be used because of the risk of staining of fetal tissues.

A negative SLNB should identify those patients without axillary node involvement, thus obviating the need for ALND with its greater risk of morbidity. The risk of arm morbidity, particularly lymphoedema, is significantly lower after SLNB than ALND. A recent systematic review, performed by the ASCO expert guidelines panel, included 69 eligible trials of SLNB in early stage breast cancer, representing 8059 patients\(^{18}\). The SLN was identified using radiocolloid, blue dye, or both. Overall, 95 percent had a SLN successfully identified. The false negative rate overall was 7.3 percent.

Management of the Patient with Tumour-Positive SLNB

Further axillary treatment is no longer considered mandatory in all cases of tumour-positive sentinel nodes. In its Consensus Statement\(^{62}\) of March 2015, the Association of Breast Surgery (ABS) recommends:

**Isolated Tumour Cells and/or Micrometastases**
No further axillary treatment is required in addition to breast conserving surgery or mastectomy.

**For 1-2 Sentinel Nodes with Macrometastases**
Further axillary treatment is no longer mandatory in patients who meet these criteria:
- Receiving breast conservation with whole breast radiotherapy
- Post-menopausal
- Have T1, Grade 1 or 2, ER Positive and HER2 Negative tumours.

Further axillary treatment is recommended in this group of patients who meet these criteria:
- Are undergoing mastectomy
- Or who have tumours with one or more of the following features: T3, Grade 3, ER Negative or HER2 Positive.

*These patients could also be entered into the POSNOC or equivalent clinical trial.*

Radiotherapy to the axilla is a valid alternative treatment to axillary lymph node dissection in patients with a low burden of axillary disease.

The ABS Group did not reach consensus on the management of patients with one or more of the following features:
- Pre-menopausal status
• T2 tumours
• Lymphovascular invasion
• Extra-nodal spread

These cases will require individual MDT decisions

3 or More Sentinel Nodes with Macrometastases
Patients should usually be recommended to have further axillary surgical treatment.

The preferred technique is axillary lymph node dissection (ALND) because it gives additional staging information. Where further surgery is deemed inappropriate following MDT discussion, radiotherapy to the lymph node drainage areas may be considered.

Level of Dissection — ALND extent can be defined by either the number of axillary LNs resected or their anatomic location. Axillary LNs are divided into three levels based upon their relationship to the pectoralis minor muscle:

- Level I — inferior and lateral to the pectoralis minor muscle
- Level II — posterior to the pectoralis minor and below the axillary vein
- Level III (infraclavicular) — medial to the pectoralis minor and against the chest wall.

Dissection of the axilla to Level III is unlikely to be of additional benefit over dissection of Levels I and II unless the patient has gross disease at the apex of the axilla and does carry an increased risk of lymphoedema and shoulder dysfunction.

The possibility of breast reconstruction should be discussed. The data in studies are inconclusive as to the perceived benefits from reconstructive surgery following mastectomy or breast conserving surgery (20).

Larger tumours or with palpable nodes

- Mastectomy and axillary node clearance to level 2 or 3 is currently the standard treatment in patients with proven axillary node disease.

- In patients in whom axillary ultrasound is negative' sentinel node biopsy is an acceptable alternative to axillary dissection.

- The possibility of immediate or delayed breast reconstruction should be discussed unless this is deemed inappropriate by the MDT, usually on the basis of risk of inadequate excision in the case of immediate reconstruction or risk of recurrence and/or death in the case of delayed reconstruction.

- If considered of doubtful operability, or where downstaging to enable breast conservation is desired, patients may be eligible for pre-operative systemic treatment with either chemo- or hormone therapy. Where possible this should be in a clinical trial.

- The Clinical Trials units at NCCC and JCUH have a portfolio of clinical trials including neoadjuvant treatment of breast cancer. Further information may be
Complications of Surgery:

1. Breast conserving surgery. Patients should be warned that the cosmetic results may not be ideal but all surgeons should employ Level I oncoplastic techniques to minimise the risk of poor cosmesis. The primary aim of therapy is to remove the cancer with a low risk of recurrent disease. Level II oncoplastic techniques, such as reduction mammoplasty, may allow larger tumours to be removed whilst preserving the breast in suitable ladies. Similarly, central breast tumours may be considered for breast conserving surgery. The axillary incision can lead to tethering of the axillary skin leading to restrictive movement in the shoulder. All patients prior to breast cancer surgery should be seen pre-operatively by the Physiotherapist and instructed in the post operative exercises; this should continue post-operatively. Damage to the intercosto-brachial nerve results in hypoesthesia in the upper inner arm which may not fully recover. All patients should be warned of lymphoedema and facilities should exist for treatment of this condition at Cancer Unit level.

2. Mastectomy. Patients should be warned of the likely cosmetic appearance following this surgery; this should include practical information about the timing and type of prosthesis available. A small number of patients with large breasts or who are obese may require scar revision subsequently.

3. All types of surgery. Axillary seroma formation, wound haematoma and infection are possibilities and should be explained.

4. Lymphoedema: is a swelling of the arm due to poor lymphatic drainage, which can be caused by surgery, radiotherapy, lymphatic obstruction from tumour, trauma or infection. Venous obstruction can also cause a similar clinical picture. Acute lymphoedema should therefore trigger appropriate investigations or if a recurrence is suspected.

Lymphoedema is common in patients who have had an axillary dissection (2–10%). The combination of axillary irradiation therapy with axillary dissection increases the risk of arm oedema to 13–18%, with some studies putting the risk is this case as high as 38%. Axillary recurrence following adequate axillary surgery is so infrequent (0–2%) that routine axillary radiotherapy is not generally indicated.

Lymphoedema can affect quality of life and activities of daily living, depending on severity. It can lead to reduced movement due to arm weight, pain, cosmetic disfigurement, reduced wound healing, and cellulitis.

Prior to axillary surgery patients should be informed of the risk of lymphoedema and given appropriate preventative advice. Information should be reinforced throughout the patient’s journey and on discharge from the CNS caseload. This should include: avoidance of venepuncture, injections or blood pressure recording on the affected side, as well as wearing gloves for gardening,
moisturising the arm daily with a bland emollient to keep the skin in good condition, avoiding insect bites and heat, and being vigilant for signs of infection.

Any signs of infection in the “at risk” arm should be treated promptly with antibiotics as per guidelines - British Lymphology Society (BLS) Guidelines for the use of antibiotics in lymphoedema – available at www.thebls.com

Patients should be taught specific exercises following surgery, which will help to reduce the risk of lymphoedema developing. Prevention of lymphoedema must be highlighted and reinforced throughout the patient journey and supported with written advice.

Treatment of lymphoedema involves skin care, exercises, simple lymph massage and wearing a lymphoedema sleeve, or sometimes compression bandaging. Where appropriate patients should be referred into a specialist service for MLD – Manual Lymph Drainage, a specialised massage to reduce limb size, improve the condition of the skin, and soften sub-cutaneous tissues. All patients should be able to access a local lymphoedema clinic.

Cosmetic Breast Reconstruction:

In the presence of both invasive and non-invasive cancer, immediate reconstruction must be discussed in the MDT meeting prior to the procedure.

Immediate reconstruction following mastectomy is suitable for patients not likely to require adjuvant radiotherapy:

- Patients with small tumours with likely clear margins and negative nodes who request a mastectomy
- DCIS
- Small but centrally placed lesions
- Prophylactic mastectomy

Delayed breast reconstruction is suitable for the following categories of patients:

- Patients who were at high risk of local recurrence but have been disease free for a period of time, generally regarded as 2 to 5 years

To minimise the risk of loco-regional recurrence in patients undergoing reconstruction, patients should be advised against reconstruction according to the following criteria:

- High local recurrence risk such as with extensive lymph node involvement
- Extensive skin infiltration
- Disease attached to the chest wall
- Active cancer at any site
Pre and Peri-operative Staging

Minimum

- Full blood count and liver biochemistry should be the minimum baseline investigation for proven invasive breast cancer and should performed before surgery in all patients.

For Higher Risk Cancers

Gerber et al. studied the frequency of distant metastases in a series of more than 1000 patients with early breast cancer(21). Approximately 3% of patients were found to have metastases. The overwhelming majority of patients had one of the following risk factors:

- Primary tumour > 5cm
- 4 or more involved axillary nodes

It is recommended that patients meeting these criteria should have additional staging in the form of a CT scan of chest and abdomen and bone scan.

Less than 1 in 800 patients without a risk factor have metastases and these patients should not be fully staged unless there is clinical suspicion.

Patients undergoing neoadjuvant therapy with either chemotherapy or hormones should be fully staged before treatment if they have a tumour > 5cm in diameter or palpable axillary lymphadenopathy.
RADIOTHERAPY FOR BREAST CANCER

Adjuvant Radiotherapy for Invasive Breast Cancer
(For non invasive breast cancer, see below)

Introduction

Ideally should begin within 6 weeks of completion of surgery or chemotherapy dependant on wound healing, shoulder mobility and the timing of chemotherapy. Delays of >8 weeks may be detrimental. A recent meta-analysis of 15 000 patients confirmed that delay in starting radiotherapy was associated with a significant increase in local relapse rate. This increase was seen when radiotherapy was delayed beyond 8 weeks following surgery corresponding to an increase in local recurrence rate from 5.8% to 9.1% at 5 years (22).

Anthracycline, capecitabine and taxane chemotherapy are radiosensitizers, therefore a gap of at least 3 weeks is recommended before commencing adjuvant radiotherapy. CMF has been given concurrently with radiotherapy. However, the incidence of acute radiotherapy side effects is increased although there is no evidence of an increase in long term side effects. In the absence of long term cardiac toxicity data on Herceptin and radiotherapy, at present adjuvant Herceptin is to be started after completion of radiotherapy and not concomitantly. This is in accordance with NICE guidelines. There is data from the American Intergroup trial N9831 suggesting that herceptin given concurrently with radiotherapy does not result in increased cardiac or other toxicity and hence, if confirmed, this policy may require review.

All patients should receive adjuvant breast radiotherapy after breast conserving surgery (23). The EBCCTG radiotherapy overview (24) found that:-

1. ¾ of local recurrence occurred in the first 5 years.
2. Local recurrence was reduced by 2/3 by radiotherapy after wide local excision in node negative (reduced from 30% to 10%) and node positive breast cancers (reduced from 45% to 15%) at 15 years.
3. There was a 5% survival benefit from radiotherapy in node negative and 7% in node positive breast cancer after breast conserving surgery at 15 years.
4. Local recurrence was reduced by 2/3 by radiotherapy after mastectomy in node negative (reduced from 8% to 3%) and node positive breast cancers (reduced from 30% to 8%) at 15 years. Survival benefit of 5% was seen only in node positive breast cancer after mastectomy.
5. There was an excess mortality from heart disease (rate ratio 1.27, SE 0.07, 2p=0.0001) and lung cancer (rate ratio 1.78, SE 0.22, 2p=0.0004).

