Diagnosis, staging and treatment of patients with breast cancer

National Clinical Guideline No. 7

Summary

Guideline Development Group

The National Clinical Guideline on the diagnosis, staging and treatment of patients with breast cancer in Ireland was developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, librarians and stakeholder groups.

This Guideline Summary should be read in conjunction with the full version National Clinical Guideline.

The full version of this National Clinical Guideline, is available on the websites: www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer

The complete list of references can be found in the full version of the National Clinical Guideline.

Notice to Health Professionals and Disclaimer

The Guideline Development Group's expectation is that health professionals will use clinical knowledge and judgement in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgement in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.

National Clinical Effectiveness Committee (NCEC)

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative. The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

NCEC Terms of Reference
1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

The full version of this guideline and further information on the NCEC and endorsed National Clincial Guidelines is available at: http://health.gov.ie/patient-safety/ncec/

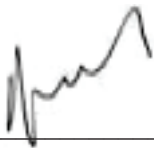## Using this National Cancer Control Programme National Clinical Guideline

The NCCP is part of the Health Service Executive (HSE) and was established in 2007 to implement the recommendations of the National Cancer Strategy. The NCCP is responsible for national cancer control by helping to prevent cancer, treat cancer and increase survival and quality of life for those who develop cancer, by converting the knowledge gained through research and surveillance into strategies and actions. The need to follow evidence-based clinical guidelines covering a patient's journey from early detection, diagnosis, treatment, monitoring and end-of-life care is a key priority for the NCCP.

It is critical to have a range of health professionals working together to plan and deliver care for cancer patients. The target users of the guideline are the multidisciplinary clinical team caring for patients with breast cancer.

The development of this National Clinical Guideline would not have been possible without the enormous contribution of the members of the Guideline Development Group, the NCCP Guideline Steering Group and the reviewers. We are grateful for the commitment shown by all who contributed to the development of this guideline. In particular the invaluable input of the clinicians and the HSE/hospital librarians in this process is acknowledged and we thank them for giving generously of their time and expertise.

This full version of this National Clinical Guideline is available at:
www.health.gov.ie/patient.safety/ncec and www.hse.ie/cancer

This Guideline Summary should be read in conjunction with the full version National Clinical Guideline.

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1 Definition and impact of breast cancer

1.1 Need for National Clinical Guideline

In 2006, the second national cancer strategy, A Strategy for Cancer Control in Ireland (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:
- Improvements in the quality of clinical decisions,
- Improvement in patient outcomes,
- Potential for reduction in morbidity and mortality and improvement in quality of life,
- Promotion of interventions of proven benefit and discouragement of ineffective ones, and
- Improvements in the consistency and standard of care.

1.2 Clinical impact of breast cancer

The diagnosis, staging and treatment of patients with breast cancer requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery, chemotherapy and radiation therapy. A proportion of patients may also require palliative care.

1.3 Scope of National Clinical Guideline

This National Clinical Guideline was developed to improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.

The guideline focuses on the diagnosis, staging and treatment of patients with breast cancer. This guideline does not include recommendations covering every aspect of diagnosis, staging and treatment. This guideline focuses on areas of clinical practice:
- known to be controversial or uncertain,
- where there is identifiable variation in practice (Specifically Qs 2.2.2, 2.2.4, 2.2.5, 2.2.6, 2.3.3, 2.3.8, 2.3.9 and 2.5.3),
- where there is new or emerging evidence,
- where guidelines have potential to have the most impact.

This guideline focuses solely on the clinical management of patients with breast cancer.

For information on NCCP general practitioner (GP) referral guidelines, standardised GP referral forms, and GP electronic referral for patients with breast cancer and the cancer survivorship programme (including information on lymphedema) see the full version of this National Clinical Guideline.

Patient information booklets/leaflets covering various aspects of the cancer journey are available on the NCCP website.

This guideline does not cover breast cancer screening. This is carried out by the National Screening Service (NSS).

The NCCP have prioritised the development of clinical guidelines for those cancers that have the highest burden of illness. Breast Cancer was the largest solid tumour diagnosed annually in Ireland.

The Guideline Development Group (GDG) endorses the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP) clinical guideline (Wolff et al., 2013) for the following two pathology clinical questions:

1. What is the optimal testing algorithm for the assessment of HER2 status?
2. What strategies can help ensure optimal performance, interpretation, and reporting of established assays?

Patients that are covered by this guideline are:
Adults (18 years or older) with newly diagnosed early and locally advanced breast cancer.

The scope of this guideline does not include patients with metastatic disease or breast cancer recurrence.

1.4   Levels of evidence and grading of recommendations

Tables 1 and 2 outline the categories used for levels of evidence and grading of recommendations.

Table 1 Levels of evidence for diagnostic studies (Oxford CEBM, 2009)

1a	Systematic review (with homogeneity*****) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
1b	Validating****** cohort study with good reference standards" " "; or CDR tested within one clinical centre.
1c	Absolute SpPins (specificity) and SnNouts (sensitivity)" ".
2a	Systematic review (with homogeneity*****) of Level >2 diagnostic studies.
2b	Exploratory****** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
3a	Systematic review (with homogeneity*****) of 3b and better studies.
3b	Non-consecutive study; or without consistently applied reference standards.
4	Case-control study, poor or non-independent reference standard.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).
** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.
§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 2 Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
C	Level 4 studies; or Extrapolations from level 2 or 3 studies.
D	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.

Table 3 Levels of evidence for interventional studies (SIGN grading system 1999-2012)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table 4 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

> **Good practice point**
> Recommended best practice based on the clinical experience of the Guideline Development Group.

2   National Clinical Guideline recommendations

2.1   Summary of national recommendations

Responsibility for implementation: The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline. Each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

There are various entry points for patients within the scope of this guideline.

Radiology

2.2.1.1   For all patients being investigated for invasive breast cancer, pre-treatment ultrasound evaluation of the axilla should be performed and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered. **(B)**

2.2.2.1   Ultrasound guided lymph node sampling (fine needle aspiration/core needle biopsy) is recommended in patients with breast cancer where ultrasound demonstrates lymph nodes of cortical thickness of ≥3mm or if the node demonstrates abnormal morphological features. **(C)**

2.2.3.1   In patients with a clinically suspicious examination (S4, S5) and normal imaging (mammography and ultrasound), clinically guided core biopsy should be performed. **(C)**

2.2.4.1   The routine use of MRI of the breast is **not** recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ. **(B)**

2.2.4.2   Offer MRI of the breast to patients with invasive breast cancer, if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment, or if breast density precludes accurate size assessment. **(B)**

2.2.4.3   In patients with invasive lobular cancer, MRI can be considered to assess tumour size, if breast conserving surgery is a treatment option. **(C)**

2.2.5.1   Breast MRI is indicated in the clinical setting of occult primary breast cancer (typically, axillary lymphadenopathy) and following negative clinical breast examination and negative conventional imaging. **(B)**

2.2.6.1   In the setting of negative conventional imaging, MRI can facilitate treatment planning for patients with Paget's disease. **(C)**

2.2.7.1   In newly diagnosed patients with breast cancer who have symptoms suggestive of metastases, appropriate imaging investigations should be performed, regardless of tumour stage. **(B)**

2.2.7.2   In newly diagnosed asymptomatic patients with breast cancer, evidence does **not** support the use of routine imaging for metastatic disease in pathological stage I and II disease. **(B)**

2.2.7.3   In newly diagnosed asymptomatic patients with breast cancer, use of staging imaging for metastatic disease is recommended for stage III and IV disease. **(B)**

2.2.8.1   In patients with newly diagnosed breast cancer who require staging, contrast enhanced CT chest, abdomen and pelvis and whole body isotope bone scan are recommended. **(B)**

2.2.8.2   PET-CT is **not** routinely recommended. However, it may be considered in specific cases. **(C)**

Surgery

2.3.1.1   Women with ductal carcinoma in situ who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy. **(B)**

2.3.1.2   Women with ductal carcinoma in situ may be offered breast conserving surgery and radiotherapy except where there are indications for mastectomy and sentinel lymph node biopsy. **(A)**

2.3.2.1   Women with invasive breast cancer who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy. **(A)**

2.3.3.1   In the general population, there is no evidence that a contralateral risk reducing mastectomy improves a patient's prognosis. However, a contralateral risk reducing mastectomy may be undertaken to address specific patient concerns if it is discussed at a multidisciplinary team meeting and the benefits, risks and alternatives have been discussed with the patient. **(B)**

2.3.3.2   There are subsets of patients who may benefit from a contralateral risk reducing mastectomy, such as genetic mutation carriers. **(C)**

2.3.4.1 A discussion regarding breast reconstruction should be undertaken with all patients undergoing mastectomy for breast cancer. **(A)**

2.3.5.1 Patients with operable (invasive) breast cancer with no clinical or radiological evidence of axillary lymph nodes metastases at initial diagnosis should be considered for sentinel node biopsy. **(A)**

2.3.7.1 Patients with isolated tumour cells and micrometastases do **not** require an axillary clearance. **(B)**

2.3.7.2 In patients undergoing breast conserving surgery and radiotherapy who are clinically and radiological node negative at presentation and have one or two macrometastatic sentinel lymph nodes in a sentinel lymph node biopsy, the avoidance of axillary lymph node dissection may be considered following a discussion at multidisciplinary team meeting and with the patient. **(B)**

2.3.8.1 For all patients treated with breast conserving surgery and radiotherapy for ductal carcinoma in situ, a minimum of 2mm radial margin of excision is recommended. **(B)**

2.3.9.1 For patients receiving breast conserving surgery and postoperative radiotherapy for invasive breast cancer, the excision should have a clear margin; the tumour should not be touching ink. **(B)**

Medical oncology

2.4.1.1 Adjuvant chemotherapy should be considered for all patients with breast cancer whose disease is at moderate/high risk of recurrence. **(A)**

2.4.1.2 Adjuvant trastuzumab should be considered in all patients with HER2 positive breast cancer who receive adjuvant chemotherapy. **(A)**

2.4.1.3 The standard duration of treatment with adjuvant trastuzumab is one year. **(A)**

2.4.1.4 Adjuvant trastuzumab should preferably be given concurrently with taxane based regimens. It should **not** be given concurrently with anthracyclines. **(A)**

2.4.2.1 Premenopausal women with hormone receptor positive breast cancer should be treated with tamoxifen. **(A)**

2.4.2.2 The standard duration of treatment with tamoxifen for premenopausal women with hormone receptor positive breast cancer is at least five years, but there is evidence to support up to 10 years of use. **(A)**

2.4.2.3 Currently, the routine use of adjuvant ovarian ablation/suppression is **not** considered standard practice. **(B)**

2.4.3.1 Postmenopausal women with hormone receptor positive breast cancer should be treated with hormonal therapy for at least five years. The options include:
- Tamoxifen for five years followed by five years of an aromatase inhibitor. **(A)**
- An aromatase inhibitor as initial adjuvant therapy for five years. **(A)**
- Tamoxifen for two to three years followed by an aromatase inhibitor to complete five years of adjuvant endocrine therapy or tamoxifen for two to three years followed by five years of adjuvant endocrine therapy. **(A)**

2.4.3.2 In postmenopausal women, the use of tamoxifen alone for five years can be considered for those who decline, have a contraindication to, or are intolerant of aromatase inhibitors. **(A)**

2.4.4.1 Any patient who is a candidate for adjuvant systemic therapy can be considered for neoadjuvant systemic therapy. **(A)**

2.4.4.2 Neoadjuvant chemotherapy can be considered as part of a multimodal treatment approach for patients with stage IIa, IIb, and III breast cancer. **(A)**

2.4.4.3 For patients with locally advanced or inflammatory breast cancer preoperative chemotherapy is the preferred option. **(A)**

2.4.4.4 Patients with HER2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab. **(A)**

2.4.4.5 Neoadjuvant endocrine therapy is an option for patients with oestrogen-receptor positive breast cancer considered unsuitable for neoadjuvant chemotherapy or primary surgery. **(C)**

Radiation oncology

2.5.1.1 Postmastectomy radiotherapy should be recommended in patients with lymph node positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and/or T3/T4 primary tumour). **(A)**

2.5.1.2 Postmastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1-3 nodes) and individual patients should be discussed at multidisciplinary team meeting. **(B)**

2.5.2.1 All patients with ductal carcinoma in situ having breast conserving surgery should be considered for adjuvant radiotherapy. **(A)**

2.5.3.1 Radiotherapy is recommended for all patients undergoing breast conserving surgery for early breast cancer. **(A)**

2.5.3.2 Hypofractionation schedules are recommended for patients with early breast cancer. **(A)**

2.5.4.1 In patients who have undergone breast conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations. **(A)**

2.5.5.1 In patients who have breast conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis. **(A)**

2.5.5.2 Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high grade invasive cancers). **(A)**

2.5.6.1 Women who have undergone surgery for breast cancer should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery. **(C)**

2.5.7.1 Recommend adjuvant radiation to the supraclavicular fossa in patients with four or more positive axillary nodes. **(C)**

2.5.7.2 Consider adjuvant radiation to the supraclavicular fossa in selected patients with 1-3 positive axillary nodes. **(C)**

2.5.7.3 Consider irradiation to the internal mammary chain in patients with positive axillary nodes and/or inner quadrant tumours. **(B)**

2.5.7.4 Consider adjuvant radiation to the axilla in patients with positive axillary nodes who have not had an axillary dissection. **(B)**

Palliative care

2.6.1.1 For patients with cancer, early provision of palliative care can improve patient outcomes. **(C)**

2.6.1.2 Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need. **(D)**

Good practice points
Recommended best practice based on the clinical experience of the Guideline Development Group.