Post Breast Conserving Surgery

No subgroup of tumours has been identified which does not benefit from lower local recurrence rates following radiotherapy. However, elderly patients with good prognostic features are at low risk of recurrence. According to the CALGB trial in patients aged >70 with T1N0 ER+ve breast cancer, the five year recurrence rate following breast conserving surgery was 4% without radiotherapy versus 1% with radiotherapy(25). Patients with early breast cancer should be considered for the PRIME II study. The PRIME II trial is currently looking at radiotherapy versus
observation in patients aged >65, with grade 1 or 2, <3cm in diameter, ER positive, node negative tumours.

Indications for radiotherapy to lymph node drainage areas are as for post mastectomy (see below).

Post Mastectomy

High Risk
The following patients should be offered adjuvant chest wall radiotherapy post-mastectomy:-

- all T3 (>5cm) breast cancers
- all T4 breast cancers (involving chest wall or skin)
- breast cancers with 4 or more positive lymph nodes in the axilla.
- margin<1mm
- Indications for axillary and/or supraclavicular fossa radiotherapy (see below)

Intermediate risk
Relative indications for adjuvant chest wall radiotherapy post-mastectomy include 2 or more of the following factors: age<40 years, grade 3, 3+ nodes positive or lymphovascular invasion (LVI).

Locoregional failure rates following mastectomy without RT are 5 to 15 percent for women with 1 to 3 positive nodes, and these women should be offered entry into the SUPREMO study. Eligibility criteria include N1 disease or T2 tumours which are G3 and/or have evidence of LVI.

Indications for radiotherapy to lymph node drainage areas:

1. Axilla
   - Positive node(s) in patients who have not had an axillary node dissection and don’t wish to have further surgery.
   - Relative indication:-
     - >1mm extracapsular or perinodal infiltration
     - SCF node involvement
     - Apical node involved

2. Supraclavicular fossa
   - Four or more positive nodes
   - Apical node involved
   - SCF node involvement
   - Relative indications:-
     - After neo-adjuvant chemotherapy for inflammatory or locally advanced breast cancer
     - 1-3 positive nodes and other poor prognostic factors (eg T3, grade 3 +/- LVI)

These apply to patients treated surgically by either mastectomy or breast conserving surgery.
Patients unsuitable for surgery:

A small group of patients are unsuitable for primary surgery resulting from medical incapacity, infirmity or where there is high risk from general anaesthetic (preferably as assessed by the anaesthetist). Hormone therapy is the mainstay of treatment provided the tumour is hormone receptor positive. In one study of 113 patients, hormonal therapy with Tamoxifen provided local control for a median time of 2.5 to 3 years (27). Letrozole has been proven to be superior compared to tamoxifen in terms of time to progression (28). Radiotherapy may be considered appropriate if the tumour is ER –ve, or upon progression on hormonal therapy. Some patients with fungating, bleeding or painful tumours who require a faster response can also be offered primary radiotherapy.

NECN recommendation for palliative radiotherapy for locally advanced breast cancer:-
Dose 40 Gy in 15 fractions over 3 weeks by tangential fields.

Alternative fractionation:-
Dose 32Gy in 4 fractions delivered once a week over 4 weeks. There is no published data on this fractionation regime but it has been used previously at the NCCT in a limited number of frail patients who would not be able to cope with daily travel.

Radiotherapy technique
The breast/chest wall, and axilla if indicated, are treated by isocentric tangential fields. It is not possible to completely exclude the axilla with this technique, but the superior and lateral field borders can be positioned to include the axilla when required or, conversely, to exclude most of the axilla.

If indicated a supraclavicular fossa field is matched on to cover the apex of the axilla and supraclavicular fossa nodes.

The chest wall may be treated by electrons in suitable patients.

Treatment is 3D planned to achieve as nearly as possible dose homogeneity to within +7%/-5% (prescribed according to ICRU 50/62).

The recommended prescribed dose is **40 Gy in 15 fractions over 3 weeks**.

In certain situations 50Gy in 25 fractions over 5 weeks may be preferred. The indications are all relative rather than absolute:

- For patients in whom >2cm lung is included on any slice.
- Patients requiring axillary and/or SCF node irradiation.
- Suboptimal Dose distribution. Dose homogeneity of +7%/-5% as recommended by ICRU 50/62 is the ultimate aim but cannot be routinely achieved. An improved technique is being introduced with the aim of achieving a dose distribution of +10%/-5% in most patients.
- Following breast reconstruction.

The indication for using 50Gy/25f should be specified on the prescription.
Tumour bed boost with electrons

A breast boost is not routinely recommended but should be considered in those at above average risk of local recurrence in the region of the tumour bed. It has been demonstrated in an EORTC trial to reduce local recurrence rates following breast conserving surgery in selected patients (29). All patients in the EORTC trial had microscopically complete excision margins. The greatest benefit was seen in those <40 years old (10% vs 20%), a modest benefit in those between 40 and 50 (5% vs 10%) and no benefit in women over 50 years old (3% vs 4%). However, cosmetic appearance was poorer after boost. At 3 years, 86% of patients in the no-boost group had an excellent or good result, compared to 71% in the boost group (p = 0.0001).

A 2007 update of the EORTC trial (J Clin Oncol 2007 25-22:3259-67) no longer suggests a statistically significant interaction by age group, but the absolute reduction at 10 years was largest in the under 40s. The authors suggested increasing the age for boost to 60.

The NCCC policy has been to use boosts for those with margins <5mm. An audit of local recurrence rates in women <40 years at NCCT (2008) found a low recurrence rate of 5%.

The NECN recommendation is that a boost is given to the following groups:
- Women under the age of 40
- Women >40 years old with a resection margin of <1mm

Other factors should be considered in patients who do not fall into the above groups. They represent relative indications for a breast boost and should not be considered in isolation. These factors include
- Lymphovascular invasion
- Grade 3
- ER/PR negative
- Presence of extensive in-situ carcinoma (>25%)
- T3

It is preferable that the boost is planned using information from the pathology report, surgical notes and pre-operative mammograms. Surgical clips in the tumour bed, where present, aid localisation. Electron energy is prescribed to ensure that 90% of the prescribed dose reaches the surface of pectoralis major. Study of the planning CT scan improves accuracy in deciding the electron energy and a method of planning the boost on the planning scan is being developed. The electron mark-up is currently done clinically, with the aim to cover the at risk area with a 1.5cm to 2cm margin.

Dose for boost = 10Gy in 5 fractions in one week.

Unwanted side effects of radiotherapy

Immediate side effects during adjuvant breast irradiation include fatigue and skin erythema or desquamation. To prevent this from happening, patients should be advised to avoid deodorant on the treated side, wear loose clothing and pat skin dry after washing to minimize friction and epithelial loss.
During radiotherapy skin reaction is managed with aqueous cream and if symptomatic with 1% hydrocortisone cream unless there is evidence of moist desquamation. Moist desquamation should be managed with barrier dressings including geliperm and colloid dressings during radiotherapy. After the completion of radiotherapy, flamazine ointment can be used if there is moist skin desquamation.

NIH CTCAE Version 3.0 for Radiation Acute Skin Reaction

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Asymptomatic mild redness of skin, commonly seen in the 2nd week of breast radiotherapy</td>
<td>Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema. May be seen in the third week of breast radiotherapy.</td>
<td>Moist desquamation other than skin folds and creases; bleeding induced by minor abrasions. Rarely seen with breast radiotherapy.</td>
<td>Skin necrosis ulceration of full thickness dermis; spontaneous bleeding from involved site. Never seen with breast radiotherapy.</td>
</tr>
</tbody>
</table>

**Radiation pneumonitis:** is a clinical syndrome of cough, fever and/or shortness of breath accompanied by radiographic changes consistent with a non-infectious infiltrate. It usually comes on six weeks after radiotherapy and resolves completely by six months. In a retrospective analysis of 1624 women treated with conservative surgery and adjuvant breast irradiation at a single institution, the overall incidence of symptomatic radiation pneumonitis was only 1% at a median follow-up of 77 months, although this increased to 3% with the addition of a supraclavicular field (30). Administering concomitant chemotherapy with SCF irradiation lead to radiation pneumonitis in 8.8%. One study of 140 patients found no case of radiation pneumonitis in patients in whom less than 3.35 cm lung was measured at the central axis of the simulation film, with all cases of radiation pneumonitis occurring in patients with more than 4 cm of lung irradiated, suggesting that the central lung depth is a guide to risk (31).

The NECN recommendation is that the central lung depth be kept to <3cm in all patients receiving tangential field radiotherapy.

**Lymphoedema:** is a swelling of the arm due to poor lymphatic drainage, which can be caused by surgery, radiotherapy, or lymphatic obstruction from tumour. Venous obstruction can also cause a similar clinical picture. Acute lymphoedema should therefore trigger appropriate investigations.

Mild lymphoedema is common in patients who have had an axillary dissection (2–10%). The combination of axillary irradiation therapy with axillary dissection (level 2) increases the risk of arm oedema to 13–18%. Axillary recurrence following adequate
Axillary surgery is so infrequent (0–2%) that routine axillary radiotherapy is not generally indicated (see indications above).

Lymphoedema can affect quality of life and activities of daily living depending on severity. It can lead to reduced movement due to arm weight, pain, cosmetic disfigurement and reduced wound healing. A difference of more than 2 cm between the affected and normal arms is considered clinically significant.

Patients with axillary surgery are told following surgery to avoid venepuncture on the affected side. Any signs of infection in the at risk arm should be treated promptly with antibiotics. Patients should be taught exercises following surgery.

Treatment of lymphoedema involves skin care, simple lymphatic drainage, exercise and compression hosiery/bandaging. Patients should be able to access a local lymphoedema clinic and all units are encouraged to develop links with such a clinic or set up their own service.

Brachial plexus injury: No cases of this injury were recorded in the recently reported START trials or in the RCR survey of patients treated by 50 Gy in 25 fractions and therefore the expected incidence in patients treated according to this guideline is expected to be exceedingly low or absent.

Cardiac toxicity: An increased risk of cardiac deaths was noted 10-15 years following older techniques for breast irradiation. This risk should be much reduced for patients with modern techniques and should approach a maximum of < 0.5% (32). Whilst every care should be taken whilst planning to avoid the heart, including the use of MLC shielding, priority should be given to coverage of the tumour bed, especially in high risk cancers.

The indications for radiotherapy may need to be modified in individual patients in the light of their perceived individual risk of any of the above late effects. For example previous radiotherapy or pregnancy would be absolute and radiation sensitivity syndromes relative contraindications to conservative surgery with radiotherapy rather than mastectomy.

**Adjuvant Radiotherapy for DCIS**

- Three large randomised trials (NSABP-B17, EORTC and UKCCCR DCIS) have shown that adjuvant radiotherapy reduces the risk of local recurrence and the development of ipsilateral invasive cancer by around 50%, although no effect was seen on survival.

- NSABP-B17 has reported 12 year data on adjuvant radiotherapy. Radiotherapy reduced local recurrence from 32% to 16%. Around half of the recurrences were invasive.

- EORTC trial 10853 has reported 10-year follow-up, and found that the group receiving RT had significantly fewer invasive (8 versus 13 percent) and noninvasive (5 versus 14 percent) recurrences as compared to surgery alone.
In the UKCCCR study, the hazard ratio with adjuvant radiotherapy was 0.36 and 0.45 for DCIS and invasive cancer respectively (16). All patients had complete surgical excision of the lesion confirmed by specimen radiography and histology (unlike NSABP and the EORTC studies).

From the Silverstein data, there is a subgroup of patients that would have a very low risk of recurrence despite omission of radiotherapy.

The NECN recommendations for adjuvant radiotherapy in DCIS

The following are indications to consider adjuvant radiotherapy:-

- Margin<2mm following local excision and if further surgery not possible
- Margin<1mm if patient has had a mastectomy
- All high grade DCIS following breast conserving surgery
- All DCIS with comedo necrosis following breast conserving surgery

Electron boost may be used in DCIS if the MDT feels that there is risk of residual disease after surgical resection that cannot be improved by further surgery, although the evidence for this is weak.
ENDOCRINE THERAPY FOR INVASIVE BREAST CANCER

Oestrogen and Progesterone receptor status should be identified in all patients with invasive breast cancer. No decisions on systemic hormone therapies should be made until the test result is known.

The EBCCTG overview confirms that five years of tamoxifen in the adjuvant setting reduces the risk of death by 31% per annum in receptor positive breast cancer (33). ER and/or PR positivity are strong predictive factors for benefit from hormonal therapy. Hormone treatments should not be offered to ER and PR negative patients (34). ER status is determined using the Allred Quickscore, ranging from zero to eight.

The Allred Quickscore:

<table>
<thead>
<tr>
<th>Score for proportion</th>
<th>Score for intensity</th>
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<tbody>
<tr>
<td>0=no stain</td>
<td>0=no stain</td>
</tr>
<tr>
<td>1=&lt;1%</td>
<td>1=weak stain</td>
</tr>
<tr>
<td>2=1-10%</td>
<td>2=moderate stain</td>
</tr>
<tr>
<td>3=11-33%</td>
<td>3=strong stain</td>
</tr>
<tr>
<td>4=34-66%</td>
<td></td>
</tr>
<tr>
<td>5 =67-100% nuclei staining</td>
<td></td>
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</tbody>
</table>

Summed to give a maximum out of 8. Quickscore zero to two are deemed receptor negative, and Quickscore three to eight are deemed receptor positive.

Hormone Treatment Recommendations

- Always consider the current NCRN Trial Portfolio when considering anti-endocrine therapies.
- All ER and/or PR +ve patients should be offered endocrine treatment unless there is a contraindication to its use. Treatment should be offered for five years. In light of the results of the ATLAS and aTTom Trials61, showing further benefit in continuing tamoxifen to ten years, this should be considered in patients who are tolerating the treatment and who wish to continue.
- Tamoxifen for at least five years is the standard of care for all premenopausal women.
- AROMATASE INHIBITORS ARE ONLY EFFECTIVE IN POST MENOPAUSAL WOMEN. It is, therefore, critical that the menopausal status is known accurately and, if necessary, should be confirmed by measuring blood FSH and oestradiol levels.
- Letrozole for 5 years is the standard of care for all postmenopausal women. NICE guidance CG 80 recommends initial treatment with an aromatase inhibitor for all post-menopausal women, except those with low risk of recurrence. Following review of the most recent randomised clinical trials, including BIG 1-98, the NECN guideline treatment of choice is letrozole.
- The NICE guidance on aromatase inhibitors recommends use of each aromatase inhibitor within its license taking and taking recurrence risk into account:
  - Letrozole for a further 4 years after completion of 4-5 years Tamoxifen in node positive patients.
  - Letrozole, in addition, is licensed for Neoadjuvant treatment.
Both chemotherapy and tamoxifen can induce temporary amenorrhoea, and therefore if patients are being considered for switch therapy to an aromatase inhibitor, they must have gone through the menopause before starting chemotherapy as standard assays of E2 are unreliable in this setting.

In those node positive patients who were premenopausal prior to the start of tamoxifen but who now appear to be postmenopausal following systemic therapy the question of extended endocrine treatment with an AI may arise. Where this is felt to be clinically appropriate an MDT discussion is recommended. Menopausal status should be assessed 2 months after stopping tamoxifen using estimation of FSH and oestradiol. A sensitive oestradiol measurement is more accurate than standard serum oestradiol but is not available locally.

Where a high risk patient remains premenopausal after 5 years of tamoxifen, extended tamoxifen should only be considered after a full discussion of the risks and benefits of continuing therapy with the patient.

**Sequencing of Chemotherapy and Endocrine therapy**

- Endocrine therapy should never be started until receptor status is known.
- Endocrine therapy should not, ideally, be started until the patient has been discussed in an MDM and the possibility of clinical trials has been considered.
- Endocrine therapy should be deferred/interrupted in patients receiving chemotherapy because of trial data suggesting a survival advantage when Tamoxifen was given in sequence compared to concurrently.
- Don’t forget to start Endocrine Therapy after chemotherapy has finished, usually 3-4 weeks after the last injection.

**Complications of Endocrine Therapy**

These are well documented and each Unit should have written information for patients for whom endocrine therapy is proposed.

In summary:

1. **Bone loss:** bone mineral density should be assessed with a baseline dual energy X-ray absorptometry (DEXA) scan in the following patients:
   - Those starting aromatise inhibitors
   - Those having a treatment-induced menopause
   - Those starting ovarian ablation/suppression therapy
   The future screening and treatment of these patients with bisphosphonates should be offered according to the “Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK expert group (2008), see appendix 2.

2. **Menopausal symptoms:** the following may be helpful for some patients with distressing symptoms:
   - Oil of Evening Primrose
   - Auricular acupuncture
Selective serotonin re-uptake inhibitor antidepressants, paroxetine and fluoxetine may be offered for reliving hot flushes, except in those taking tamoxifen in whom they may reduce the effectiveness of tamoxifen.

Clonidine, venlafaxine and gabapentin should only be offered after patients have been fully informed of the significant side effects.

3. Abnormal or irregular vaginal bleeding should always be investigated fully because it may, very rarely, be a Tamoxifen-induced endometrial carcinoma.

4. Tamoxifen increases the risk of venous thromboembolic disease. Patients should be warned of this and advised on sensible precautions during e.g. long haul air travel.
Endocrine Therapy For Metastatic Disease

Where possible, a patient presenting with new metastatic disease should undergo biopsy of one of the metastatic deposits. This will allow histological confirmation and will also permit assessment of Hormone Receptor and HER2 status of the metastatic disease since this may not be concordant with the status of the original primary tumour.

Endocrine therapy should be considered as first-line treatment for the majority of patients with hormone receptor positive disease, particularly where disease is confined to the bone. Where there is significant visceral disease chemotherapy, followed by endocrine therapy is likely to be the preferred option.

Pre-menopausal

- Tamoxifen is the first line hormonal therapy of choice for patients with ER-Positive metastatic breast cancer (who are not already taking adjuvant tamoxifen). Those patients who have not previously taken Tamoxifen or who have completed a 5 year course more than one year before are suitable for consideration of Tamoxifen.
- In women already taking Tamoxifen, consider ovarian suppression +/- an aromatase inhibitor.

Post-menopausal

- Aromatase inhibitors are the treatment of choice for post-menopausal women with ER-Positive breast cancer. A change from a non-steroidal to a steroidal AI may give benefit in women who have previously received both a non-steroidal aromatase inhibitor and Tamoxifen.
- Progestogens may be considered in both pre and post-menopausal women when antioestrogens have failed.

**Hormone replacement therapy (HRT)**

It is advised that every patient diagnosed with breast cancer should cease HRT. There are newer forms now becoming available which may be sufficiently selective to confer a reduced risk to patients with respect to recurrence of their breast cancer. There is currently an NCRN study looking at this.
CHEMOTHERAPY FOR INVASIVE BREAST CANCER

Adjuvant Chemotherapy

Chemotherapy should start within 31 days of the completion of surgery, or earliest clinically appropriate date. Hormone treatments should be interrupted or delayed until chemotherapy is complete.

Anthracycline containing polychemotherapy (e.g. FAC) reduces the annual risk of death by 38% for women under age 50, and by 20% for women aged 50 to 69 [39]. The absolute benefit would be proportional to the individuals’ risk of recurrence and this can be estimated using the adjuvantonline tool available at www.adjuvantonline.com. This tool is to be used by health professionals familiar with the issues in the adjuvant treatment of breast cancer. The intention is that this tool be used to provide information that will then be helpful in shared decision making by the patient and the health professional.

For women < 70 years old, the St Gallen Consensus statement recommends that:
- All women with Node positive breast cancer and all women with Receptor negative breast cancer should be offered chemotherapy and so should be referred for an oncology opinion [40].

Some women, for example those age >35 with T1, N0, ER+ve Grade 1, HER2 -ve tumours are unlikely to benefit from chemotherapy and do not need to be referred.

NICE[63] has recommended the use of the Oncotype DX Gene Array Assay to help in guiding adjuvant chemotherapy decisions where suitable funding arrangements are in place and where the decision regarding chemotherapy is not clear-cut. This includes patients in whom:
- The tumour is ER-Positive, Node Negative and HER2 Negative
- The assessment is of intermediate risk
- Information provided by Oncotype DX is likely to help in decision making
- The manufacturer provides the assay in accordance with the confidential pricing agreement arranged with NICE

NECN encourages the use of Oncotype DX in appropriate situations.

HER2 positive breast cancer is a feature which increases (up to double) the risk of recurrence. All patients with HER2 positive breast cancer with tumour size >1cm should be referred to the medical/clinical oncologist for discussion of adjuvant chemotherapy followed by Herceptin (Trastuzumab).

Choice of Adjuvant Chemotherapy Regimen:

Choice of individual regimen requires an assessment of the risks and benefits for the individual patients.

Always consider entry to the NCRN adjuvant trials portfolio.

Node –negative patients who are suitable for adjuvant chemotherapy should receive an anthracycline containing regimen. Appropriate regimens are:
- EC X 6 (Epirubicin 90mg/m2 Cyclophosphamide 600mg/m2)
- FEC X 6 (5FU 600mg/m2 Epi 75mg/m2 Cyclo 600mg/m2)

Dose intensity should be maintained using secondary prophylaxis with G-CSF in event of neutropenic sepsis. Dose reductions are accepted both from the outset and in response to toxicity depending on performance status and clinical judgement of the treating physician.

In patients wishing to minimise the risk of alopecia, or who have a contra-indication to anthracyclines, classical CMF would be an alternative.