2.2 Radiology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.2.1

In patients with breast cancer, should all patients have pretreatment ultrasound of the axilla to determine node status and treatment options?

Evidence statement

Current guidelines (NICE, 2009) and a systematic review with a meta-analysis with pooled estimates (Alvarez et al., 2006) addressed this question.

The majority of patients with axillary lymph node disease do not have clinically obvious lymph node involvement, but imaging of the axilla can detect lymph nodes that may contain metastatic disease. Imaging alone is insufficiently accurate as a basis for treatment but if it suggests nodal involvement, ultrasound guided needle sampling of abnormal lymph nodes detects 40%-50% of patients with axillary node metastases. (NICE, 2009)

The systematic review by Alvarez et al. (2006) performed a meta-analysis of staging outcomes for 'grey scale' axillary ultrasound based on 16 case series studies. The meta-analysis provided pooled estimates of staging outcomes. When patients with palpable and non-palpable axillary lymph nodes were combined, lymph nodes that were suspicious on ultrasound based on their size (>5mm), sensitivity was 69.2% (63.4% – 74.6%) and specificity was 75.2% (70.4% – 79.6%). Many of the summary results obtained after meta-analysis show a heterogeneity that disappears, on excluding the studies that use a double gold standard. (NICE, 2009)

At present, there is no entirely reliable technique to identify tumour positive lymph nodes intraoperatively and a second operation on the axilla may be required. It is therefore advisable to identify those patients who can be shown to have involved lymph nodes by preoperative testing wherever possible. (NICE, 2009)

By offering axillary dissection to those proven preoperatively to have nodal metastases, two stage axillary procedures (i.e. SLNB or 4 node sampling) can be avoided in a significant number of patients. However, because of the low negative predictive values of these techniques, patients with no ultrasound evidence of abnormal lymph nodes or with negative ultrasound-guided needle sampling require surgical staging with sentinel lymph node biopsy as part of their initial surgical treatment. (NICE, 2009)

Recommendation 2.2.1.1	Grade
For all patients being investigated for invasive breast cancer, pretreatment ultrasound evaluation of the axilla should be performed and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.	B

Good practice point
When breast cancer is suspected, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration cytology). It is best practice to perform these assessments during the same visit.

Clinical question 2.2.2

In patients with breast cancer who have had ultrasound of the axilla performed, what features on ultrasound indicate that fine needle aspiration or core biopsy are required?

Evidence statement
Four retrospective studies (Abe et al., 2009, Britton et al., 2009, Garcia-Ortega et al., 2011, Deurloo et al., 2003) addressed this question.

The features described in all papers are consistent; however there is high degree of variability in the evidence on the measurement of cortical thickness that requires sampling, which ranges from 2-4mm.

The absence of a fatty hilum had the highest positive predictive value (93%). Cortical thickening combined with non-hilar blood flow (NHBF) in the same lymph node had the second highest positive predictive value (81%), which was higher than those of cortical thickening alone (73%) and NHBF alone (78%). Cortical thickening had the highest sensitivity (79%) but the lowest specificity (64%) among the three findings. There were significant differences in cortical thickness (P<0.001) and overall size (P<0.01) between the metastatic and non-metastatic lymph nodes. With the cortical thickness cut-off point set at 3mm, the sensitivity and specificity of this parameter for the detection of metastatic nodes were 95% and 6%, respectively. With 4mm as the cut-off point, sensitivity decreased slightly to 88% and specificity increased to 42%. (Abe et al., 2009)

The benefit of performing a fine needle aspiration (FNA) is the avoidance of unnecessary sentinel lymph node biopsy (SLNB) if positive findings are found on FNA. If the maximum cortical thickness is set too low, and FNA is positive, more extensive axillary surgery may be mandated that may not benefit the patient.

Compared with a smooth cortex, a unilobulated cortex may suggest a higher risk of malignancy (odds ratio of 2.1 (0.7 to 6.0)) and a multilobulated cortex indicated a significantly higher risk (3.8 (1.6 to 8.8)). There was no clear evidence of a relationship with increasing longitudinal size or the longitudinal size:transverse size (LS:TS) ratio. There was however a significant relationship with increasing size in the transverse plane. Compared with nodes smaller than 5mm, the risk of malignancy nearly tripled for each increment of 5mm in dimension (odds ratio 2.8 (1.6 to 4.9)). In multiple regression, absence of identifiable hilum, non-smooth cortex morphology and size in transverse section remained significant independent predictors of lymph node positivity. (Britton et al., 2009)

Maximum cortex thickness is the main feature to predict metastatic involvement (area under Receiver Operating Characteristic (ROC) curve (AZ)=0.87). (Deurloo et al., 2003)

'Maximum cortex thickness' and 'appearance of cortex' turned out to be the most effective features to discriminate between normal and malignant nodes. 'Appearance of hilus', 'shape', 'length' and 'width' were also effective features, showing moderate ability to predict metastatic involvement. (Deurloo et al., 2003)

Deurloo et al. (2003) recommend using the characteristic that is the easiest to implement in clinical practice which is maximum cortex thickness.

It may be appropriate to sample nodes with cortical thickness of 3mm or greater, and/or if there are abnormal morphological features.

Recommendation 2.2.2.1	Grade
Ultrasound guided lymph node sampling (fine needle aspiration/core needle biopsy) is recommended in patients with breast cancer where ultrasound demonstrates lymph nodes of cortical thickness of ≥3mm or if the node demonstrates abnormal morphological features.	C

Clinical question 2.2.3

In patients aged over 35 with a palpable breast lesion with normal imaging (mammography and ultrasound), when should clinical core biopsy be performed?

Evidence statement
Two relevant papers were identified to answer this question (Gumus et al., 2012, Sundara-Rajan et al., 2012). Following appraisal for quality and applicability only one paper was included (Gumus et al., 2012).

Two hundred and fifty one patients with palpable abnormalities on presentation with negative ultrasound and mammography had clinically guided biopsies (CGBs). Three (1.2%) of the 251 CGBs were reported as malignant; two (0.8%) of which were invasive. Forty-six (18.3%) of the 251 cases were regarded as clinically suspicious or malignant, while the remaining 215 examinations were categorised as benign or probably benign. All three malignancies were in the clinically suspicious or malignant group. (Gumus et al., 2012)

A negative ultrasound and mammogram in patients with a palpable abnormality does not exclude breast cancer; however, the likelihood is very low (1.2%). In the study by Gumus et al. (2012) 81.7% of biopsies could have been avoided if CGB was reserved for the clinically suspicious or malignant group only, without missing any malignancies. (Gumus et al., 2012)

Combined breast ultrasound and mammography is very powerful in assessing clinically palpable lesions and in 98.8% of the cases will accurately rule out malignancy. Gumus et al. (2012) has shown that if CGB is performed only for clinically suspicious or malignant lesions no cancers will be missed while 81.7% of CGB could be avoided. Therefore, it is recommended that women with negative imaging and clinically low-risk palpable abnormalities should be followed in the short term by clinical examination and CGB should be performed only for clinically high-risk patients. (Gumus et al., 2012)

Recommendation 2.2.3.1	**Grade**
In patients with a clinically suspicious examination (S4, S5) and normal imaging (mammography and ultrasound), clinically guided core biopsy should be performed.	C

S4 – Findings suspicious of malignancy
S5 – Findings highly suspicious of malignancy (Maxwell et al., 2009)

Clinical question 2.2.4

In patients with biopsy proven breast cancer, what is the role of breast magnetic resonance imaging (MRI) in the preoperative staging of:
- **Patients with biopsy proven ductal carcinoma in situ**
- **Patients with biopsy proven invasive breast cancer**
    - **Lobular**
    - **Ductal**

Evidence statement

Current guidelines (NICE, 2009, NCCN 2014a), recommendations from the EUSOMA working group (Sardanelli et al., 2010), two meta-analyses (Houssami et al., 2013, Mann et al., 2008) and an UpToDate review (Esserman and Joe, 2014a) addressed this question.

Breast MRI is highly sensitive and can identify foci of cancer that are not evident on physical examination, mammogram, or ultrasound. Although advocates of MRI cite as potential benefits improved selection of patients for breast conserving surgery (BCS), a decrease in the number of surgical procedures needed to obtain clear margins, and the synchronous detection of contralateral cancers, there are no data from prospective randomised trials that demonstrate improved outcomes from the addition of breast MRI to the diagnostic evaluation of newly diagnosed breast cancer. Furthermore, because of limited specificity, the use of breast MRI increases the number of unnecessary biopsies, delays definitive treatment, and increases the number of patients undergoing mastectomy. As a result, breast MRI is not recommended as a routine component of the diagnostic evaluation of breast cancer for most women. (Esserman and Joe, 2014a)

Ductal carcinoma in situ (DCIS)

The majority of cases of DCIS are detected through screening and 90% are identified as microcalcifications found on mammography. Mammographic extent alone will underestimate size of the disease extent in approximately 40% of cases. Ultrasound and MRI are unreliable for assessing the extent of DCIS but may be useful in detecting unsuspected associated invasive disease. MRI may also overestimate the extent of DCIS. (NICE, 2009)

Invasive breast cancer

Routine methods for assessing the extent of disease in the breast are clinical examination, mammography and ultrasound. In a significant number of cases, the true extent of disease is underestimated, particularly with invasive lobular cancer. MRI is more accurate for assessing the size of invasive tumour, for detecting the presence of multiple invasive foci in the ipsilateral breast and concurrent contralateral breast cancer. However, MRI identifies a significant number of false positive abnormalities which then requires further investigation. The incidence of multifocal tumour shown on MRI is much higher than the observed local recurrence rates following BCS and radiotherapy (RT), suggesting that mastectomy may not always be necessary in this situation. Nevertheless, preoperative MRI is increasingly being used. (NICE, 2009)

In a systematic review of patients with invasive lobular carcinoma (Mann et al., 2008), MRI had a pooled sensitivity of 93% and a high correlation with pathology (r=0.81–0.97); additional ipsilateral lesions were detected in 32% of patients and contralateral lesions in 7%. Surgical management was changed by MRI in 28% of cases (Mann et al., 2008). However, it has to be noted that in a study retrospectively comparing women treated for invasive lobular carcinoma and for invasive ductal carcinoma, no significant difference was found for success rate of BCS and RT or for number of surgical operations to obtain negative margins (Morrow et al., 2006). (Sardanelli et al., 2010)

The use of MRI in the preoperative staging of patients with invasive lobular cancer (ILC) is currently an area under much deliberation. A meta-analysis (Mann et al., 2008) found that MRI

has a high sensitivity for ILC, not achieved by other imaging modalities. The underestimation by other imaging modalities results in more failure of BCS and RT, more re-excisions and more conversion to mastectomy in series where MRI is not used. Therefore, MRI is helpful in cases where conventional imaging is inconclusive. Correlation with pathology ranges from 0.81 to 0.97; overestimation of lesion size occurs but is rare. In 32% of patients, additional ipsilateral lesions are detected and in 7% contralateral lesions are only detected by MRI.

A second meta-analysis (Houssami et al., 2013) states the evidence showed that MRI significantly increased mastectomy rates (43.0% vs. 40.2%) and suggests an unfavourable harm-benefit ratio for routine use of preoperative MRI in breast cancer. The authors found weak evidence that MRI reduced re-excision surgery in patients with ILC, although this was at the expense of increased mastectomies and the overall patient benefit from MRI in ILC is uncertain.

In the majority of patients with early invasive ductal carcinoma or cancer of no special type (NST), the size and extent of disease in the breast can be accurately assessed on the basis of clinical examination, mammography and ultrasound and a decision made on whether BCS can be considered. Invasive lobular cancer is difficult to size accurately using the same methods and MRI has been shown to be more accurate when assessing the size in this type of invasive breast cancer. (NICE, 2009)

Another interesting subgroup analysis was performed by Deurloo et al. (2006). They studied 165 patients eligible for BCS and RT. Preoperative MRI was more accurate than conventional imaging in the assessment of tumour extent in approximately one of four patients. Patients younger than 58 years old with irregular lesion margins at X-ray mammography (XRM) and discrepancy in tumour extent by more than 10mm between X-ray mammography and ultrasound had a 3.2 times higher chance of accurate assessment at MRI (Deurloo et al., 2006). (Sardanelli et al., 2010)

If MRI imaging of the breast is performed, it should be done with a dedicated breast coil, with consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI guided biopsy. (NCCN, 2014a)

There is insufficient evidence to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes (NICE, 2009).