A taxane containing regimen should be considered in all node-positive patients and offered where clinically appropriate. The regimen of choice is FEC-T (Docetaxel). TC (Docetaxel + Cyclophosphamide) is an accepted alternative in patents with cardiac co-morbidity.

A network-wide audit of FEC-T chemotherapy has shown rates of neutropenic sepsis rates in excess of 20% in unsupported patients. The use of primary prophylaxis with GCSF is therefore recommended with this regimen.

**Cardiac Monitoring & Anthracyclines**

Transient ECG changes can occur during anthracycline therapy and are not in themselves an indication to discontinue treatment. There is, therefore, no absolute need for an ECG at baseline although is may be a useful marker of cardiac disease.

There is a risk of cardiomyopathy in patients with increasing cumulative exposure to anthracyclines and patients with any of the following risk factors should have a baseline assessment of LVEF by either echocardiogram or MUGA scan.

- Age above 65
- Hypertension requiring medication
- Heart failure
- Left ventricular hypertrophy
- Mediastinal irradiation
- Myocardial Infarction
- Planned cumulative doxorubicin dose > 360 mg/m2 or epirubicin doce > 600 mg/m2
  - In these patients repeat assessment during chemotherapy is recommended
- Any other identified cardiac risk factor

**Adjuvant Tastuzumab (Herceptin)**

20 percent of breast cancers overexpress HER2, a cell surface tyrosine kinase receptor. The addition of Herceptin to adjuvant chemotherapy is recommended for women with HER2-overexpressing tumors that are >1 cm or N+.

Two North American Cooperative Group trials were initially designed as parallel clinical trials. In NSABP trial B-31, 1736 women with HER2-positive, node-positive
(N+) breast cancer received AC x 4 followed by Paclitaxel (175 mg/m2 over 3 hours) x 4; they were randomly assigned to no further therapy (group NSABP-1) or weekly trastuzumab (initial loading dose 4 mg/kg, then 2 mg/kg weekly for one year, NSABP-2), beginning with the first dose of paclitaxel (39). The North Central Cancer Treatment Group (NCCCTG)-coordinated Intergroup trial N-9831 tested the value of adding trastuzumab to sequential AC and paclitaxel. Combined analysis of both trials confirm a 49 percent reduction in the risk of disease recurrence and a 37 percent reduction in the risk of death (four-year OS 93 versus 89 percent) (45). Similar figures were reported for the HERA trial (46).

In the FinHer trial (47), women with N+ or high-risk node-negative breast cancer were randomly assigned to three courses of docetaxel or vinorelbine followed by FEC x 3. The 232 women with HER2-positive breast cancer were randomly assigned to receive nine weekly trastuzumab infusions after completing chemotherapy. DFS was significantly better among those who received trastuzumab (89 versus 78 percent, p = 0.01), similar in magnitude as other studies using one year of Herceptin.

There was a higher incidence of cardiac toxicity in the patients that received adjuvant Herceptin. A recent meta-analysis of five randomised control trials of adjuvant Herceptin found a 7.2% increased risk of significant drop in cardiac function and 1.61% increased risk of symptomatic NYHA grade 3-4 heart failure following one year of Herceptin (48).

Management of cardiac events in trastuzumab-treated patients

1. **Baseline cardiac assessment prior to cytotoxic chemotherapy**
   - Medical history & physical examination including BP measurement
     - To detect pre-existing cardiac disease and risk factors.
     - 12-lead electrocardiogram (ECG), with echocardiogram if abnormal
   - LVEF measurement using Echo or radionucleotide multiple-uptake gated acquisition (MUGA) scan.

2. **Interventions at baseline**
   - Referral to a cardiologist
     - recommended for patients with significant cardiac co-morbidity.
   - Modification of planned chemotherapy regimen
     - In patients with low or borderline LVEF
     - Prophylactic ACE inhibitor therapy may also be considered.
   - Initiation of ACE inhibitors to control hypertension
     - Hypertension is a potent modifiable risk factor for the development of heart failure during Trastuzumab treatment.
     - Blood pressure above 140/85 mmHg should be treated with an ACE inhibitor, with primary care supervision of dose and renal function
   - Lifestyle recommendations
     - Smoking cessation, healthy diet & alcohol intake, optimising weight

3. **Management of cardiac function during trastuzumab**
   - Assessment of LVEF prior to starting trastuzumab treatment
     - LVEF should be assessed after chemotherapy and before Trastuzumab. Patients with an LVEF >= institution LLN should start Trastuzumab.
Patients with LVEF < institutional LLN should not start Trastuzumab but should be started on an ACE inhibitor and referred to a cardiologist. Repeat assessment of cardiac function should take place after 3 months.

- Sharp falls in LVEF (> 0.10) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on Trastuzumab. Prophylactic ACE inhibitor therapy may be considered for such patients.

- Routine LVEF monitoring is recommended after 4 and 8 months.
  - Assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment.
  - Additional testing is required in patients who have LV failure.

- Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted, receive an ACE inhibitor and be referred to a cardiologist.\(^{33,44,45}\)

- If the LVEF falls to ≤ 0.40, (representing biologically important LV systolic dysfunction) trastuzumab should be interrupted the patient should receive an ACE inhibitor and be referred to a cardiologist for treatment.\(^{33,44,45}\)

- After Trastuzumab interruption and appropriate medical therapy, LVEF should be re-checked after 6–8 weeks. Trastuzumab may be re-initiated if the LVEF is restored to a level above the LLN.

- If the LVEF falls to below the LLN but > 0.40, trastuzumab may be continued, but an ACE inhibitor should be initiated.
  - If the patient is already on an ACE inhibitor, they should be referred to a cardiologist.
  - LVEF assessment should be repeated after 6–8 weeks.

- If the LVEF falls by 0.10 points or more but remains above the LLN, trastuzumab may be continued. Intervention with an ACE inhibitor is recommended in an attempt to reduce the risk of further LVEF decline of symptomatic CHF.
  - LVEF Monitoring should be repeated after 6–8 weeks.

Traffic light system

Navigation through these guidelines may be facilitated by the adoption of a traffic light system.

- A green light indicates LVEF above the LLN, no signs or symptoms of CHF and any trastuzumab-related LVEF fall being < 0.10.
- An amber light indicates LVEF between the LLN and 0.40, with no signs or symptoms of CHF, or a trastuzumab-related LVEF reduction of 0.1 or more.
- A red light indicates LVEF ≤ 0.40 or symptoms and signs of cardiac failure.

Prior to chemotherapy, green indicates go. Red or amber indicates careful consideration of decision to start chemotherapy, with consideration of non-anthracycline-containing regimens. Both amber and red are indications for the initiation of ACE inhibitors, and referral to cardiology for the optimisation of cardiac function.

Post chemotherapy, green indicates go. Amber indicates defer until green. Red indicates that it is unlikely to be safe to start trastuzumab. Both amber and red are indications for the initiation of ACE inhibitors and referral to cardiology for the optimisation of cardiac function. It is recommended that LVEF is reassessed after 3 months, and that trastuzumab is not commenced unless LVEF is within normal limits at that point.
During trastuzumab, green is an indication to continue treatment. Amber is also an indication to continue chemotherapy, but patients should also be taking an ACE inhibitor. Patients who drop into the amber range while on an ACE inhibitor should be referred for a cardiology opinion. Red is an indication to interrupt trastuzumab, start on an ACE inhibitor (not already taking one) and refer for a cardiology opinion.

Patients whose trastuzumab is interrupted (i.e. red light) should not restart until LVEF is within the normal range (i.e. green light).

**Neo-Adjuvant Chemotherapy**

For patients with locally advanced disease or tumours where downstaging might facilitate conservative surgery, including inflammatory breast cancers, neo-adjuvant therapy, ideally in the context of a clinical trial should be considered.

The diagnosis must be established by core biopsy and ER, PR and HER-2 status should be ascertained.

If T3 or node positive, staging investigation including a CT scan of thorax and abdomen ± bone scan should take place before the commencement of neoadjuvant chemotherapy.

FEC or EC for 4-6 cycles is the off trial standard treatment. There are no data on the benefits of post-surgical chemotherapy in patients who have received neoadjuvant treatment, although sequences of chemotherapy (eg. Anthracycline followed by taxane) appear to be superior to anthracycline only combinations in this setting.

Patients who are ER positive should routinely be offered Tamoxifen after surgery.

In ER negative patients post-surgical treatment should be discussed carefully on a case by case basis and may include Taxane monotherapy.

**Chemotherapy In Metastatic Disease**

Where possible, a patient presenting with new metastatic disease should undergo biopsy of one of the metastatic deposits. This will allow histological confirmation and will also permit assessment of Hormone Receptor and HER2 status of the metastatic disease since this may not be concordant with the status of the original primary tumour.

Chemotherapy should be offered as first-line treatment for patients with advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral involvement, providing they have had an opportunity to discuss the likely side effects and are prepared to accept them. The alternative of endocrine therapy should always be considered in hormone receptor positive patients.

This should always be discussed with the appropriate breast oncologist, taking into account the patient’s wishes, prevailing NICE guidance and available clinical trial options. The following sequence of drugs may be considered in patients with metastatic disease, bearing in mind previous exposure in the adjuvant setting:-
1. Anthracycline
2. Taxane, 3 weekly docetaxel being the treatment of choice in the younger, fitter patient, weekly taxol being an alternative in others.
3. Capecitabine or Vinorelbine
4. Vinorelbine or Capecitabine
5. Others
6. Platinum-containing regimes for metastatic breast cancer

All suitable patients should be offered treatment within a clinical trial. Where none exists, a platinum-containing regime can be considered particularly in patients who have triple negative disease. If a taxane has not yet been used, the combination of carboplatin and paclitaxel should be considered. In the event of taxane therapy already being used, the combination of choice is gemcitabine and carboplatin. As many patients in this setting are heavily pretreated, a weekly schedule is recommended. The same regime may be considered in patients who are not triple negative, after exhausting all other available therapies, only after a frank discussion about risks and likely response rates.

In all patients receiving palliative chemotherapy consideration should be given to criteria for assessing treatment response including method of assessment and assessment interval.

Patients should have adequate baseline assessment at a time that allows for realistic on-treatment documentation of response.

**Trastuzumab in metastatic disease**

In HER2 positive patients who relapse after completing adjuvant Trastuzumab, this may be reintroduced, where clinically appropriate, in the metastatic setting. For the best response rates Trastuzumab should be used in combination with chemotherapy, usually a taxane though vinorelbine may be an alternative in some patients. It is recognised that, in a very small number of patients who would be suitable for trastuzumab, chemotherapy is not always appropriate, or may even be refused by the patient. In this setting single agent trastuzumab may be considered.

Treatment is not recommended beyond tumour progression with the exception of those patients responding to Trastuzumab in non-CNS sites and who relapse in brain and where the intention is to give radiotherapy. In this instance Trastuzumab should continue until either un-treatable CNS progression or progression in a systemic site.

**Further information on chemotherapy and its side effects and dose adjustments in organ failure can be found at:**
http://www.bccancer.bc.ca/HPI/DrugDatabase/default.htm
BISPHOSPHONATES FOR BONY SECONDARIES

Bisphosphonate therapy prevents skeletal complications from osteolytic bone involvement by inhibiting osteoclasts. In the seminal paper by Hortobagyi in 1996, the median time to the occurrence of the first skeletal complication was greater when IV pamidronate 90 mg was delivered 4 weekly compared to the placebo group (13.1 vs. 7.0 months, P=0.005)(53). In 2001, Zoledronic acid (4 mg) via 15-minute intravenous infusion was published to be as effective and well tolerated as 90 mg of pamidronate given over 2 hours in the treatment of bone metastases in patients with metastatic breast cancer(54). Similar results are available for oral clodronate and ibandronate(55). Upper GI adverse events were higher with oral ibandronate and it should be stressed to the patient that she should drink a full glass of liquid with the tablet and remain upright for at least ½ an hour after taking the tablet.

Serious complications from bisphosphonates

An association has been noted between bisphosphonate therapy and development of the renal impairment due to a number of different mechanisms, including collapsing focal glomerulosclerosis. Because of the potential for renal toxicity, ASCO guidelines recommend that creatinine be monitored prior to each dose(56). An increase of >44 micromol/L in serum creatinine, or an absolute level of >124 micromol/L among patients with normal baseline values should prompt temporary discontinuation. If renal function returns to baseline, therapy can be restarted cautiously.

Osteonecrosis of the jaw is an uncommon complication affecting usually the mandible. In one study, the incidence of ONJ was 1.5 percent among patients treated with these agents for 4 to 12 months, rising to 7.7 percent after treatment for 37 to 48 months.

The following variables were predictive for the development of osteonecrosis (or avascular necrosis) of the jaw:

- Dental extraction
- Sequential therapy with pamidronate/zoledronic acid
- Longer follow-up time
- Older age at diagnosis

Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition. The NECN recommends stopping bisphosphonates 3 weeks prior to and for 3 weeks after any dental procedure for patients on bisphosphonates.
BREAST CANCER FOLLOW UP

Although there is no evidence that routine follow up by a specialist increases long term survival, it is believed that many women welcome the reassurance of regular review whether this is by specialist or by GP. A recent randomised controlled trial suggested that an improved quality of life occurred when patients had access to a breast CNS for one year following surgery \(^{(57, 58)}\).

The purpose of follow up is:
1. To identify salvageable local recurrence. The incidence of local recurrence after conservative surgery and radiotherapy is reported to be about 10\% @ 5 years, rising at 1\% per year\(^{(16)}\).
2. To detect and manage treatment-related toxicity.
3. To screen for new primary tumours.
4. Patient psychosocial support.
5. To assess treatment outcomes/audit.
6. Teaching of Trainees in all disciplines.

There is no evidence for the use of tumour markers in the follow up of asymptomatic patients and these are not recommended.

North of England Cancer Network follow up protocol for patients treated in the adjuvant setting (complies with NICE guidance)

After completion of definitive treatment (includes surgery, radiotherapy, chemotherapy and herceptin if appropriate)

- Low/moderate risk (T1-2, N0, MO)
- 6 monthly clinical review year 1
- Annual clinical review years 2,3,4,5
- Review up to and including year 3 is carried out by either the surgical team or oncology team according to local practice. Follow up may be within nurse-led clinics.
- Annual mammography for 5 years then discharge.

- High risk (T3-4, N1,M0-1)
- After active treatment including herceptin
- 6 monthly clinical reviews year 1 and 2
- Annual clinical review years 3,4,5.
- Review up to and including year 3 is carried out by either the surgical team or oncology team according to local practice. Follow up may be within nurse-led clinics.
- Annual mammograms for 5 years.

In ER and/or PR positive, node positive patients whose initial treatment was Tamoxifen, a discussion about extended adjuvant endocrine therapy should take place after 5 years. This discussion will be led by either the breast team or oncology team. Such patients should continue annual clinical review until this is completed. This may be in a nurse-led clinic.

- If under 50 after 5 years continue 2 yearly mammograms until screening age.
- In younger patients with dense breast tissue MRI scans may be used following discussion at the MDT.
- Annual clinical exam can be continued until 50 if patient prefers.

Follow up can be by a surgeon, oncologist or appropriately trained specialist breast care nurse. The professional carrying out the follow up will be clearly stated on the patient’s
follow up care plan, so that both the patient and their GP are aware who is taking responsibility for this part of their care. This professional will also be responsible for arranging and monitoring the breast imaging required during the active follow up period.

At each follow up visit the patient will be assessed not just for evidence of breast cancer recurrence, but also for any problems associated with the cancer treatments they have received. This will include the following:

Assessment of cosmesis following surgery and radiotherapy.
- This should include a discussion of any body image problems and the patient’s satisfaction with the outcome. Where follow up is not being carried out by an oncoplastic surgeon, referral on to such a team may be required should the patient wish.

Examination for evidence of lymphoedema in those patients who have undergone axillary surgery.
- Immediate referral to a specialist in the treatment of lymphoedema should be made for assessment and treatment if lymphoedema is detected.

Assessment of any side effects caused by systemic therapy.
- This should include advise about the management of any reported symptoms and if necessary referral on to appropriate treatment or support services.
- Monitoring of bone densitometry measurements in patients receiving aromatase inhibitors.

The patient should have the name and contact number of their specialist breast care nurse or key worker, who can be contacted for advice in case of any concerns or new symptoms. Each MDT should have an agreed pathway for early patient review if deemed appropriate following contact by the patient. The following symptoms should precipitate early clinical review:

- New lumps or changes in treated or other breast
- Palpable axillary or supraclavicular fossa lymph nodes
- New and persistent changes in the skin at site of surgery
- Any swelling of arm or hand raising the concern of lymphoedema
- Any new or persistent changes in general health that are unexplained and last for more than a few weeks e.g. shortness of breath or cough, persistent aches or pains

Clinical trial follow up requirements take precedence over these guidelines.

Patient information
- Patients treated for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals), a copy sent to the GP and a personal copy given to the patient. This plan should include:
  - designated named healthcare professionals
  - dates for review of any adjuvant therapy
  - details of surveillance mammography
  - signs and symptoms to look for and seek advice on
  - contact details for immediate referral to specialist care, and
  - contact details for support services, for example support for patients with lymphoedema.

The NECN written care plan proforma is shown in appendix 3
THE BREAST CARE CLINICAL NURSE SPECIALIST (CNS)

The CNS is part of the multidisciplinary team and should be available for any patients undergoing treatment for breast cancer if they so wish. Patients should be aware of the CNS availability when attending a breast clinic.

- The CNS should be present at the time of diagnosis when any options for treatment are discussed.

- A suitable room with adequate privacy should be available at this time. The patient may be emotionally shocked and may not be able to assimilate the information given, the presence of a companion such as a partner or friend is encouraged.

- The CNS will initiate a plan of care and arrange further contact with the patient/family as needed, ensuring the patient is aware of how to contact the CNS.

- The CNS will assess each patient’s need for information and advice regarding their condition. This may include treatment choices, arm care and mobility, prosthetics, bra advice and treatment options as well as body image and psychosexual issues. The information may be written and/or verbal as desired by the patient.

- Support must be available both pre- and postoperatively and on subsequent outpatient visits to the hospital when patients may be receiving their results and further treatment may be discussed. The CNS should ensure a suitably trained nurse fits mastectomy patients with a temporary prosthesis prior to hospital discharge.

- The CNS will assess the patient for signs of anxiety and depression and refer to other health care professionals as appropriate.

- The CNS will establish links with the primary health care team (PHCT) and other relevant health care professionals to foster collaborative working and improve the patient journey.

- There must be an agreed programme of continuing education for the CNS, including IPR, nursing research and evidence of professional development plans. The CNS needs to be involved in the education of nursing staff on breast disease, both formally and informally, in the hospital setting and elsewhere.

- Ideally breast units need at least 2 CNSs to provide cross cover and it is mandatory that a CNS attends each multidisciplinary team meeting and is a core member of that team.

- The CNS is responsible for ensuring the details of the patient’s key worker are recorded in the medical notes.
PALLIATIVE CARE

1. The median survival of a patient with metastatic breast cancer is 24 months, with between 5 and 20% of patients surviving over 5 years depending on site of metastases. Therefore provision must be made for management of symptoms attributed to secondaries. The hospital team must have access to expertise in palliative care, in order to provide good symptom management advice during OP clinics when necessary, and in order to offer the best possible palliative care to in-patients. Palliative care services should work in liaison with the breast care team and the patient’s primary care team.

2. Lymphoedema treatment clinics use a combination of compression, massage and exercise to reduce and control lymphoedema, emphasising the importance of self-management to patients. This is a specialist treatment, and the swollen limb needs careful monitoring to avoid or treat skin damage, thrombosis and cellulitis, whilst monitoring for recurrent disease. Breast cancer units should have access to a local lymphoedema service. The lymphoedema service for breast cancer patients should be fully funded by the NHS, even if it does not take place on NHS premises.

The involvement of palliative care teams in the Hospital and the community should be sought (BASO Guidelines).

Palliative care provision:

Palliative care for breast cancer patients should be available as part of the NHS provision for their care: NCN cancer guidelines should specify this component of treatment, which can be purchased by PCTs via charities (eg local Hospices) or via Trusts. It is not acceptable to assume that a palliative care service funded by charitable means will have the capacity to respond to the needs of all patients referred by practitioners in the NHS. Breast Cancer Units should calculate their potential use of palliative care services, and include these costs in their negotiations with PCTs (see below)\(^{59, 60}\).

The ideal provision of palliative care services might include:

- CNS in palliative care: ideally, available to attend the breast clinic for symptom management advice, patient and carer support. The palliative care nurse is thus introduced by and integrated as part of the breast care team.
- CNS in palliative care: available for ward consultations for in-patients with palliative care needs.
- CNS in palliative care: in community, for home visits to continue symptom review and psychological support, where needed.
- Consultant in palliative medicine: available to see breast cancer patients with more complex symptoms, either in combined breast clinic or via the consultant’s own OP clinic.
- Consultant in palliative medicine: availability to see patients with advanced disease on hospital wards or in their own homes, act as a resource to clinical nurse specialists, offer informal advice to breast care team.
- Attendance at breast cancer MDT, or liaison with breast care team following MDT, to discuss appropriate referrals.
Network wide guidelines exist for the management of certain core symptoms and situations in palliative care. These have been incorporated into a small A5 sized booklet and are distributed across the network. They are also available on the North of England cancer network website where other guidelines and links will be available at: [http://www.necn.nhs.uk/](http://www.necn.nhs.uk/)

We also feel it can be helpful to give an explanation of some of the different terms often encountered when ‘palliative care’ is discussed.