There is insufficient evidence on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS. (NICE, 2009)

Recommendation 2.2.4.1	Grade
The routine use of MRI of the breast is **not** recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ.	B

Recommendation 2.2.4.2	Grade
Offer MRI of the breast to patients with invasive breast cancer, if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment, or if breast density precludes accurate size assessment.	B

Recommendation 2.2.4.3	Grade
In patients with invasive lobular cancer, MRI can be considered to assess tumour size, if breast conserving surgery is a treatment option.	C

Clinical question 2.2.5

In patients with metastatic deposits in axillary nodes where no primary cancer has been identified clinically or on conventional imaging, what is the role of breast MRI?

Evidence statement

Recommendations from the EUSOMA working group (Sardanelli et al., 2010), three UpToDate reviews (Esserman and Joe, 2014a, Kaklamani and Gradishar, 2014, Slanetz, 2014) and a small cohort study (Orel et al., 1999) addressed this question.

Occult primary breast cancer has been classically defined as a condition characterised by a histopathologically confirmed cancer of breast type first presenting as metastatic disease (mainly as axillary lymphadenopathy) with negative clinical breast examination. It represents a type of 'carcinoma of unknown primary' syndrome and accounts for up to 1% of breast cancers (Henry-Tillman et al., 1999, Olson et al., 2000). To detect the breast origin in these patients has relevant treatment and prognostic implications (Orel et al., 1999, Bugat et al., 2002). However, in these patients, X-ray mammography detects the cancer in only about one-third of cases (Henry-Tillman et al., 1999). When X-ray mammography (XRM) and ultrasound fail to detect the primary tumour and needle sampling or surgical excision of lymphadenopathy suggests a breast origin of the cancer, this condition creates a dilemma with regard to treatment. Treatments reported in the literature in these patients are very different, ranging from mastectomy to quadrantectomy, RT of the breast and the axilla or watchful waiting. The suggested intervention is axillary dissection and breast RT (Galimberti et al., 2004). (Sardanelli et al., 2010)

Considering 10 studies published on occult primary breast cancer between 1997 and 2008 (Henry-Tillman et al., 1999, Olson et al., 2000, Orel et al., 1999, Morris et al., 1997, Tilanus-Linthorst et al., 1997, Schorn et al., 1999, Obdeijn et al., 2000, Buchanan et al., 2005, Ko et al., 2007, Lieberman et al., 2008), MRI enables the detection of an occult primary breast cancer in 35%–100% of cases. Pooling these results from case series and observational studies, MRI detected the occult breast carcinoma in 143 of 234 patients (61%). (Sardanelli et al., 2010)

Olson et al. (2000) reported that 16 of 34 women (47%) who underwent surgical treatment preserved their breast and four of five women with negative MRI who underwent mastectomy had no tumour in the mastectomy specimen. The authors conclude that MRI of the breast can identify occult breast cancer in many patients and may facilitate breast conservation. It was also found that negative breast MRI predicts low tumour yield at mastectomy (Sardanelli et al., 2010).

Breast MRI is useful for detection of an occult primary breast cancer when a patient presents with metastatic disease in the axillary lymph nodes with no evident primary breast lesion. Several observational series have demonstrated that breast MRI can detect a primary breast cancer in the majority of women who present with axillary adenocarcinoma (DeMartini and Lehman, 2008, Stomper et al., 1999, Orel et al., 1999, Buchanan et al., 2005, Olson et al., 2000, Chen et al., 2004, Obdeijn et al., 2000, Schorn et al., 1999, Henry-Tillman et al., 1999, Tilanus-Linthorst et al., 1997, Brenner and Rothman, 1997, Morris et al., 1997, Fourquet, 2004). (Slanetz, 2014)

A systematic review on the clinical utility of breast MRI in occult breast cancer included eight retrospective studies, totalling 250 patients (de Bresser et al., 2010). A lesion suspect for primary breast cancer was located by MRI in 72% of cases (pooled mean), which in 85% to 100% of cases represented a malignant breast tumour. The pooled sensitivity and specificity of MRI for breast cancer detection in the only two studies that reported histopathologic confirmation was 90% and 31% respectively. Breast MRI revealed a lesion that was amenable to lumpectomy in about one-third of cases, although some of the patients who were eligible for lumpectomy elected to undergo mastectomy instead. (Kaklamani and Gradishar, 2014)

Breast MRI should be performed with a dedicated breast coil by expert breast imaging radiologists at institutions that have the capability to perform MRI guided needle biopsy and/or wire localisation of the findings (Olson et al., 2000, Obdeijn et al., 2000, Bedrosian et al., 2002, Floery and Helbich, 2006, Liberman et al., 2005, Kuhl et al., 2001). (Esserman and Joe, 2014a)

MRI is very sensitive for the detection of mammographically and clinically occult breast cancer in patients with malignant axillary adenopathy. In these patients, MRI offers potential not only for cancer detection but also for staging the cancer within the breast, which may be useful for treatment planning. (Orel et al., 1999)

Recommendation 2.2.5.1	Grade
Breast MRI is indicated in the clinical setting of occult primary breast cancer (typically, axillary lymphadenopathy) and following negative clinical breast examination and negative conventional imaging.	B

Clinical question 2.2.6

In patients with nipple discharge, inversion, Paget's disease or breast dimpling who have normal ultrasound and mammography, what is the role of breast MRI?

Evidence statement
Current guidelines (NICE, 2009, NCCN 2014b), three UpToDate reviews (Esserman and Joe, 2014a, Killelea and Sowden, 2014, Slanetz, 2014) and a narrative review (Da Costa et al., 2007) addressed this question.

Nipple discharge
There is insufficient evidence on the benefit of MRI for women with normal ultrasound and mammography to recommend the routine use of MRI in the clinical context of suspicious nipple discharge.

MRI imaging of the breast has been proposed for the evaluation of spontaneous nipple discharge when mammography and ultrasound of the periareolar area fail to identify a focal finding (Cilotti et al., 2007, Nakahara et al., 2003, Mortellaro et al., 2008, Ballesio et al., 2008, Tokuda et al., 2009, Morrogh et al., 2007). However, a negative MRI does not preclude disease and pathologic nipple discharge should be managed with a terminal duct excision. (Slanetz, 2014)

Nipple inversion
There is insufficient evidence on the benefit of MRI for women with normal ultrasound and mammography to recommend the routine use of MRI in the clinical context of nipple inversion.

Acute nipple inversion is defined as having duration of less than six months (Kalbhen et al., 1998). When nipple inversion occurs rapidly, the underlying cause can be inflammation, postsurgical changes, or an underlying malignancy. The reported incidence of an underlying breast carcinoma in this setting varies from 5% to greater than 50% (Neville et al., 1982). (Da Costa et al., 2007)

A thorough evaluation is required for new onset acquired nipple inversion. This work-up should include physical exam, imaging, and biopsy of any suspicious findings. (Killelea and Sowden, 2014)

Acquired nipple inversion in an adult woman requires evaluation by physical examination and imaging studies, starting with diagnostic mammography (Kalbhen et al., 1998). Retroareolar breast cancers, within 2cm of the nipple areolar complex, are most likely to be associated with nipple inversion. However, retroareolar breast cancers are more difficult to identify with mammography than tumours elsewhere in the breast due to dense retroareolar tissue. (Killelea and Sowden, 2014)

Ultrasound is a useful adjunct to mammography in the evaluation of nipple inversion and may identify a retroareolar mass that is not visible on mammography (Giess et al., 1998). (Killelea and Sowden, 2014)

Contrast-enhanced MRI is not part of the usual evaluation of nipple inversion, but may be useful when mammographic and sonographic findings are inconclusive (Da Costa et al., 2007, An et al., 2010). Breast MRI can differentiate tumour confined to the retroareolar location from the nipple areolar complex. (Killelea and Sowden, 2014)

Paget's disease

Paget's disease of the nipple is a malignant condition that affects the nipple/areola complex from where it may spread to the surrounding skin. Patients present with a thickened, reddened, weeping or crusted area on the nipple. Nipple discharge and ulceration may sometimes occur, and there may be an associated palpable breast lump. Microscopic examination shows intraepithelial infiltration by malignant cells which, in most cases, originate from an underlying in situ or invasive cancer. The latter is usually located centrally (within 2cm of the areola) but may occasionally be more peripheral and multifocal. In 5%-10% of cases, Paget's disease is the only manifestation of breast cancer and no other underlying tumour can be found. The treatment of Paget's disease of the nipple has traditionally been by mastectomy. Increasingly BCS with nipple removal is being offered for central localised lesions, particularly now that oncoplastic repair techniques are available, but there have been no randomised trials comparing these treatments. Comprehensive breast imaging by; mammography, ultrasound and, when appropriate, MRI is indicated to avoid missing extensive or multifocal disease. (NICE, 2009)

Punch biopsy of skin or nipple biopsy should be performed following imaging findings consistent with an overall Breast Imaging Reporting and Data System (BI-RADS®) assessment category 1-3. Antibiotics may or may not be given, depending on the clinical scenario, but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathological correlation should be reassessed. In addition, a breast MRI, a repeat biopsy, and consultation with a breast specialist should be considered. (NCCN, 2014b)

For women with Paget's disease of the breast who have a negative physical examination and mammogram, breast MRI may be used to define the extent of disease and aid in treatment planning (Morrogh et al., 2008, Frei et al., 2005). (Esserman and Joe, 2014a)

Breast dimpling

There is insufficient evidence on the role of MRI in breast dimpling with negative imaging to make a recommendation.

Recommendation 2.2.6.1	Grade
In the setting of negative conventional imaging, MRI can facilitate treatment planning for patients with Paget's disease.	C

In women with breast cancer, who/what subgroups should have staging investigations performed to detect metastases?

Evidence statement

Current guidelines (NCCN, 2014a, Cancer Care Ontario, 2011), a systematic review (Brennan and Houssami, 2012), a cohort study (Barrett et al., 2009) and an UpToDate review (Esserman and Joe, 2014b) addressed this question.

The yield for metastases is likely to be higher in women presenting with more advanced stages of disease. However, there is no consensus on the stage, tumour size or number of lymph nodes that should act as thresholds to prompt the routine use of imaging tests for staging newly diagnosed women. (Brennan and Houssami, 2012)

Patients with symptoms suggestive of metastatic disease should have appropriate imaging investigations regardless of pathological stage. The instance of metastasis in asymptomatic newly diagnosed breast disease is very low (Barrett et al., 2009).

Current guidelines generally do not recommend the routine use of staging investigations at the time of diagnosis for cases of early breast cancer. (NCCN, 2014a, Cancer Care Ontario, 2011)

This question was addressed in a systematic review by Brennan and Houssami (2012). The evidence confirmed the extremely low prevalence of asymptomatic distant metastases (DM) in Stage I and II breast cancer (median 0.2% and 1.2% respectively). Much higher prevalence of DM was seen in stage III cancer (median 13.9%), especially in the subgroup of inflammatory breast cancer (median 39.6% with DM). (Brennan and Houssami, 2012)

Examination of data from primary studies with large sample size and reporting stage-specific data (Barrett et al., 2009, Dillman and Chico, 2000, Kim et al., 2011, Koizumi et al., 2001, Lee et al., 2005) (all of which were studies of conventional imaging only) showed that while the overall proportion with DM in each of these studies was relatively low, there was strong and consistent evidence (P<0.001 all within-study analyses) that the proportion with DM significantly increased with increasing stage at presentation, with increasing T-stage, or with increasing nodal involvement. (Brennan and Houssami, 2012)

Prevalence of metastatic disease in stage I breast cancer was reported in seven studies, all reporting on conventional imaging alone: median 0.2%, range 0%-5.1%. In the three studies reporting prevalence by site, metastatic disease was reported in lung in 0%-0.2% of patients, liver in 0%-1.6% and bone in 0%-5.1% (Kasem et al., 2006, Kim et al., 2011, Puglisi et al., 2005). (Brennan and Houssami, 2012)

For stage II breast cancer, prevalence of metastatic disease from 11 studies was reported (seven reporting conventional imaging only – Barrett et al., 2009, Dillman and Chico, 2000, Kasem et al., 2006, Kim et al., 2011, Koizumi et al., 2001, Lee et al., 2005, Puglisi et al., 2005, one reporting positron emission tomography–computed tomography [PET-CT] - Groheux et al., 2008, one reporting both – Segaert et al., 2010). The median prevalence of metastases for studies reporting conventional imaging was only 1.1% (Groheux et al., 2008). In four studies reporting metastases prevalence by subgroups, the median was 0.5% for Stage IIa and 6.3% for Stage IIb. In the three studies reporting prevalence by site, metastatic disease was reported in lung in 0% of patients, liver in 0%-2.1% and bone in 0%-5.8% (Kasem et al., 2006, Kim et al., 2011, Puglisi et al., 2005). (Brennan and Houssami, 2012)

For stage III breast cancer, prevalence was reported in 11 studies (six reporting findings in conventional imaging only – Barrett et al., 2009, Dillman and Chico, 2000, Kim et al., 2011, Koizumi et al., 2001, Lee et al., 2005, Puglisi et al., 2005 (median prevalence 8.0%), four reporting PET or PET-CT – Alberini et al., 2009, Carkaci et al., 2009, Groheux et al., 2008, Van der Hoeven et al., 2004 (median prevalence 26.0%) and one reporting both – Segaert et al., 2010 (prevalence 34.3%)). In the two studies reporting prevalence by site, metastases were reported in lung in 6% of patients, liver in 2.2%-5.7% and bone in 14% (Kim et al., 2011, Puglisi et al., 2005). Two studies included only cases of inflammatory breast cancer and the prevalence of metastatic disease in these studies was 30.5% and 48.8% (Alberini et al., 2009, Carkaci et al., 2009). (Brennan and Houssami, 2012).