**Supportive Care**
- “Umbrella” term for all services which help patient and family to cope with the condition and its treatment – from pre-diagnosis, through diagnosis and treatment, to cure, continuing illness or death and into bereavement
- Aims to help patient maximise benefits of treatment and to live as well as possible with the effects of the disease
- Should be given equal priority alongside diagnosis and treatment.

Supportive care includes:
- Self help and support
- User involvement
- Information giving
- Psychological support
- Symptom control
- Social support
- Rehabilitation
- Complementary therapies
- Spiritual support
- End of life and bereavement care

**Palliative Care**
- Part of, and embraces many elements of, supportive care.

Defined (NICE 2004) thus: “the active holistic care of patients with advanced progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments”.

**Key features of palliative care**
- Affirm life and regard dying as a normal process.
- Provide relief from pain and other distressing symptoms.
- Integrate the psychological and spiritual aspects of patient care.
- Offer a support system to help patients live as actively as possible until death.
- Offer a support system to help the family cope during the patient’s illness and in their own bereavement.

**General Palliative Care** is that care delivered by health professionals whose main role is not working with palliative care patients but who necessarily come across these patients in their work. This care is therefore delivered by a majority of healthcare professionals.

**Specialist Palliative Care** is delivered by professionals for whom the majority of their working role is in managing patients with palliative care needs. These professionals would therefore manage, or be advising in the care of, patients and
their families whose needs are more complex, challenging, time consuming and refractory to usual input, and where this demand exceeds that which can reasonably be expected to be delivered by a professional whose main role is in another discipline.

**End of Life Care**

- An approach that enables the supportive and palliative care needs of both patient and family to be identified and met throughout the last phase of life and into bereavement.

**Key features of end of life care**

- Anticipation and management of deterioration in the patient’s condition
- Advance care planning in accordance with patient preferences
- Patient choice about place of care and death
- Effective co-ordination of care across all teams and providers of care (in statutory, voluntary and independent sectors) who are involved in the care of patient and family

**Care of the Dying**

- Care of the patient and family in the last hours and days of life.
- Incorporates four key domains of care, physical, psychological, social and spiritual
- Supports the family through this phase and into bereavement.

**References**

- National Council for Palliative Care Palliative Care Explained http://www.ncpc.org.uk
CLINICAL TRIALS

The Cancer Reform Strategy states that “in order to ensure that we build for the future of cancer services there is a need for increased support for research”. This statement underpins the need for promoting research to fill the gaps in the evidence and spreading good practice.

The NECN Research Networks will work with the Service Network to promote integration of research into routine practice.

Both NECN Research Networks will be meeting the performance based working proposals for the National Cancer Research Network (NCRN). This includes maintaining overall accrual and improving accrual into randomised controlled studies, (RCT’s) with the aim being to provide as wide reaching a portfolio as possible across the NECN. There is a need to ensure that the Networks portfolios are inclusive of trials for all disease groups and that there is an expansion of pre-malignancy and non-cancer screening trials. Both Networks believe it is important that patients within the NECN have equity of access to trials open.

- New initiatives to strengthen research into prevention of cancer are underway The Research Networks will work with key stake holders and the Primary Care Research Networks to ensure that patients in the North East and Cumbria have access to these trials.
- The CRS states that there is funding for screening trials and the Research Networks will support the setting up and coordination of screening trials.
- The NCRN has an important role in identifying potential new therapies and making sure that clinical trials are undertaken in a timely manner. NCRN engages with Industry and NICE with the aim of maximising the impact of NCRN trials on subsequent NHS Practice There will be further investment over the next 10 years into researching cures and treatments of the future. The Research Networks will ensure they maintain a wide reaching balanced portfolio and promote industry trials.
- Access to high quality information is a prerequisite for patients to be able to participate in decision making about their care and this includes research trials. All staff need to be aware of research portfolios so they can ensure they provide patients with relevant information.
- Reducing inequalities in equity of access to cancer trials.
- Promoting research proposals on cancer in equalities – encouraging more trials which include older people and ensuring that children and young adults are treated at centers where a complete portfolio of relevant trials is supported.
- NCRI will help fund research on data collected by the National Cancer Intelligence network (NCIN), facilitating a more informed analysis of cancer services.
- To ensure research is incorporated in World Class Commissioning for cancer.
- To work more closely with our Patient and Carer Group, particularly in relation to equity of access for patients to clinical trials. We hope they will be able to help us provide a patients perspective and help support us raise awareness.

The Cancer Reform Strategy supports the need for promoting integration of research into routine practice and the NECN Research Networks are keen to advance this concept.
AUDIT

Data on patients in the NHSBSP are collected as part of QA for the programme.

- Audit data should be collected on all patients with breast cancer.
- Measures should include basic demographics, treatment and outcomes.
- Individual Trusts retain the responsibility for data collection required to demonstrate adherence to prevalent cancer standards.
- Funding for collection of “BASO” data is not available from the NECN.

A network-wide audit will be agreed annually and the results discussed at the March NSSG meeting.
PATIENT SUPPORT GROUPS

BACUP
3 Bath Place,
Rivington St,
London
EC2A 3JR
Tel: 0171 696 9003 (Admin)
Tel: 0171 613 2121 (Info)
www.cancerbackup.org.uk

Cancerhelp
Cancer information Department
Cancer Research UK
P.O. Box 123
Lincoln’s Inn Fields
London WC2A 3PX
www.cancerhelp.co.uk

Cancer Relief Macmillan Fund
15-19 Britten St,
London
SW3 3TZ
Tel: 0171 351 7811
www.macmillan.org.uk

Cancerlink
17 Britannia St,
London
WC1X 9JN
Tel: 0171 833 2451
www.cancerlink.org


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## Appendix 1 – TNM Staging of Breast Cancer

### Staging of breast cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
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</tr>
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<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>No primary found.</td>
</tr>
<tr>
<td>Tis</td>
<td>In-situ ductal, lobular or Paget disease of the nipple only.</td>
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</tbody>
</table>
| T1               | T1mic: Microinvasion not larger than 0.1 cm in greatest dimension  
|                  | T1a: Tumor larger than 0.1 cm but not larger than 0.5 cm in greatest dimension  
|                  | T1b: Tumor larger than 0.5 cm but not larger than 1.0 cm in greatest dimension  
|                  | T1c: Tumor larger than 1.0 cm but not larger than 2.0 cm in greatest dimension |
| T2               | Tumor larger than 2.0 cm but not larger than 5.0 cm in greatest dimension |
| T3               | Tumor larger than 5.0 cm in greatest dimension |
| T4               | T4a: Extension to chest wall, not including pectoralis muscle  
|                  | T4b: Edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast  
|                  | T4c: Both T4a and T4b  
|                  | T4d: Inflammatory carcinoma |

### Pathologic classification (pN)

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)</th>
</tr>
</thead>
</table>
| pN0              | No regional lymph node metastasis histologically, or only isolated tumor cells (ITC)  
|                  | (Note: ITCs are defined as single tumor cells or small cell clusters not larger than 0.2 mm) |
| pN1              | pN1mi: Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)  
|                  | pN1a: Metastasis in one to three axillary lymph nodes  
|                  | pN1b: Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent**  
|                  | pN1c: Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent. |
| pN2              | pN2a: Metastasis in four to nine axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)  
|                  | pN2b: Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis |
| pN3              | pN3a: Metastasis in ten or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or, metastasis to the infraclavicular lymph nodes  
|                  | pN3b: Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**  
<p>|                  | pN3c: Metastasis in ipsilateral supraclavicular lymph nodes |</p>
<table>
<thead>
<tr>
<th>AJCC Stage Groupings</th>
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<tr>
<td><strong>Stage 0</strong></td>
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<td><strong>Stage I</strong></td>
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<tr>
<td><strong>Stage IIIA</strong></td>
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<tr>
<td><strong>Stage IIIB</strong></td>
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<tr>
<td><strong>Stage IIIC</strong></td>
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<tr>
<td><strong>Stage IV</strong></td>
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Appendix 2 – Algorithms for Management of Breast Cancer Treatment-Induced Bone Loss

Guidance for the management of breast cancer treatment-induced bone loss

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

- **High Risk**
- **Medium Risk**
- **Low Risk**

**Oophorectomy, treatment-induced menopause or ovarian suppression therapy planned**

**Measure BMD by axial DXA (spine and hip) within 3 months of commencing treatment**

**With or without aromatase inhibitor (AI) use**

- **With AI**
  - T-score < -1.0 or known vertebral fracture
  - Assess for secondary osteoporosis
  - Treat with bisphosphonates at osteoporosis doses and calcium + vitamin D supplementation
  - Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months

- **Without AI**
  - T-score < -1.0 but > -2.0
  - Lifestyle advice: Calcium + vitamin D supplementation if clinically deficient
  - Repeat axial BMD after 24 months of therapy
  - Annual rate of bone loss of >4% at lumbar spine or total hip and/or T score < -2.0
    - Yes
    - No

---

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

b Meclizinate 30 mg per week, risedronate 35 mg per week, indomethacin (150 mg po monthly or 3 mg iv 3 monthly), niacinamide 4 mg iv 6 monthly
c To be given as 1 g of calcium + 1000 UI of vitamin D
d Biochemical markers such as serum C-terminal telopeptide of type 1 collagen or urinary N-telopeptide of type 1 collagen
Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors

High Risk

Medium Risk

Low Risk

Age ≥75 years and ≥1 clinical risk factors

Measure BMD by axial DXA (spine and hip) within 3–6 months

Low T-score <−2.0 or known vertebral fracture

Assess for secondary osteoporosis: Calcium + vitamin D supplementation if clinically deficient

Treat with bisphosphonates at osteoporosis doses and calcium + vitamin D supplementation

Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months

Low T-score <−1.0 but ≥−2.0

Lifestyle advice: Calcium + vitamin D supplementation if clinically deficient

Repeat axial BMD, if available, after 24 months of therapy

Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months

Both T-scores <−1.0

Lifestyle advice: Reassure patient: No further assessment unless clinically indicated

Notes:

a Previous low-trauma fracture after age 50, parental history of hip fracture
b ALendronate 70 mg per week, raloxifene 35 mg per week, ibandronate alcohol intake of >4 units/day, diabetes associated with secondary osteoporosis, prior orthopaedics for ≥6 months, low BMI (<20)
c ESRI, FRAX, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / ALT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

d To be given as ≥3 g of calcium + ≥800 IU of vitamin D

Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen
Appendix 3 - Follow-Up Care After Treatment For Breast Cancer

This leaflet will explain your follow-up care. It is possible to transfer your follow-up care after your treatment has finished, please advise us if you wish to do so.

Follow-up appointments

You will be followed up in the clinic regularly for five years. During the first year, your appointments will be variable depending on your treatment. After the first year or when you finish treatment your appointments will be yearly. This appointment will include an examination by your team which will be your surgical, oncology or nurse team, a review of your medication and an opportunity to discuss any worries or concerns. If you have no further problems your care will be transferred to your general practitioner after five years of treatment.

If you are taking part in a clinical trial, or are under fifty years of age, your follow-up may be longer than five years.