Analysis of the five studies with large subject numbers and reporting stage-specific metastases data (allowing calculation of reliable estimates of prevalence across stage-groups (Koizumi et al., 2001, Barrett et al., 2009, Lee et al., 2005, Dillman and Chico, 2000, Kim et al., 2011) showed consistent evidence that the proportion of patients with asymptomatic DM significantly increased with advancing stage (P<0.001 for each study). For Koizumi et al. (2001) the proportion of patients with asymptomatic DM significantly increased with increasing T-stage (P<0.0001). Similarly, there was evidence (Koizumi et al., 2001, Ravaioli et al., 1998) that the proportion of patients with asymptomatic DM significantly increased with increasing nodal involvement (P<0.001). (Brennan and Houssami, 2012)

Based on a systematic review in 2012, the prevalence of asymptomatic DM detected with imaging in early stage breast cancer (stage I and II) is very low, and the reported evidence does not support routine use of imaging for staging these women. In more advanced breast cancer presentations (stage III, inflammatory cancer, and in extensive lymph node involvement) the prevalence of DM was consistently high and may justify systematic staging in this group of women. (Brennan and Houssami, 2012)

In a study of 2,612 patients (Barrett et al., 2009), 91.7% were found to be appropriately investigated. However in the subset of lymph node negative stage II patients, only 269 out of 354 (76%) investigations were appropriate. No patients with stage 0 or I disease had metastases; only two patients (0.3%) with stage II and ≤3 positive lymph nodes had metastases. Conversely, 2.2%, 2.6% and 3.8% of these groups had false-positive results. The incidence of occult metastases increased by stage, being present in 6%, 13.9% and 57% of patients with stage II (≥4 positive lymph nodes), III and IV disease, respectively. (Barrett et al., 2009)

Overall, the yield for detecting metastases is low in such asymptomatic patients, with no occult metastases detected in any patient with stage 0 or I disease. The results showed the benefit of a risk-stratified staging protocol for early breast cancer but underline the importance of making inclusion criteria clear and less open to interpretation. In this way the majority of occult metastases can be detected with minimal false positives, incidental findings and unnecessary radiation exposure. Although the inclusion of patients with T4 disease or any evidence of malignant lymphadenopathy is very clear, the inclusion of 'patients with more locally advanced disease' is open to interpretation. (Barrett et al., 2009)

Women presenting with signs or symptoms of metastatic breast cancer should undergo additional imaging with a biopsy of at least one metastatic lesion to confirm the diagnosis of metastatic breast cancer. (Esserman and Joe, 2014b)

Multiple studies have shown that extensive imaging has little yield for most patients with newly diagnosed breast cancer (Myers et al., 2001, Puglisi et al., 2005, Ravaioli et al., 2002). (Esserman and Joe, 2014b)

Recommendation 2.2.7.1	Grade
In newly diagnosed patients with breast cancer who have symptoms suggestive of metastases, appropriate imaging investigations should be performed, regardless of tumour stage.	B

Recommendation 2.2.7.2	Grade
In newly diagnosed asymptomatic patients with breast cancer, evidence does **not** support the use of routine imaging for metastatic disease in pathological stage I and II disease.	B

Recommendation 2.2.7.3	Grade
In newly diagnosed asymptomatic patients with breast cancer, use of staging imaging for metastatic disease is recommended for stage III and IV disease.	B

Clinical question 2.2.8

In women with breast cancer who are being staged, what investigations should be performed?

Evidence statement
Current guidelines (NCCN, 2014a), a systematic review (Houssami and Costello, 2012) and two cohort studies (Morris et al., 2010, Barrett et al., 2009) addressed this question.

Bone scan
For patients with clinical stage IIIA (T3, N1, M0), additional staging studies including bone scan or sodium fluoride PET scan, abdominal imaging using diagnostic computed tomography (CT) or MRI, and chest imaging using diagnostic CT should be considered. (NCCN, 2014a)

Houssami and Costelloe, (2012) found little evidence on which to base recommendations regarding single photon emission computed tomography (SPECT) or whole-body MRI for bone metastases (BM). The authors concluded that there is no definitive evidence supporting that any of the imaging tests discussed in their review can be used as a replacement to bone scan (BS) in first-line imaging for evaluation of bone lesions or symptoms, or in staging and restaging, in breast cancer. Eligible studies (n=16) included breast cancer cases which had imaging evaluation for suspected BM or for staging/restaging in suspected local or distant relapse. Median prevalence of BM was 34% (range 10%–66.7%). (Houssami and Costelloe, 2012)

There is some evidence of enhanced incremental accuracy for some of the above-mentioned tests where used as add-on in patients selected to more than one imaging modality, with little evidence to support their application as a replacement to BS in first-line imaging of BM. PET-CT appears to have high accuracy and is recommended for further evaluation. (Houssami and Costelloe, 2012)

CT vs. Ultrasound
Barrett et al. (2009) found a difference in the accuracy of the four different imaging modalities (CXR, US, CT, BS) used. There were three true-positive (0.2%) and 20 (1.3%) false-positive results out of 1,556 CXRs, six true-positive (1.8%) and 13 (3.8%) false-positive results out of 339 liver US, 23 true-positive (6.2%) and 51 (13.7%) false-positive results out of 373 bone scans, and 21 true-positive (26.9%) and 3 (3.8%) false-positive results out of 78 CTs. CT was the only modality in which the percentage of true-positive results was higher than the false-positive results. (Barrett et al., 2009)

The increased specificity of CT may reduce follow-up investigations, which could partially offset the increased radiation dose, limit the psychological burden of false-positive results and reduce the need for further invasive testing. The advantages of CT in relation to improved sensitivity and patient convenience, have led to recommending this as the baseline imaging modality of choice in patients presenting with asymptomatic newly diagnosed breast cancer. CT had a lower rate of false-positive results (3.8%) than ultrasound and bone scan. (Barrett et al., 2009)

PET scan
The use of PET or PET-CT scanning in the staging of patients with stage I-IIB disease is not recommended. This is supported by the high false-negative rate in the detection of lesions that are small (<1cm) and/or low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false-positive scans (Carr et al., 2006, Khan et al., 2007, Kumar et al., 2006, Podoloff et al., 2007, Rosen et al., 2007, Wahl et al., 2004). (NCCN, 2014a)

Fluorodeoxyglucose (FDG) PET-CT is most helpful in situations where standard imaging results are equivocal or suspicious. However, limited studies (Podoloff et al., 2007, Rosen et al., 2007, Aukema et al., 2010, Fuster et al., 2008, Groheux et al., 2008, Van der Hoeven et al., 2004, Niikura

et al., 2011) support a potential role for FDG PET-CT to detect regional node involvement as well as distant metastases in locally advanced breast cancer, including T3, N1, M0, disease (NCCN, 2014a).

The use of either bone scan or PET-CT is appropriate for staging possible bone metastases, but not both. PET-CT may be superior to bone scan alone. (Morris et al., 2010)

Chest X-ray
Preoperative CXR is not necessary as a staging investigation (Barrett et al., 2009).

Recommendation 2.2.8.1	Grade
In patients with newly diagnosed breast cancer who require staging, contrast enhanced CT (chest, abdomen and pelvis) and whole body isotope bone scan are recommended.	B

Recommendation 2.2.8.2	Grade
PET-CT is **not** routinely recommended. However, it may be considered in specific cases.	C

2.3   Surgery

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.3.1

In patients with ductal carcinoma in situ, what is the evidence that breast conserving surgery and radiotherapy is more or less effective than mastectomy?

Evidence statement
This question was addressed in current guidelines (NCCN 2014a, SIGN, 2013, NICE, 2009).

There are no randomised controlled trials (RCTs) that compare breast conserving surgery (BCS) and radiotherapy (RT) with mastectomy for patients with ductal carcinoma in situ (DCIS). However, this has been addressed for invasive breast cancer in a number of RCTs.

A meta-analysis of six RCTs (NSABP B-06, WHO (Milan), NCI-USA, IGR (Paris), EORTC 10801, Danish) showed that BCS and RT to the breast resulted in similar long term mortality rates compared with mastectomy, in patients with operable invasive breast cancer (pooled odds ratio (OR) 1.070; 95% confidence interval (CI) 0.935–1.224; P=0.33). In four of the six trials, mastectomy significantly reduced the risk of locoregional recurrence compared to BCS (OR 1.561, 95% CI 1.289 to 1.890) (Jatoi and Proschan, 2005). (SIGN, 2013)

There are four RCTs (Fisher et al., 2001, Emdin et al., 2006, Bijker et al., 2006, Houghton et al., 2003) that compare BCS and RT to BCS without RT. These RCTs have demonstrated that BCS and RT is an effective treatment for women with DCIS. In an RCT comparing local excision and RT with local excision alone, Bijker et al. (2006) found that the 10 year local recurrence-free rate was 74% in the group treated with local excision alone compared with 85% in the women treated by local excision plus RT (P<0.0001; hazard ratio [HR]=0.53). The risk of DCIS and invasive local recurrence (LR) was reduced by 48% (P=0.0011) and 42% (P=0.0065) respectively. Reporting on the sweDCIS trial, Emdin et al. (2006) observed 44 recurrences in the group who received post operative RT compared to 117 in the control group.

Although mastectomy provides maximum local control, the long-term, cause-specific survival with mastectomy appears to be equivalent to that with excision and whole breast irradiation (Bijker et al., 2006, Fisher et al., 1998, Vargas et al., 2005). (NCCN, 2014a)

The traditional management for DCIS was mastectomy, but breast conservation has become a more common method of treatment for apparently localised DCIS. However there is a 25% risk of local recurrence over 10 years without further therapy and half of these recurrences will be of invasive cancer. (NICE, 2009)

Recommendation 2.3.1.1	**Grade**
Women with ductal carcinoma in situ who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy.	B

Recommendation 2.3.1.2	**Grade**
Women with ductal carcinoma in situ should be offered breast conserving surgery and radiotherapy except where there are indications for mastectomy and sentinel lymph node dissection.	A

Clinical question 2.3.2

In patients with operable invasive breast cancer, what is the evidence that breast conserving surgery and radiotherapy is more or less effective than mastectomy?

Evidence statement
Current guidelines (SIGN, 2013), a meta-analysis (Yang et al., 2008) and three RCTs (Fisher et al., 2002a, 2002b, Hughes et al., 2013) addressed this question.

A meta-analysis of six RCTs (NSABP B-06, WHO (Milan), NCI-USA, IGR (Paris), EORTC 10801, Danish) showed that BCS and RT to the breast resulted in similar long term mortality rates compared with mastectomy, in patients with operable invasive breast cancer (pooled odds ratio (OR) 1.070; 95% confidence interval (CI) 0.935–1.224; P=0.33). In four of the six trials, mastectomy significantly reduced the risk of locoregional recurrence compared to BCS (OR 1.561, 95% CI 1.289 to 1.890) (Jatoi and Proschan, 2005). (SIGN, 2013).

Yang et al. (2008) state that local or regional recurrence represents the main disadvantage of BCS and RT. Some RCTs reported that BCS and RT was associated with higher rates of positive margins and the incidence of local failure than mastectomy (Fisher et al., 2002a, Van Dongen et al., 2000, Morrow et al., 2002, Veronesi et al., 2002, Freedman et al., 2002, Neuschatz et al., 2003). (Yang et al., 2008)

Reporting on the 25 year findings of the NSABP B-04 RCT, Fisher et al. (2002b) found that no significant differences were observed among the three groups of women with negative nodes or between the two groups of women with positive nodes with respect to disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival, showing no advantage to radical mastectomy. (Fisher et al., 2002b)

A 20 year follow up on the NSABP B-06 RCT (Fisher et al., 2002a), concluded that lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumour and an acceptable cosmetic result can be obtained. (Fisher et al., 2002a)

A study by Hughes et al. (2013) determining whether there is a benefit to adjuvant RT after BCS and tamoxifen in women age ≥70 years with early-stage breast cancer, concluded that with long-term follow-up, the previously observed small improvement in locoregional recurrence with the addition of RT remains. However, this does not translate into an advantage in overall survival, distant disease-free survival, or breast preservation. Depending on the value placed on local recurrence, tamoxifen alone remains a reasonable option for women age ≥70 years with oestrogen-receptor (ER) positive early-stage breast cancer.

Therapeutic mammoplasty is only indicated in a small cohort of patients. Typically these patients would have large ptotic breasts with a tumour in an appropriate location. Cases should be discussed individually at a multidisciplinary team meeting and patients should be informed that they may require a contralateral procedure and it should be executed incorporating all the standard principles associated with wide local excision.