Endocrine therapy/medication

If you are pre-menopausal you will usually be prescribed Tamoxifen tablets for five years. If you are post-menopausal you may be prescribed a different endocrine drug, i.e an aromatase inhibitor drug. Not everyone is suitable for this type of therapy and this will be discussed with you.

If you are prescribed an aromatase inhibitor drug i.e Anastrazole, Letrozole, Exemestane, (a type of hormone treatment sometimes used to treat post menopausal women with breast cancer) you will need to have a DEXA scan (a scan to check your bone mineral density) as these drugs can cause a reduction in bone thickness. This scan will be arranged by your hospital team or GP when you first start this medication and then may be repeated at two years and five years if necessary. You will be advised if you need further scans.

Your medication will be reviewed at your appointment but if you have any problems with your medication in between your appointment then contact your breast care nurse or GP.

Mammogram follow-up

An x-ray of your breasts (mammogram) will be carried out each year for five years. Your hospital team will arrange this. The breast unit will inform you of the results by letter within three weeks. After five years you will be offered mammograms on the National Breast Screening Programme every three years. Once you are over seventy years old you are still entitled to have a mammogram but you will have to organise this yourself by contacting your local breast screening unit or GP. Occasionally you may be offered other forms of radiology testing for example ultrasound or MRI, you will be advised if you require these tests.

If you are under fifty you may be discharged after 5 years or you may be reviewed yearly till you are fifty. Your hospital team will discuss this with you.

What symptoms do I need to look for between my appointments?

If you noticed any of the following symptoms then you should contact your breast care nurse, GP or hospital team for advice:
- If you develop any swelling in your arm/hand and are concerned you are developing lymphoedema
- Recent changes in the area of your surgery including rashes or spots that don’t go away
- New lumps at the site of your surgery
- New lumps in your armpits or neck
- New lumps or changes in the other breast or armpit

**Any new or persistent changes in your general health that is unexplained and last for more than a few weeks, for example:**

- Any new persistent shortness of breath or cough
- Any new persistent neck or back pains
- Any new persistent aches or pains

**These symptoms may not be related to your previous breast problem but should be checked out if they are persistent.**

**Concern between appointments**

If you have any other concerns or problems between your follow-up appointments contact your breast care nurse/key worker who will give you advice and if necessary bring your hospital appointment forward

**Your breast care nurse/key worker is**..........................................................

**Contact number** ..........................................................
NECN CHEMOTHERAPY TREATMENT ALGORITHM FOR BREAST

“Quality and safety for every patient every time”

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For more information regarding this document, please contact:

NSSG Chair: Dr L Lunt
INTRODUCTION

The 2011 Peer Review Chemotherapy Measures require each Network Site Specific group (NSSG) to agree in consultation with the Network Chemistry Group (NCG) a set of site specific chemotherapy treatment algorithms for the Network.

Peer Review Definitions

Chemotherapy treatment algorithm
A guideline which specifies the acceptable ranges of regimen options for named steps on the patient pathway. Treatment algorithms are cancer site-specific. Thus, the treatment algorithm for the Breast NSSG includes a statement of the range of regimens agreed as acceptable.

Chemotherapy
The term 'chemotherapy' refers to the use of those cytotoxic agents commonly understood and accepted as being covered by this term and includes other agents such as, biological therapy and small molecule tyrosine kinase inhibitors used for the systemic treatment of cancer.

In NECN Treatment Algorithms are included in each NSSG’s Clinical Guidelines which can be found under the tumour specific page of the guidelines section of the website, e.g. for Lung Cancer at: http://www.necn.nhs.uk/group/lung-nssg/

SUPPORTING DOCUMENTS

As new regimens are approved by NICE / NECDAG protocols for use of the new treatment will be uploaded to the chemotherapy site specific pages. The NSSG will be asked to update their algorithm with each new treatment approval.

The availability of the Cancer Drug Fund (CDF) has increased the number of treatments potentially available to patients. CDF funded drugs may not be included in the NSSG clinical guidelines due to the dynamic nature of CDF funding (i.e. treatments can be removed as well as added).

Any deviation from the algorithm should be recorded by the local Trust clinical chemotherapy service and brought to the NCG for discussion. The Network Policy on managing deviations from approved protocols/ algorithms is on the website: http://www.nescn.nhs.uk/chemotherapy-documents/

LIST OF APPROVED REGIMENS

The NESCN website provides the most up to date list of approved regimens and should be regularly checked. Appendix One below summarises the Breast regimens on the website.
CHEMOTHERAPY FOR INVASIVE BREAST CANCER

Adjuvant Chemotherapy

Chemotherapy should start within 31 days of the completion of surgery, or earliest clinically appropriate date. Hormone treatments should be interrupted or delayed until chemotherapy is complete.

Anthracycline containing polychemotherapy (e.g. FAC) reduces the annual risk of death by 38% for women under age 50, and by 20% for women aged 50 to 69 (39). The absolute benefit would be proportional to the individuals’ risk of recurrence and this can be estimated using the adjuvantonline tool available at www.adjuvantonline.com. This tool is to be used by health professionals familiar with the issues in the adjuvant treatment of breast cancer. The intention is that this tool be used to provide information that will then be helpful in shared decision making by the patient and the health professional.

For women < 70 years old, the St Gallen Consensus statement recommends that:

- All women with Node positive breast cancer and all women with Receptor negative breast cancer should be offered chemotherapy and so should be referred for an oncology opinion (40).

Some women, for example those age >35 with T1, N0, ER+ve Grade 1, HER2 -ve tumours are unlikely to benefit from chemotherapy and do not need to be referred.

HER2 positive breast cancer is a feature which increases (up to double) the risk of recurrence. All patients with HER2 positive breast cancer with tumour size >1cm should be referred to the medical/clinical oncologist for discussion of adjuvant chemotherapy followed by Herceptin (Trastuzumab).

Choice of Adjuvant Chemotherapy Regimen:

Choice of individual regimen requires an assessment of the risks and benefits for the individual patients.

Always consider entry to the NCRN adjuvant trials portfolio.

Node –negative patients who are suitable for adjuvant chemotherapy should receive an anthracycline containing regimen. Appropriate regimens are:

- EC X 6 (Epirubicin 90mg/m2 Cyclophosphamide 600mg/m2)
- FEC X 6 (5FU 600mg/m2 Epi 75mg/m2 Cyclo 600mg/m2)

Dose intensity should be maintained using secondary prophylaxis with G-CSF in event of neutropenic sepsis. Dose reductions are accepted both from the outset and in response to toxicity depending on performance status and clinical judgement of the treating physician.

In patients wishing to minimise the risk of alopecia, or who have a contra-indication to anthracyclines, classical CMF would be an alternative.
A taxane containing regimen should be considered in all node-positive patients and offered where clinically appropriate. The regimen of choice is **FEC-T (Docetaxel)**. **TC (Docetaxel + Cyclophosphamide)** is an accepted alternative in patients with cardiac co-morbidity.

A network-wide audit of FEC-T chemotherapy has shown rates of neutropenic sepsis rates in excess of 20% in unsupported patients. The use of primary prophylaxis with GCSF is therefore recommended with this regimen.

**Cardiac Monitoring & Anthracyclines**

Transient ECG changes can occur during anthracycline therapy and are not in themselves an indication to discontinue treatment. There is, therefore, no absolute need for an ECG at baseline although is may be a useful marker of cardiac disease.

There is a risk of cardiomyopathy in patients with increasing cumulative exposure to anthracyclines and patients with any of the following risk factors should have a baseline assessment of LVEF by either echocardiogram or MUGA scan.

- Age above 65
- Hypertension requiring medication
- Heart failure
- Left ventricular hypertrophy
- Mediastinal irradiation
- Myocardial Infarction
- Planned cumulative doxorubicin dose > 360 mg/m2 or epirubicin dose > 600 mg/m2
  - In these patients repeat assessment during chemotherapy is recommended
- Any other identified cardiac risk factor

**Adjuvant Tastuzumab (Herceptin)**

20 percent of breast cancers overexpress HER2, a cell surface tyrosine kinase receptor. The addition of Herceptin to adjuvant chemotherapy is recommended for women with HER2-overexpressing tumors that are >1 cm or N+.

Two North American Cooperative Group trials were initially designed as parallel clinical trials. In NSABP trial B-31, 1736 women with HER2-positive, node-positive (N+) breast cancer received AC x 4 followed by Paclitaxel (175 mg/m2 over 3 hours) x 4; they were randomly assigned to no further therapy (group NSABP-1) or weekly trastuzumab (initial loading dose 4 mg/kg, then 2 mg/kg weekly for one year, NSABP-2), beginning with the first dose of paclitaxel (39). The North Central Cancer Treatment Group (NCCTG)-coordinated Intergroup trial N-9831 tested the value of adding trastuzumab to sequential AC and paclitaxel. Combined analysis of both trials confirm a 49 percent reduction in the risk of disease recurrence and a 37 percent reduction in the risk of death (four-year OS 93 versus 89 percent) (45). Similar figures were reported for the HERA trial (46).

In the FinHer trial (47), women with N+ or high-risk node-negative breast cancer were randomly assigned to three courses of docetaxel or vinorelbine followed by FEC x 3.
The 232 women with HER2-positive breast cancer were randomly assigned to receive nine weekly trastuzumab infusions after completing chemotherapy. DFS was significantly better among those who received trastuzumab (89 versus 78 percent, p = 0.01), similar in magnitude as other studies using one year of Herceptin.

There was a higher incidence of cardiac toxicity in the patients that received adjuvant Herceptin. A recent meta-analysis of five randomised control trials of adjuvant Herceptin found a 7.2% increased risk of significant drop in cardiac function and 1.61% increased risk of symptomatic NYHA grade 3-4 heart failure following one year of Herceptin (48).

Management of cardiac events in trastuzumab-treated patients

1. Baseline cardiac assessment prior to cytotoxic chemotherapy
   - Medical history & physical examination including BP measurement
     - To detect pre-existing cardiac disease and risk factors.
     - 12-lead electrocardiogram (ECG), with echocardiogram if abnormal
   - LVEF measurement using Echo or radionucleotide multiple-uptake gated acquisition (MUGA) scan.