Cavity margins should be clipped for orientation to facilitate re-excision of margins, if required, and direct postoperative radiation treatment.

Recommendation 2.3.2.1	**Grade**
Women with invasive breast cancer who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy.	**A**

Good practice point
The choice of surgery must be tailored to the individual patient, who should be fully informed of the options (breast conserving surgery and radiotherapy or mastectomy) and made aware that breast irradiation may be required following conservation and that further surgery may be required if the margins are positive.

Good practice point
Appropriately selected patients may be considered for oncoplastic procedures instead of mastectomy.

Good practice point
Cavity margins should be clipped for orientation to facilitate re-excision of margins, if required, and direct postoperative radiation treatment.

Clinical question 2.3.3

In patients undergoing mastectomy for operable breast cancer (in situ or invasive), what is the evidence for prophylactic mastectomy in the following groups:
- **Those who have had a previous breast cancer and now have a local recurrence/second primary breast cancer in the ipsilateral or contralateral breast**
- **Those with breast cancer and who had previously been identified as being at an increased risk (medium or high) and those identified with BRCA 1/2?**

Evidence statement
Current guidelines (NICE, 2013, NCCN, 2014b), a cohort study (Evans et al., 2013) and an SSO position statement (Giuliano et al., 2007) addressed this question.

In the general population there is insufficient evidence to support contralateral risk reducing mastectomy (CRRM), however in the high-risk population (genetic mutation carriers) CRRM may be indicated (Lostumbo et al., 2010). (NICE, 2013)

Evans et al. (2013) reports that in women electing for CRRM, the 10-year overall survival was 89% (n=105) compared to 71% in the non-CRRM group (n=593); (P<0.001). Survival was assessed by proportional hazards models, and extended to a matched analysis using stratification by risk reducing bilateral salpingo-oophorectomy (RRBSO), gene, grade and stage. The survival advantage remained after matching for oophorectomy, gene, grade and stage (HR 0.37, 0.17–0.80, *P*=0.008) contralateral risk-reducing mastectomy appeared to act independently of RRBSO. CRRM appears to confer a survival advantage. Although endocrine therapy, including RRBSO, chemotherapy and lifestyle factors reduce contralateral breast cancer risk (Schaapveld et al., 2008, Gronwald et al., 2006), surgery is by far the most effective intervention (Yi et al., 2009, McDonnell et al., 2001, Van Sprundel et al., 2005, Kaas et al., 2010). (Evans et al., 2013).

Evans et al. (2013) also state that the estimation of survival after CRRM is confounded by the propensity of carriers of BRCA1/2 mutations to undergo RRBSO, which substantially reduces the risk of: ovarian cancer; relapse from the primary breast cancer; and contralateral breast cancer (Schaapveld et al., 2008, Gronwald et al., 2006). (Evans et al., 2013)

Although women with CRRM had apparently reduced breast cancer and non-breast cancer mortality, this result is potentially confounded by several factors including:
- The trend for risk-reducing operations to be performed more recently over the period of study;
- Concomitant RRBSO;
- Differences in median follow-up (8.8 years for the CRRM group and 7.3 years for the non-CRRM group); and
- Differences in time to BRCA1/2 mutation testing (median of 3.6 years from the primary surgery in the CRRM group and of 7.1 years in the non-CRRM group). (Evans et al., 2013)

Retrospective analyses with median follow up periods of 13 to 14 years have indicated that bilateral risk-reducing mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA 1/2 mutation carriers (Hartmann et al., 1999, Hartmann et al., 2001). An analysis of the results from the study by Hartmann et al. (1999) determined that to prevent one case of breast cancer in women with high-risk, the number needed to be treated with RRM was equal to six (Hamm et al., 1999). Results from smaller prospective studies with shorter follow up periods have provided support for concluding that RRM provides a high degree of protection against breast cancer in women with a BRCA 1/2 mutation (Meijers-Heijboer et al., 2001, Rebbeck et al., 2004). An NCCN breast cancer risk reduction guideline development panel supports the use of RRM for carefully selected women at high risk of breast cancer who desire this intervention (e.g. women with a BRCA 1/2, TP53,

PTEN, CDH1, or STK11 mutation or, possibly, for a woman with a history of lobular carcinoma in situ (LCIS)). (NCCN, 2014b)

In the NCCN report on breast cancer risk reduction, the consensus of the NCCN panel is that consideration of RRM is an option for women with LCIS without additional risk factors, it is not a recommended approach for most of these women. There are no data regarding RRM in women with prior mantle radiation exposure. (NCCN, 2014b)

The Society of Surgical Oncology (SSO) issued a position statement in 2007 (Giuliano et al., 2007) stating clinicopathologic presentations that portend an additional risk of the development of breast cancer and that justify proceeding with bilateral prophylactic mastectomies which included those with a known mutation of BRCA1 or BRCA2 or other strongly predisposing breast cancer susceptibility genes, a family history of breast cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer (family cancer syndrome) and those with high-risk histology such as, atypical ductal or lobular hyperplasia, or lobular carcinoma in situ confirmed on biopsy. (Giuliano et al., 2007)

Recommendation 2.3.3.1	Grade
In the general population, there is no evidence that a contralateral risk reducing mastectomy improves a patient's prognosis. However, a contralateral risk reducing mastectomy may be undertaken to address specific patient concerns if it is discussed at a multidisciplinary team meeting and the benefits, risks and alternatives have been discussed with the patient.	B

Recommendation 2.3.3.2	Grade
There are subsets of patients who may benefit from a contralateral risk reducing mastectomy, such as genetic mutation carriers.	C

Clinical question 2.3.4

In patients with breast cancer undergoing mastectomy who are suitable for breast reconstruction, is there any evidence that breast reconstruction, timing of reconstruction, and type of reconstruction effect outcome?

Evidence statement

Current guidelines (NICE, 2012, NICE 2009), a meta-analysis (Barry and Kell, 2011) and an NHS audit report (2012) addressed this question.

Breast reconstruction is not suitable for everyone, consideration must be given to patient factors and cancer features. All patients requiring a mastectomy for the treatment of their primary breast cancer should have a discussion regarding the risks, benefits and alternatives of an immediate/delayed breast reconstruction. Patients with locally advanced, inflammatory breast cancer, smokers, patients with diabetes or those with a body mass index (BMI) greater than 30 may not be suitable candidates.

Timing of reconstruction

Breast reconstruction can be carried out at the same time as mastectomy (immediate) or at any point in the future (delayed) (NICE, 2009). However, in the absence of level I evidence, the current data suggests that immediate breast reconstruction with postmastectomy radiotherapy (PMRT) may be undertaken (Barry and Kell, 2011).

Immediate reconstruction has the advantage of offering one primary breast procedure and offering the possibility for limited skin removal, preservation of the inframammary fold and the skin envelope.

Chest wall RT may significantly reduce the cosmetic outcomes of reconstruction. (NICE, 2009)

There is some evidence to support delaying reconstruction in the context of PMRT (fewer complications associated with PMRT (perioperatively) when compared to immediate).

One study (Barry and Kell, 2011) which systematically reviewed and examined postoperative morbidity following immediate or delayed breast reconstruction with combined RT was identified. These results suggested that where immediate reconstruction is undertaken with the necessity of PMRT, an autologous flap results in less morbidity when compared with implant-based reconstruction. (NICE, 2012)

Type of reconstruction

There are options for reconstruction: autologous and implant-expander-based. A national audit of mastectomy and breast reconstruction was performed by the National Health Service (NHS) in the UK and found that autologous tissue may give a better outcome, in both immediate and delayed reconstruction. However, implant expander-based reconstruction is widely practiced with acceptable results (NHS, 2012).

Autologous tissue may provide reduced post operative morbidity in the setting of PMRT compared with expander based reconstruction (Barry and Kell, 2011).

There is a paucity of data currently available to draw definitive conclusions on the potential impact of RT on increased rates of complications and reconstruction loss.

Recommendation 2.3.4.1	Grade
A discussion regarding breast reconstruction should be undertaken with all patients undergoing mastectomy for breast cancer.	A

Good practice point
The timing, type, patient suitability for this procedure, and the potential impact of radiotherapy on breast reconstruction should be the basis of this discussion with the patient.

Clinical question 2.3.5

What is the appropriate management of the axilla in patients with operable (invasive) breast cancer who have no evidence of axillary lymph nodes metastases at initial diagnosis?

Evidence statement

Current guidelines (SIGN, 2013), an RCT (Krag et al., 2010) and an UpToDate review (Harlow and Weaver, 2014) addressed this question.

In a meta-analysis of eight RCTs (Canavese et al., 2009, Purushotham et al., 2005, Veronesi et al., 2010, 2006, 2003, Fleissig et al., 2006, Mansel et al., 2006, Del Bianco et al., 2008, Zavagno et al., 2008, Ashikaga et al., 2010, Land et al., 2010, Krag et al., 2010, 2009, Smith et al., 2009, Gill, 2009, Giuliano et al., 2011, 2010, Lucci et al., 2007) comparing the effectiveness and safety of SLNB with axillary lymph node dissection (ALND), there was no statistical difference in overall survival, disease-free survival or regional lymph node recurrence between the SLNB and ALND groups (Wang et al., 2011). Postoperative morbidity is significantly reduced in patients undergoing SLNB rather than ALND (Kell et al., 2010, Wang et al., 2011, Lee et al., 2008). (SIGN, 2013).

The NSABP B-32 trial randomly assigned patients into two groups, sentinel node resection plus axillary dissection (Group 1) or sentinel node resection alone with axillary dissection only, if sentinel nodes were positive (Group 2). Krag et al. (2010) found that overall survival, disease-free survival, and regional control were statistically equivalent among the study groups. When the sentinel node is negative, sentinel node surgery alone with no further axillary dissection is an appropriate, safe and effective therapy for patients with breast cancer with clinically negative lymph nodes. (Krag et al., 2010)

A systematic review, performed by the ASCO expert guidelines panel, included 69 eligible trials of sentinel lymph node dissection (SLND) in early stage breast cancer, representing 8059 patients (Kim et al., 2006, Lyman et al., 2005). The sentinel lymph node (SLN) was identified using radiocolloid, blue dye, or both. SLN identification was successful in 95 percent of patients. The false negative rate was 7.3 % (range 0% to 29%). The combination of radiocolloid and blue dye resulted in a significantly higher success rate in SLN mapping with a lower false negative rate, compared to blue dye alone. (Harlow and Weaver, 2014)

Recommendation 2.3.5.1	Grade
Patients with operable (invasive) breast cancer with no clinical or radiological evidence of axillary lymph node metastases at initial diagnosis should be offered sentinel node biopsy.	A

Clinical question 2.3.6

What is the appropriate management of the axilla in patients with operable (invasive) breast cancer undergoing neoadjuvant chemotherapy (node-positive/node-negative at diagnosis)?

Evidence statement
Current guidelines (SIGN, 2013) and an UpToDate review (Sikov, 2014) addressed this question.

For SLNB after neoadjuvant chemotherapy two meta-analyses of 2,148 and 1,799 node-negative patients have shown identification rates of 90.9% and 89.6%, respectively, and false negative rate of 10.5% and 8.4%, respectively (Kelly et al., 2009, Van Deurzen et al., 2009). The impact on axillary recurrence is unknown. (SIGN, 2013)

Outside of a clinical trial, patients who are candidates for neoadjuvant chemotherapy and have a clinically negative axillary examination at presentation (cN0) may have a SLNB either prior to or after neoadjuvant chemotherapy. The timing is often determined by preferences of the local treating physician, and in the absence of data suggesting a preferred strategy, either is reasonable. If the SLNB is negative (pN0), no further axillary evaluation is required. (Sikov, 2014)

For patients with clinically detected or pathologically confirmed axillary node involvement prior to neoadjuvant chemotherapy (e.g., by axillary ultrasound and fine needle aspiration or SLNB), an ALND should be performed. All patients should meet with a radiation oncologist to discuss the role of RT. (Sikov, 2014)

Following neoadjuvant chemotherapy, an ALND should also be performed in patients at high risk for recurrence, including:
- Women with multiple involved sentinel nodes (pN1 or greater),
- Women in whom adjuvant RT is not planned. (Sikov, 2014)

Good practice point
It is good practice to do a sentinel lymph node biopsy following neoadjuvant chemotherapy in clinically/ radiologically node negative patients.

Clinical question 2.3.7

What is the appropriate surgical management of the axilla in patients with operable (invasive) breast cancer with sentinel node positive isolated tumour cells, micromets or macromets?

Evidence statement

Two RCTs (Sola et al., 2012, Giuliano et al., 2011), an UpToDate review (Harlow and Weaver, 2014) and a retrospective review (Pepels et al., 2012) addressed this question.

Sola et al. (2012) investigated whether refraining from completion ALND suffices to produce the same prognostic information and disease control as proceeding with completion ALND in patients with early breast cancer showing micrometastasis at sentinel node (SN) biopsy. There were no differences in disease-free survival (P=0.325) between arms and no cancer-related deaths. The authors suggest their results show that in patients with early breast cancer with sentinel node micrometastases, selective sentinel node lymphadenectomy suffices to provide for locoregional and distant disease control, without significant deleterious effects on survival.

It is important to stress that the results of the Z0011 trial may only be applicable for women who have low-volume nodal disease, receiving adjuvant systemic therapy and breast conserving treatment with tangential irradiation fields (Pepels et al., 2012). Giuliano et al. (2011) claim that despite the limitations of the Z0011 trial, its findings could have important implications for clinical practice. Examination of the regional nodes with SLNB can identify haematoxylin-eosin–detected metastases that would indicate a higher risk for systemic disease and the need for systemic therapy to reduce that risk. Results from Z0011 indicate that women with a positive SLN and clinical T1-T2 tumours undergoing lumpectomy with radiation therapy followed by systemic therapy do not benefit from the addition of ALND in terms of local control, disease-free survival, or overall survival.

Weaver et al. (2011) conducted a pathologic evaluation for occult metastases in a randomised trial of 3,887 women who underwent SLNB alone or SLNB plus ALND for invasive breast cancer and detected occult metastases in 16% of patients (isolated tumour cell clusters in 11%, micrometastases in 4%, and macrometastases in 0.4%). The following findings were noted:

- Occult metastases were an independent adverse prognostic factor with an increased risk of distant disease and death (Harlow and Weaver, 2014).
- Smaller metastases had less of an adverse effect on outcomes than larger metastases, and the risk associated with isolated tumour cell clusters was less than the risk associated with micrometastases (Harlow and Weaver, 2014).
- At five years, the differences in outcomes for patients with and without occult metastases were statistically significant but relatively small with respect to overall survival (95% versus 96%), disease free survival (86% versus 89%), and distant disease free interval (90% versus 92%) (Harlow and Weaver, 2014).
- The presence of occult metastases was not a discriminatory predictive factor; 85% of women with occult metastases were alive without recurrent breast cancer (Harlow and Weaver, 2014).

Recommendation 2.3.7.1	**Grade**
Patients with isolated tumour cells and micrometastases do **not** require an axillary clearance.	**B**

Recommendation 2.3.7.2	**Grade**
In patients undergoing breast conserving surgery and radiotherapy who are clinically and radiological node negative at presentation and have one or two macrometastatic sentinel lymph nodes in a sentinel lymph node biopsy, the avoidance of axillary lymph node dissection may be considered following a discussion at a multidisciplinary team meeting and with the patient.	**B**

Clinical question 2.3.8

For patients receiving breast conserving surgery and postoperative radiotherapy for ductal carcinoma in situ, what constitutes an adequate surgical margin?

Evidence statement
Current guidelines (NICE, 2009), a meta-analysis (Dunne et al., 2009), and a 2013 American society of breast surgeons position statement addressed this question.

A meta-analysis of 20 studies (Dunne et al., 2009) identified that a negative margin was associated with the lowest risk of tumour recurrence after BCS. Negative margins are associated with a 64% reduction in ipsilateral recurrence. A radial margin of 2mm (excluding anterior and posterior margin) was associated with less risk of ipsilateral recurrence than a narrower margin but the effect of wider margins remains unclear. The authors defined a positive margin as tumour touching an inked surface (Dunne et al., 2009).

This meta-analysis consists of randomised and non-randomised trials (including observational, prospective and retrospective studies). Approximately 17% of patients were from randomised trials. There was heterogeneity in terms of patients and radiation dose. The length of follow-up was variable and in some studies there was a short timeframe for the outcomes that were being observed. Radiotherapy has changed considerably since these studies were undertaken.

Re-excision should be considered if the margin is less than 2mm after discussion of the risks and benefits with the patient (NICE, 2009) and after discussion at a multidisciplinary team meeting.

The American Society of Breast Surgeons (2013) issued a position statement on lumpectomy margins and proposed an algorithm based on best available data and recognition of the controversy surrounding surgical margin status which states that, if all margins are ink negative and ≤1mm, no further surgery is required.

Recommendation 2.3.8.1	**Grade**
For all patients treated with breast conserving surgery and radiotherapy for ductal carcinoma in situ, a minimum of 2mm radial margin of excision is recommended.	B

Clinical question 2.3.9

For patients receiving breast conserving surgery and postoperative radiotherapy for invasive breast cancer, what constitutes an adequate surgical margin?

Evidence statement
A meta-analysis (Houssami et al., 2014) addressed this question.

Ink on tumour cells, a universally accepted definition of a positive margin, is associated with an increased risk of local recurrence (LR), but the amount of normal breast tissue which constitutes the optimal negative margin remains controversial. (Houssami et al., 2014)

Houssami et al. (2014) confirm that positive and close margins (combined) significantly increase the odds of LR (OR 1.96; P<0.001) relative to negative margins. However, the distance used to declare negative margins across studies was either weakly associated or not associated with the odds of LR in their two models respectively, and once adjusted for study-specific median follow-up time, there was no statistical evidence that the distance used to define a negative margin significantly contributed to the risk of LR (Houssami et al., 2014).

Overall, data synthesis in 28,162 patients indicates that the risk of LR is not driven by the distance defining negative margins. The implications for practice are that the association between margins and the risk of LR is largely driven by margin status, and ensuring negative margins in BCS and RT contributes to reducing the risk of LR; however, the threshold distance for defining negative margins does not significantly contribute to the odds of LR. The adoption of wider margins for declaring negative margins in BCS and RT is unlikely to have a substantial additional benefit for long-term local control over a minimally defined negative margin (Houssami et al., 2014).

Recommendation 2.3.9.1	Grade
For patients receiving breast conserving surgery and postoperative radiotherapy for invasive breast cancer, the excision should have a clear margin; the tumour should not be touching ink.	B

Good practice point
If ductal carcinoma in situ is present in conjunction with invasive breast cancer, the decision regarding re-excision of margins should be decided at a multidisciplinary team meeting.

2.4 Medical oncology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.4.1

In patients with breast cancer:
   a) What is the evidence that adjuvant chemotherapy is effective?
   b) What is the optimal chemotherapy regimen?

Evidence statement
Current guidelines (SIGN, 2013), two meta-analysis (Coleman et al., 2013, Peto et al., 2012) and two UpToDate reviews (Burstein et al., 2014a, Burstein et al., 2014b) addressed this question.

Adjuvant chemotherapy
The decision to use adjuvant chemotherapy in breast cancer takes into account patient factors (e.g. age, comorbidities and menopausal status) and disease factors (tumour histology, size, grade, breast cancer subtype, immunohistochemistry [ER/PR/HER2], lymph node involvement) and 21 gene recurrence score (e.g. Oncotype DX®). The choice of chemotherapy (anthracycline containing regimes vs. non anthracyclines) must be balanced with potential benefits.

The Early Breast Cancer Trialists' Collaborative Group (Peto et al., 2012) meta-analysis of greater than 100,000 patients have shown that the use of adjuvant chemotherapy has led to a significant reduction in breast cancer recurrence and improvement in overall survival. This meta-analysis compared adjuvant chemotherapy using an anthracycline-based regimen or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no treatment and found that both regimens were associated with significant improvement in the risk of recurrence and a reduction in both breast cancer mortality and overall mortality at 10 years.

A Cochrane meta-analysis of 11,991 women with human epidermal growth factor receptor 2 (HER2) positive breast cancer showed improved disease free survival and overall survival with the addition of trastuzumab to standard chemotherapy (DFS HR 0.6, 95% CI 0.50 to 0.71, P<0.00001; OS HR 0.66, 95% CI 0.57-0.77, P<0.00001) (Moja et al., 2012). (SIGN, 2013)

There is currently no standard regimen for adjuvant chemotherapy. The following regimens should be considered:
- Non-anthracycline containing regimens
- Anthracyline containing regimens
- Taxane containing regimens
- Trastuzumab containing regimens.

In treating HER2 positive breast cancer, trastuzumab administered for 12 months in the adjuvant setting was associated with an improvement in overall survival (HR 0.67, 95% CI 0.57-0.80). (Burstein, 2014a)

A recent meta-analysis (Coleman et al., 2013) presented at the 2013 San Antonio Breast Cancer Symposium and randomised controlled trials of adjuvant bisphosphonates compared to placebo have shown a reduction in bone metastasis and an improvement in breast cancer mortality and all-cause mortality in post menopausal women. This is early data and a recommendation cannot be made at this time.

Optimal chemotherapy regimen
There is no single worldwide standard adjuvant chemotherapy regimen in the treatment of breast cancer, and the preferred regimens vary by prescribing clinician, institution, and/or geographic region.

Commonly used regimens include:
ACT (doxorubicin plus cyclophosphamide followed by weekly paclitaxel)
Dose Dense ACT (doxorubicin plus cyclophosphamide followed by weekly paclitaxel)
TAC (docetaxel, doxorubicin, and cyclophosphamide)
Oral CMF (oral cyclophosphamide plus methotrexate and fluorouracil)
IV CMF (IV cyclophosphamide plus methotrexate and fluorouracil)
FEC (fluorouracil, epirubicin, plus cyclophosphamide)
FEC-Taxane (Paclitaxel) (fluorouracil, epirubicin, plus cyclophosphamide followed by weekly paclitaxel)
FEC-Taxane (Docetaxel) (fluorouracil, epirubicin, plus cyclophosphamide followed by weekly docetaxel)
TC (docetaxel plus cyclophosphamide)

Commonly used regimens for HER2 positive breast cancer include:
ACTH (doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab)
TCH (Trastuzumab plus carboplatin followed by docetaxel)

The overall results of a meta-analysis (Bonilla et al., 2010) support the use of 'dose-dense' treatment as a standard of care for women with human epidermal growth factor receptor 2 (HER2) negative breast cancer; more dramatic differences are seen particularly when administered to women with ER negative disease. (Burstein, 2014b)

Dose-dense therapy is not associated with an increase in treatment-related adverse events (Bonilla et al., 2010). In one of these trials (Citron, 2008), patients treated with dose-dense treatment experienced fewer episodes of fever and neutropenia compared with those treated every three weeks because of the use of growth factors. When the shortened cumulative time of treatment (16 versus 24 weeks for dose-dense versus every three weeks) is also considered, the data favour dose-dense delivery of adjuvant chemotherapy. (Burstein, 2014b)

Risk factors associated with the development of chemotherapy-related cardiotoxicity include exposure to known cardiotoxic drugs such as anthracyclines (cumulative doses of doxorubicin greater than 360mg/m^2 or epirubicin greater than 900mg/m^2) or trastuzumab. Older age, prior history of cardiac disease and chest wall radiation therapy are also risk factors for treatment-related cardiotoxicity. The short-term incidence of anthracycline-associated cardiomyopathy is rare (about 1%). Prior to anthracycline or trastuzumab treatments, patients should have a baseline assessment of cardiac function. (Burstein et al., 2014b)

Recommendation 2.4.1.1	Grade
Adjuvant chemotherapy should be considered for all patients with breast cancer whose disease is at moderate/high risk of recurrence.	A

Recommendation 2.4.1.2	Grade
Adjuvant trastuzumab should be considered in all patients with HER2 positive breast cancer who receive adjuvant chemotherapy.	A

Recommendation 2.4.1.3	Grade
The standard duration of treatment with adjuvant trastuzumab is one year.	A

Recommendation 2.4.1.4	Grade
Adjuvant trastuzumab should preferably be given concurrently with taxane based regimens. It should **not** be given concurrently with anthracyclines.	A

Good practice point
Cardiac function should be monitored in patients being treated with anthracyclines or trastuzumab.

Clinical question 2.4.2

In premenopausal women with breast cancer that is oestrogen receptor positive (ER+) and/or progesterone receptor positive (PR+):
   a) What is the evidence that adjuvant hormone therapy is effective?
   b) What is the optimum endocrine agent?
   c) What is the optimum strategy of endocrine therapy?
   d) What is the optimum duration of therapy?

Evidence statement
Current guidelines (NCCN, 2014, Burstein et al., 2014c), a meta-analysis (Petrelli et al., 2013) and an RCT (Davies et al., 2013) addressed this question.

Premenopausal women with invasive breast cancer that is hormone receptor positive should be considered for adjuvant endocrine therapy regardless of lymph node status, or whether adjuvant chemotherapy is to be administered (EBCTCG, 1998). (NCCN, 2014).

ASCO (Burstein et al., 2014c) recommend that women diagnosed with hormone receptor positive breast cancer who are pre- or peri-menopausal should be offered adjuvant endocrine therapy with:
  • Tamoxifen for an initial duration of five years.
  • After five years, women should receive additional therapy based on menopausal status.

If women are pre- or peri-menopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years.

Women who have received five years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment.
  • If women are pre- or peri-menopausal, or menopausal status cannot be ascertained, they should be offered five additional years of tamoxifen, for a total duration of 10 years of adjuvant endocrine therapy.

Tamoxifen
The most firmly established adjuvant endocrine therapy is tamoxifen for premenopausal women (EBCTCG, 2005). In women with ER positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31%, irrespective of the use of chemotherapy, patient age, menopausal status or ALN status (EBCTCG, 2005). (NCCN, 2014).

For women with ER positive disease, continuing tamoxifen to 10 years rather than stopping at five years produces a further reduction in recurrence and mortality, particularly after year 10. These results, taken together with results from previous trials of five years of tamoxifen treatment versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis (Davies et al., 2013).