2. Interventions at baseline
   - Referral to a cardiologist
     - recommended for patients with significant cardiac co-morbidity.
   - Modification of planned chemotherapy regimen
     - In patients with low or borderline LVEF
     - Prophylactic ACE inhibitor therapy may also be considered.
   - Initiation of ACE inhibitors to control hypertension
     - Hypertension is a potent modifiable risk factor for the development of heart failure during Trastuzumab treatment.
     - Blood pressure above 140/85 mmHg should be treated with an ACE inhibitor, with primary care supervision of dose and renal function
   - Lifestyle recommendations
     - Smoking cessation, healthy diet & alcohol intake, optimising weight

3. Management of cardiac function during trastuzumab
   - Assessment of LVEF prior to starting trastuzumab treatment
     - LVEF should be assessed after chemotherapy and before Trastuzumab. Patients with an LVEF >= institution LLN should start Trastuzumab.
     - Patients with LVEF < institutional LLN should not start Trastuzumab but should be started on an ACE inhibitor and referred to a cardiologist. Repeat assessment of cardiac function should take place after 3 months.
     - Sharp falls in LVEF (> 0.10) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on Trastuzumab. Prophylactic ACE inhibitor therapy may be considered for such patients.
   - Routine LVEF monitoring is recommended after 4 and 8 months.
     - Assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment.
     - Additional testing is required in patients who have LV
Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted, receive an ACE inhibitor and be referred to a cardiologist.\textsuperscript{33,44,45}

If the LVEF falls to $\leq 0.40$, (representing biologically important LV systolic dysfunction) trastuzumab should be interrupted the patient should receive an ACE inhibitor and be referred to a cardiologist for treatment.\textsuperscript{33,44,45}

After Trastuzumab interruption and appropriate medical therapy, LVEF should be re-checked after 6–8 weeks. Trastuzumab may be re-initiated if the LVEF is restored to a level above the LLN.

If the LVEF falls to below the LLN but $> 0.40$, trastuzumab may be continued, but an ACE inhibitor should be initiated.

- If the patient is already on an ACE inhibitor, they should be referred to a cardiologist.
- LVEF assessment should be repeated after 6–8 weeks.

If the LVEF falls by 0.10 points or more but remains above the LLN, trastuzumab may be continued. Intervention with an ACE inhibitor is recommended in an attempt to reduce the risk of further LVEF decline of symptomatic CHF.

- LVEF Monitoring should be repeated after 6–8 weeks.

Traffic light system

Navigation through these guidelines may be facilitated by the adoption of a traffic light system.

- A green light indicates LVEF above the LLN, no signs or symptoms of CHF and any trastuzumab-related LVEF fall being $< 0.10$.
- An amber light indicates LVEF between the LLN and 0.40, with no signs or symptoms of CHF, or a trastuzumab-related LVEF reduction of 0.1 or more.
- A red light indicates LVEF $\leq 0.40$ or symptoms and signs of cardiac failure.

Prior to chemotherapy, green indicates go. Red or amber indicates careful consideration of decision to start chemotherapy, with consideration of non-anthracycline-containing regimens. Both amber and red are indications for the initiation of ACE inhibitors, and referral to cardiology for the optimisation of cardiac function.

Post chemotherapy, green indicates go. Amber indicates defer until green. Red indicates that it is unlikely to be safe to start trastuzumab. Both amber and red are indications for the initiation of ACE inhibitors and referral to cardiology for the optimisation of cardiac function. It is recommended that LVEF is reassessed after 3 months, and that trastuzumab is not commenced unless LVEF is within normal limits at that point.

During trastuzumab, green is an indication to continue treatment. Amber is also an indication to continue chemotherapy, but patients should also be taking an ACE inhibitor. Patients who drop into the amber range while on an ACE inhibitor should be referred for a cardiology opinion. Red is an indication to interrupt trastuzumab, start on an ACE inhibitor (not already taking one) and refer for a cardiology opinion.

Patients whose trastuzumab is interrupted (i.e. red light) should not restart until LVEF is within the normal range (i.e. green light).
Neo-Adjuvant Chemotherapy

For patients with locally advanced disease or tumours where downstaging might facilitate conservative surgery, including inflammatory breast cancers, neo-adjuvant therapy, ideally in the context of a clinical trial should be considered.

The diagnosis must be established by core biopsy and ER, PR and HER-2 status should be ascertained.

If T3 or node positive, staging investigation including a CT scan of thorax and abdomen ± bone scan should take place before the commencement of neoadjuvant chemotherapy.

FEC or EC for 4-6 cycles is the off trial standard treatment. There are no data on the benefits of post surgical chemotherapy in patients who have received neoadjuvant treatment, although sequences of chemotherapy (eg. Anthracycline followed by taxane) appear to be superior to anthracycline only combinations in this setting.

Patients who are ER positive should routinely be offered Tamoxifen after surgery.

In ER negative patients post surgical treatment should be discussed carefully on a case by case basis and may include Taxane monotherapy.

Chemotherapy in Metastatic Disease

Chemotherapy should be offered as first-line treatment for patients with advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral involvement, providing they have had an opportunity to discuss the likely side effects and are prepared to accept them. The alternative of endocrine therapy should always be considered in hormone receptor positive patients.

This should always be discussed with the appropriate breast oncologist, taking into account the patient’s wishes, prevailing NICE guidance and available clinical trial options. The following sequence of drugs may be considered in patients with metastatic disease, bearing in mind previous exposure in the adjuvant setting:-

1. Anthracycline
2. Taxane, 3 weekly docetaxel being the treatment of choice in the younger, fitter patient, weekly taxol being an alternative in others.
3. Capecitabine or Vinorelbine
4. Vinorelbine or Capecitabine
5. Others
6. Platinum-containing regimes for metastatic breast cancer

All suitable patients should be offered treatment within a clinical trial. Where none exists, a platinum-containing regime can be considered particularly in patients who have triple negative disease. If a taxane has not yet been used, the combination of carboplatin and paclitaxel should be considered. In the event of taxane therapy already being used, the combination of choice is gemcitabine and carboplatin. As many patients in this setting are heavily pretreated, a weekly schedule is recommended. The same regime may be considered in patients who are not triple negative, after exhausting all other available therapies, only after a frank discussion about risks and likely response rates.
In all patients receiving palliative chemotherapy consideration should be given to criteria for assessing treatment response including method of assessment and assessment interval.

Patients should have adequate baseline assessment at a time that allows for realistic on-treatment documentation of response.

**Trastuzumab in metastatic disease**

In HER2 positive patients who relapse after completing adjuvant Trastuzumab, this may be reintroduced, where clinically appropriate, in the metastatic setting. For the best response rates Trastuzumab should be used in combination with chemotherapy, usually a taxane though vinorelbine may be an alternative in some patients.

It is recognised that, in a very small number of patients who would be suitable for trastuzumab, chemotherapy is not always appropriate, or may even be refused by the patient. In this setting single agent trastuzumab may be considered.

Treatment is not recommended beyond tumour progression with the exception of those patients responding to Trastuzumab in non-CNS sites and who relapse in brain and where the intention is to give radiotherapy. In this instance Trastuzumab should continue until either un-treatable CNS progression or progression in a systemic site.

**Further information on chemotherapy and its side effects and dose adjustments in organ failure can be found at:**  
## APPROVED LIST OF REGIMENS FOR BREAST

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<th>Doc No.</th>
<th>BREAST PROTOCOLS</th>
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<tr>
<td>CRP-09-B001</td>
<td>Protocol for Vinorelbine Intravenous</td>
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<tr>
<td>CRP-09-B002</td>
<td>Protocol for TC (Docetaxel Cyclophosphamide)</td>
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<td>CRP-09-B003</td>
<td>Protocol for Paclitaxel</td>
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<tr>
<td>CRP-09-B004</td>
<td>Protocol for Trastuzumab</td>
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<td>Protocol for Trastuzumab plus Vinorelbine</td>
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<td>Protocol for Trastuzumab plus WEEKLY Paclitaxel</td>
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<td>CRP-09-B009</td>
<td>Protocol for FEC-T (Fluorouracil, Epirubicin, Cyclophosphamide followed by Docetaxel)</td>
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<td>CRP-09-B016</td>
<td>Protocol for Docetaxel</td>
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<td>Protocol for Classical CMF (Cyclophosphamide, Methotrexate, Fluorouracil)</td>
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<td>CRP-09-B019</td>
<td>Protocol for Paclitaxel</td>
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<td>Protocol for Trastuzumab plus Oral Vinorelbine</td>
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<td>Protocol for FEC-75</td>
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<td>CRP-09-L001</td>
<td>Protocol for Oral Vinorelbine</td>
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Appendix 5, Association of Breast Surgery Consensus Statement

Association of Breast Surgery Consensus Statement

Management of the Malignant Axilla in Early Breast Cancer

The following summary statement has been agreed by the Trustees of the Association of Breast Surgery (ABS) following the ABS Multidisciplinary Consensus Meeting on the further management of the malignant axillary node, held in London on 26th January 2015. This should be read in conjunction with the ‘Summary of Proceedings’ of the meeting and the speaker presentations, both of which will be available on the ABS website. A review and full update of the ABS guidelines on the management of the axilla is under consideration and will be published shortly.

Further local treatment for the malignant sentinel lymph node in patients with early invasive breast cancer

Isolated tumour cells and micrometastases:

If the sentinel node(s) shows isolated tumour cells and/or micrometastases no further axillary treatment is required in addition to breast conserving surgery or mastectomy.

1-2 sentinel nodes with macrometastases:

Further axillary treatment is no longer mandatory in patients who are receiving breast conservation with whole breast radiotherapy, that are post menopausal and have T1, grade 1 or 2, ER positive and HER2 negative tumours.

These patients could also be entered into the POSNOC or equivalent clinical trial.

Further axillary treatment should usually be recommended for patients undergoing mastectomy, or with tumours with one or more of the following features: T3, grade 3, oestrogen receptor negative or HER2 positive.

These patients could also be entered into the POSNOC or equivalent clinical trial.

No consensus was reached on the management of patients with one or more of the following features: premenopausal status, T2 tumours, lymphovascular invasion or extranodal spread.

3 or more sentinel nodes with macrometastases:

Patients should usually be recommended to have further axillary treatment.
Axillary Treatment

Radiotherapy to the axilla is a valid alternative treatment to axillary lymph node dissection in patients with a low burden of axillary disease.

Pre-operative Axillary Staging

All patients with invasive early breast cancer should have a preoperative ultrasound examination of the axilla and subsequent ultrasound guided nodal biopsy when indicated.

Adjuvant Treatment Planning

The total number of involved axillary nodes is no longer considered to be essential information to decide on the most appropriate systemic treatment. The choice of systemic treatment should be based on the prediction of response rather than the perceived prognosis.

Consensus was not reached on the importance of the total number of involved axillary nodes as essential information for post mastectomy radiotherapy decision making.

Please refer to the summary of proceedings of the meeting.

Management of the malignant axillary node diagnosed pre-operatively by ultrasound guided FNA or core biopsy

There was considerable discussion regarding the management of the pre-operatively diagnosed positive axillary node where patients are planned to undergo breast conservation surgery with whole breast radiotherapy, and where pre-operative information indicates a likely good prognosis and low axillary nodal burden (T1 tumour, grade 1-2, ER positive and postmenopausal status).

However consensus was not reached as to whether sentinel node biopsy should be considered as the next step in such patients. Although there was support for this option, it was apparent that appropriate processes and protocols will be required before further guidelines are agreed.

The ABS Trustees aim to develop appropriate guidelines on this issue as soon as possible.

Association of Breast Surgery Trustees 16th March 2015