Petrelli et al. (2013) conducted a meta-analysis of eight trials including the ATLAS and aTTom trials (Davies et al., 2013, Gray et al., 2013). In ER positive breast cancers, extended endocrine therapy beyond five years of tamoxifen significantly improved overall survival (OR, 0.89; 95% CI 0.80-0.99; *P*=0.03), breast cancer specific survival (OR, 0.78; 95% CI 0.69-0.9; *P*=0.003), and recurrence free survival (OR, 0.72; 95% CI 0.56-0.92; *P*=0.01) compared with five years of hormonal therapy alone. Locoregional and distant relapses were reduced by 36% and 13%, respectively.

In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen (Albain et al., 2009). (NCCN, 2014).

In women with ER negative disease, use of tamoxifen had little or no effect on breast cancer recurrence or mortality (Davies et al., 2011). (SIGN, 2013)

Given the limited and conflicting evidence at this time (Higgins and Stearns, 2011), CYP2D6 testing is not recommended as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO guidelines (Visvanathan et al., 2009). (NCCN, 2014)

Reporting on 2,430 women treated with tamoxifen and a single selective serotonin reuptake inhibitor (SSRI), Kelly et al. (2010) found that paroxetine use during tamoxifen treatment is associated with an increased risk of death from breast cancer. This supports the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer.

When prescribing an SSRI, it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists. (NCCN, 2014)

Ovarian ablation/suppression
The role of adjuvant ovarian ablation or suppression in premenopausal women with hormone receptor positive breast cancer is incompletely defined (Pritchard, 2009, Puhalla et al., 2009, Tan and Wolff, 2008). (NCCN, 2014)

The role of adjuvant ovarian ablation or suppression may be clarified with the publication of the SOFT, TEXT and PERCHE trials.

Aromatase inhibitors (AI)
Premenopausal women should not be given adjuvant initial therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued oestrogen production from the ovaries without menses. Serial assessment of circulating luteinising hormone (LH), follicle stimulating hormone (FSH), and oesteradiol to assure a true postmenopausal status should be undertaken if this subset of women is to be considered for therapy with an aromatase inhibitor (Smith et al., 2006, Yu et al., 2010). (NCCN, 2014)

Recommendation 2.4.2.1	**Grade**
Premenopausal women with hormone receptor positive breast cancer should be treated with tamoxifen.	A

Recommendation 2.4.2.2	**Grade**
The standard duration of treatment with tamoxifen for premenopausal women with hormone receptor positive breast cancer is at least five years, but there is evidence to support up to 10 years of use.	A

Recommendation 2.4.2.3	**Grade**
Currently, the routine use of adjuvant ovarian ablation/suppression is **not** considered standard practice.	B

Good practice point
Aromatase inhibitors are contraindicated in premenopausal women.

Clinical question 2.4.3

In postmenopausal patients with breast cancer that is ER (+) and/or PR (+):
   a) What is the evidence that adjuvant hormone therapy is effective?
   b) What is the optimum endocrine agent?
   c) What is the optimum strategy of endocrine therapy?
   d) What is the optimum duration of therapy?

Evidence statement

Current guidelines (NCCN, 2014, SIGN, 2013, Burstein et al., 2014c) and a meta-analysis (Dowsett et al., 2010) addressed this question.

Postmenopausal patients with invasive breast cancer that is ER or PR positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered (EBCTCG, 1998). (NCCN, 2014)

In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen (Albain et al., 2009). (NCCN, 2014)

In women with ER negative disease, use of adjuvant hormonal therapy had little or no effect on breast cancer recurrence or mortality (Davies et al., 2011). (SIGN, 2013)

Aromatase inhibitors (AI)

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilised the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following two to three years of tamoxifen, or as extended therapy following four and a half to six years of tamoxifen. (NCCN, 2014)

Dowsett et al. (2010) conducted a meta-analysis of randomised trials of aromatase inhibitors compared with tamoxifen, either as initial monotherapy or after two to three years of tamoxifen. The authors documented lower recurrence rates with the aromatase inhibitor-containing regimen, with no clear impact on overall survival.

A meta-analysis of trials conducted in postmenopausal women concluded that an aromatase inhibitor is associated with higher clinical response rate, (RR 1.29, 95% CI 1.14 to 1.47) and radiological (ultrasound) response rate, (RR 1.29, 95% CI 1.10 to 1.51) when compared to tamoxifen. Aromatase inhibitors are also associated with a higher rate of breast conserving surgery than tamoxifen (RR 1.36, 95% CI 1.16 to 1.59) (Seo et al., 2009). (SIGN, 2013)

There is insufficient evidence to recommend one aromatase inhibitor over another, or for duration of therapy. (SIGN, 2013)

The optimal duration of aromatase inhibitors treatment is not known. The long-term (greater than five years) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third-generation aromatase inhibitor in postmenopausal women with hormone receptor positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumour recurrence (IBTR), contralateral breast cancer, and distant metastatic disease, when used as initial adjuvant therapy, sequential therapy, or extended therapy. (NCCN, 2014)

There is no compelling evidence that there is meaningful efficacy or toxicity differences between the aromatase inhibitors, anastrozole, letrozole, and exemestrane. All three have shown similar anti-tumour efficacy and toxicity profiles in randomised studies in the adjuvant settings. (NCCN, 2014)

Aromatase inhibitors are commonly associated with musculoskeletal symptoms, osteoporosis, menopausal symptoms, hyper-cholesterolaemia, and hypertension. (NCCN, 2014)

ASCO (Burstein et al., 2014c) recommend that women diagnosed with hormone receptor positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following options:
- Tamoxifen for a duration of 10 years.
- An AI for a duration of five years. There are insufficient data currently to recommend an AI for a duration of greater than five years.
- Tamoxifen for an initial duration of five years, then switching to an AI for up to five years, for a total duration of up to 10 years of adjuvant endocrine therapy.
- Tamoxifen for a duration of two to three years and switching to an AI for up to five years, for a total duration of up to seven to eight years of adjuvant endocrine therapy.

Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered an alternative type of adjuvant endocrine therapy. (Burstein et al., 2014c)

If women have received an AI but discontinued treatment at less than five years, they may be offered tamoxifen for a total of five years. (Burstein et al., 2014c)

If women have received tamoxifen for two to three years, they should be offered switching to an AI for up to five years, for a total duration of up to seven to eight years of adjuvant endocrine therapy. (Burstein et al., 2014c)

Women who have received five years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment. (Burstein et al., 2014c)

If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or switching to up to five years AI, for a total duration of up to 10 years of adjuvant endocrine therapy. (Burstein et al., 2014c)

Recommendation 2.4.3.1	**Grade**
Postmenopausal women with hormone receptor positive breast cancer should be treated with hormonal therapy for at least five years. The options include:	
Tamoxifen for five years followed by five years of an aromatase inhibitor.	**A**
An aromatase inhibitor as initial adjuvant therapy for five years.	**A**
Tamoxifen for two to three years followed by an aromatase inhibitor to complete five years of adjuvant endocrine therapy or tamoxifen for two to three years followed by five years of adjuvant endocrine therapy.	**A**

Recommendation 2.4.3.2	**Grade**
In postmenopausal women, the use of tamoxifen alone for five years can be considered for those who decline, have a contraindication to, or are intolerant of aromatase inhibitors.	**A**

Clinical question 2.4.4

For women with breast cancer, what subgroups of patients would benefit from neoadjuvant systemic therapy and what is the optimum regimen?

Evidence statement
Current guidelines (NCCN, 2014, SIGN, 2013), an NAC consensus statement (Kaufmann et al., 2012) and an RCT (Smith et al., 2005) addressed this question.

Neoadjuvant systemic therapy
Generally, any patient who is a candidate for adjuvant systemic therapy can be considered for neoadjuvant systemic therapy (Kaufmann et al., 2012).

Neoadjuvant chemotherapy
Neoadjuvant chemotherapy can be considered as part of a multimodal treatment approach for patients with stage IIa, IIb, and III breast cancer (Van der Hage et al., 2007). (SIGN, 2013)

Several chemotherapy regimens have been studied in the neoadjuvant setting. Regimens recommended in the adjuvant setting are appropriate to consider in the preoperative chemotherapy setting. The benefits of 'tailoring' preoperative chemotherapy (i.e., switching following limited response) or using preoperative chemotherapy to evaluate disease responsiveness have not been well studied (Hudis and Modi, 2007). (NCCN, 2014)

Neoadjuvant chemotherapy, compared with adjuvant chemotherapy, is associated with higher rates of breast conservation, with equivalent rates of overall survival and locoregional recurrence, providing surgery is part of the treatment pathway. A Cochrane review concluded that overall survival is equivalent for preoperative chemotherapy compared to adjuvant chemotherapy (HR 0.98, 95% CI 0.87 to 1.09, P=0.67) (Van der Hage et al., 2007). Increased breast conservation rates were observed in patients who received neoadjuvant chemotherapy (RR 0.82, 95% CI, 0.76 to 0.89; P<0.00001). No significant increase in locoregional recurrence rates was observed (HR 1.12, 95% CI 0.92 to 1.37, P=0.25) with neoadjuvant chemotherapy compared to adjuvant chemotherapy. Patients who achieve pathological complete response (pCR) show improved survival, compared with patients with residual disease (HR 0.48, 95% CI 0.33 to 0.69, P=0.0001) (Van der Hage et al., 2007). (SIGN, 2013)

The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy (Fisher et al., 1998). However, preoperative chemotherapy has no demonstrated disease-specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumours. NSABP B-27 is a three-arm, randomised, phase III trial of women with invasive breast cancer treated with preoperative chemotherapy with AC (doxorubicin/cyclophosphamide) for four cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for four cycles followed by local therapy, or AC followed by local therapy followed by four cycles of postoperative docetaxel. Results from this study, which involved 2,411 women, documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with four cycles of AC followed by four cycles of docetaxel versus four cycles of preoperative AC. Disease-free survival (DFS) and overall survival have not been shown to be superior with the addition of docetaxel treatment in the B-27 trial (Bear et al., 2006). A disease-free survival advantage was observed (HR, 0.71; 95% CI, 0.55-0.91; P=0.007) favouring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC. (NCCN, 2014)

There are no significant differences between adjuvant and neoadjuvant chemotherapy for postoperative complications or in recognised chemo related toxicities. Events of leucopoenia and infections (RR 0.69, 95% CI 0.56 to 0.84, P=0.0003) were significantly lower with neoadjuvant chemotherapy (Van der Hage et al., 2007). (SIGN, 2013)

HER2 positive

Trastuzumab should be incorporated in the treatment plan for women with HER2 positive breast cancer.

The addition of neoadjuvant trastuzumab to chemotherapy leads to improved disease free survival (HR 0.60, 95% CI 0.50 to 0.71, P<0.00001) and overall survival (HR 0.66, 95% CI 0.57 to 0.77, P<0.00001) (Moja et al., 2012). A meta-analysis has shown that use of neoadjuvant trastuzumab also improves pCR rates (RR 1.85, 95% CI 1.39 to 2.46, P<0.001), although no difference was seen in the rate of breast conservation surgery (OR 0.98, 95% CI 0.80 to1.19, *P*=0.82) (Valachis et al., 2011). A higher rate of breast conservation surgery has been reported in one trial of patients with locally advanced breast cancer receiving neoadjuvant trastuzumab in addition to chemotherapy (23% versus 13%) (Semiglazov et al., 2011). (SIGN, 2013)

In women with HER2 positive tumours treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by chemotherapy with FEC (fluorouracil/ epirubicin/ cyclophosphamide) was associated with an increase in the pathologic complete response rate from 26% to 65.2% (*P*=0.016) (Buzdar et al., 2005). (NCCN, 2014).

Toxicity

A combined analysis of neoadjuvant and adjuvant trials reported a significantly increased risk of congestive heart failure (RR 5.11, 90% CI 3.00 to 8.72, P < 0.00001) and left ventricular ejection fraction (LVEF) decline (RR 1.83, 90% CI 1.36 to 2.47, *P*=0.0008) when trastuzumab is added to chemotherapy (Moja et al., 2012). There was no difference in haematological toxicities. (SIGN, 2013)

A Cochrane meta-analysis of 11,991 women with HER2 positive breast cancer showed improved disease free survival and overall survival with the addition of trastuzumab to standard chemotherapy (DFS HR 0.6, 95% CI 0.50 to 0.71, P<0.00001; OS HR 0.66, 95% CI 0.57-0.77, P<0.00001) (Moja et al., 2012). (SIGN, 2013)

Inflammatory breast cancer (IBC)

Trastuzumab should be incorporated into the treatment plan of women with HER2 positive IBC.

The treatment of patients with IBC should involve a combined modality approach (Dawood and Cristofanilli, 2007) comprising preoperative chemotherapy followed by surgery (mastectomy) and radiotherapy. (NCCN, 2014)

There are no large randomised trials evaluating the optimal systemic treatment of IBC, since it is a rare disease. (NCCN, 2014)

The benefit of preoperative systemic therapy followed by mastectomy over preoperative chemotherapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach (Fleming et al., 1997). Results from a large retrospective study of patients with IBC performed over a 20-year period at The University of Texas M.D. Anderson Cancer Centre demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (i.e., radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28% (Ueno et al., 1997). (NCCN, 2014)

A retrospective study demonstrated that addition of a taxane to an anthracycline-based regimen improved progression free survival and overall survival in patients with ER negative inflammatory breast cancer (Cristofanilli et al., 2004). A systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pathologic complete response (Kim et al., 2006). A study of patients with inflammatory breast cancer (IBC),

with cytologically confirmed axillary lymph node (ALN) metastases, treated with anthracycline-based chemotherapy with or without a taxane indicated that more patients receiving the anthracycline-taxane combination achieved a pathologic complete response compared with those who received only anthracycline-based therapy. In addition, patients who had a pathologic complete response in the ALNs had superior overall and disease-free survival compared with those with residual axillary disease (Hennessey et al., 2006). (NCCN, 2014)

Preoperative systemic therapy with an anthracycline-based regimen with or without taxanes is recommended for the initial treatment of patients with IBC. (NCCN, 2014)

For these patients, chemotherapy should be provided before surgery rather than split into preoperative and postoperative stages (Kaufmann et al., 2012).

Neoadjuvant endocrine therapy
Neoadjuvant endocrine therapy is an option for patients with ER positive breast cancer considered unsuitable for neoadjuvant chemotherapy or primary surgery.

The IMPACT trial tested the hypothesis that the clinical and/or biologic effects of neoadjuvant tamoxifen compared with anastrozole alone and a combination of tamoxifen and anastrozole before surgery in postmenopausal women with ER positive, invasive, non-metastatic breast cancer might predict for outcome in the ATAC adjuvant therapy trial. The authors concluded that neoadjuvant anastrozole is as effective and well tolerated as tamoxifen in ER positive operable breast cancer in postmenopausal women, but the hypothesis that clinical outcome might predict for long term outcome in adjuvant therapy was not fulfilled (Smith et al., 2005).

A meta-analysis of trials conducted in postmenopausal women concluded that an aromatase inhibitor is associated with higher clinical response rate, (RR 1.29, 95% CI 1.14 to 1.47) and radiological (ultrasound) response rate, (RR 1.29, 95% CI 1.10 to 1.51) when compared to tamoxifen. Aromatase inhibitors are also associated with a higher rate of breast conserving surgery than tamoxifen (RR 1.36, 95% CI 1.16 to 1.59) (Seo et al., 2009). (SIGN, 2013)

There is insufficient evidence to recommend one aromatase inhibitor over another, or for duration of therapy. (SIGN, 2013)

Several randomised trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with ER positive breast cancer. These studies have generally compared the rates of objective response and rates of BCS among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provides superior rates of BCS and usually objective response when compared to tamoxifen (Ellis et al., 2001, Smith et al, 2005). Based on these trials, if preoperative endocrine therapy is to be utilised, an aromatase inhibitor is preferred in the treatment of postmenopausal women with hormone receptor positive disease. (NCCN, 2014)

The optimal duration of neoadjuvant endocrine therapy has not been elucidated. In practice, at least four to six months represents an option for ER positive or HER2 negative patients.

Recommendation 2.4.4.1	**Grade**
Any patient who is a candidate for adjuvant systemic therapy can be considered for neoadjuvant systemic therapy.	A

Recommendation 2.4.4.2	**Grade**
Neoadjuvant chemotherapy can be considered as part of a multimodal treatment approach for patients with stage IIa, IIb, and III breast cancer.	A

Recommendation 2.4.4.3	Grade
For patients with locally advanced or inflammatory breast cancer, preoperative chemotherapy is the preferred option.	A

Recommendation 2.4.4.4	Grade
Patients with HER2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab.	A

Recommendation 2.4.4.5	Grade
Neoadjuvant endocrine therapy is an option for patients with ER positive breast cancer considered unsuitable for neoadjuvant chemotherapy or primary surgery.	C

Good practice point
Trastuzumab should be used with caution in patients with significant cardiac comorbidity.

Good practice point
Cardiac function should be monitored in patients being treated with anthracyclines or trastuzumab.

2.5   Radiation oncology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.5.1

In patients who have undergone a mastectomy for breast cancer, what is the evidence that radiotherapy to the chest wall improves outcome?

Evidence statement

Current guidelines (SIGN, 2013), a meta-analysis (Clarke et al., 2005) and two RCTs (Ragaz et al., 2005, Overgaard et al., 2007) addressed this question.

A meta-analysis and randomised trials have shown that RT to the chest wall and regional lymph nodes reduced recurrence and mortality in women with node positive breast cancer (Ragaz et al., 2005, Overgaard et al., 2007, Clarke et al., 2005).

The 2005 EBCTCG meta-analysis (Clarke et al., 2005) included 8,500 patients treated with mastectomy and axillary clearance with or without RT to the chest wall and regional lymph nodes. For women with node positive breast cancer, five year local recurrence risk was reduced from 23% to 6% and 15-year breast cancer mortality risk was reduced from 60.1% to 54.7% (SE 1.3, 2P=0.0002; overall mortality reduction 4.4%, SE 1.2, 2P=0.0009) with the addition of RT.

All patients with node-positive disease benefited from postmastectomy radiotherapy (PMRT), however the benefit was greater with those patients with ≥4 positive nodes compared with those with one to three positive nodes. In these two groups, the five year risk of local recurrence with the addition of PMRT was reduced from 26% to 12% and 16% to 4% respectively. There were also significant reductions in local recurrence in patients with tumours >50mm (T3 tumours) or those invading local structures (T4). Here the local recurrence rate was reduced from 36% to 8% (Clarke et al., 2005). (SIGN, 2013)

Radiotherapy produced similar proportional reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of RT versus not (recent or older; with or without systemic therapy). Large absolute reductions in local recurrence risk were seen only if the control risk was large. For example, women with node negative disease had a five year local recurrence risk of 6% in the absence of RT. This was reduced to 2% with the addition of RT, an absolute benefit of only 4%. Radiotherapy had no impact on overall survival in women with node negative disease. (Clarke et al., 2005)

Long term data from individual trials have confirmed these benefits. In a 20 year follow-up of the British Colombia RCT of locoregional RT in patients with high-risk breast cancer receiving adjuvant chemotherapy, Ragaz et al. (2005) concluded that for patients with high-risk breast cancer treated with modified radical mastectomy, treatment with RT (schedule of 16 fractions) and adjuvant chemotherapy leads to better survival outcomes than chemotherapy alone, and it is well tolerated, with acceptable long-term toxicity. (Ragaz et al., 2005)

A subgroup analysis of the Danish trials 82 b and c was conducted comparing the recurrence and survival after RT in women with 1–3 and ≥4 nodes positive. Although women with 1–3 positive nodes had lower absolute risks, RT produced significant reductions in recurrence and overall survival at 15 years in both groups (overall survival 57% versus 48% with 1–3 nodes, 21% versus 12% with ≥4 positive nodes, P=0.03 in both cases). (Overgaard et al., 2007)

The ongoing SUPREMO (BIG 2-04) trial is further investigating this issue, randomising women with 1–3 positive nodes after mastectomy and axillary clearance to receive RT or not.

Recommendation 2.5.1.1	Grade
Postmastectomy radiotherapy should be recommended in patients with lymph node positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and/or T3/T4 primary tumour).	A

Recommendation 2.5.1.2	Grade
Postmastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1-3 nodes) and individual patients should be discussed at multidisciplinary team meeting.	B

Clinical question 2.5.2

In patients with ductal carcinoma in situ who have undergone breast conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome?

Evidence statement

A meta-analysis (Correa et al., 2010), a systematic review (Goodwin et al., 2009) and five RCTs (Bijker et al., 2006, Emdin et al., 2006, Fisher et al., 1998, Holmberg et al., 2008, Houghton et al., 2003) addressed this question.

Four of these trials (Emdin et al., 2006, Fisher et al., 1998, Holmberg et al., 2008, Houghton et al., 2003) have been analysed both in a systematic review (Goodwin et al., 2009) and in a meta-analysis (Correa et al., 2010). Both analyses concluded that the addition of RT following BCS reduced the risk of recurrence in all patients with DCIS, but had no impact on either breast cancer mortality or all-cause mortality.

The EBCTCG analysed individual patient data for 3,729 women and found that RT reduced the absolute 10 year risk of an ipsilateral breast event (either recurrent DCIS or invasive cancer) by 15.2% (SE 1.6%, 12.9% vs. 28%, P<0.0001). Radiotherapy was effective regardless of age, focality, grade, comedo-necrosis or tumour size, among other factors. Women with negative margins and small low-grade tumours have an absolute reduction in 10-year risk of ipsilateral breast events of 18% (SE 5.5, 12.1% vs. 30.1%, *P*=0.002). (Correa et al., 2010)

Based on this data it is not yet possible to confidently identify a group of women with DCIS in whom RT can be routinely omitted. However, while RT reduces the risk of recurrence, it has no impact on disease specific or overall survival. The individual risk/benefit of adjuvant RT should be discussed with all patients.

Recommendation 2.5.2.1	**Grade**
All patients with ductal carcinoma in situ having breast conserving surgery should be considered for adjuvant radiotherapy.	A

Clinical question 2.5.3

In patients with breast cancer who have undergone breast conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome and what is the optimal dose regimen?

Evidence statement
Current guidelines (SIGN, 2013), a meta-analysis (Darby et al., 2011), a Cochrane review (James et al., 2009) and two RCTs (Whelan et al., 2010, Haviland et al., 2010) addressed this question.

Adjuvant radiotherapy improves outcome
A meta-analysis of individual patient data from 10,801 women in 17 RCTs has shown significant reduction in breast cancer recurrence with RT given after BCS (Darby et al., 2011). The rate of recurrence is approximately halved at 10 years from 35% to 19.3% (absolute reduction 15.7%, 95% CI 13.7 to 17.7, 2P<0.00001). Radiotherapy also reduced 15 year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 95% CI 1.6 to 6.0, 2P=0.00005). The majority of women in this meta-analysis had node negative disease. For these women the absolute recurrence reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use and extent of surgery. Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10.

Optimal dose regimen
Two randomised controlled trials (Haviland et al., 2013, Whelan et al., 2010) and a Cochrane review (James et al., 2010) demonstrate equivalent recurrence rates in women with early breast cancer treated with BCS.

The Ontario Clinical Oncology Group compared a course of 50Gy in 25 fractions over five weeks versus 42.5Gy in 16 fractions over three weeks. Whelan et al. (2010) concluded that ten years after treatment, accelerated, hypofractionated whole breast irradiation was not inferior to standard radiation treatment in women who had undergone BCS for invasive breast cancer with clear surgical margins and negative axillary nodes. The risk of local recurrence at 10 years was 6.7% after standard radiation versus 6.2% after hypofractionated RT. Cosmetic outcome was also equivalent, with a good or excellent cosmetic outcome reported in 71.3% of the control group versus 69.8% of the hypofractionated group. (Whelan et al., 2010)

The START B trial in the UK compared a regimen of 50Gy in 25 fractions over five weeks with 40Gy in 15 fractions over three weeks. With a median follow-up of 9.9 years, local recurrence rates were not significantly different (5.5% in standard arm versus 4.3% in 40Gy arm). Breast shrinkage, telangiectasia and breast oedema were significantly less common in the 40Gy arm. There was no increase in symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease or brachial plexopathy in the 40Gy arm. Additional follow-up will be required to assess all potential late effects. (Haviland et al., 2010)

James et al. (2010), in a Cochrane review include four trials reporting on 7,095 women enrolled in trials comparing standard fractionation with doses per fraction of >2Gy. There was no difference in local recurrence risk with RR 0.97 (95% CI 0.76 to 1.22, P=0.78) or survival at five years (RR 0.89, 95% CI 0.77 to 1.04, P=0.16). Breast appearance was equivalent and acute skin toxicity was decreased with unconventional fractionation, RR 0.21 (95% CI 0.07-0.64, P=0.007). (SIGN, 2013)

Trials of even shorter fractionation schedules (FAST, FAST FORWARD) are ongoing. (SIGN, 2013)

Hypofractionated schedules such as 40/15 or 42.5/16 can be considered. These have equivalent rates for local recurrence and similar cosmetic outcomes to longer fractionation schedules (e.g. 50/25).

Recommendation 2.5.3.1	Grade
Radiotherapy is recommended for all patients undergoing breast conserving surgery for early breast cancer.	A

Recommendation 2.5.3.2	Grade
Hypofractionation schedules are recommended for patients with early breast cancer.	A

Clinical question 2.5.4

In otherwise healthy patients with breast cancer who have undergone breast conserving surgery, are there any sub populations in terms of age, tumour size and nodal involvement where radiotherapy is not necessary?

Evidence statement
Three RCTs (Hughes et al., 2013, Fisher et al., 2002, 1996, Fyles et al., 2004) addressed this question.

The NSABP B-21 trial recruited women after lumpectomy with tumours ≤1cm in size. This trial was designed for the specific purpose of comparing the value of tamoxifen, RT or both in reducing the incidence of ipsilateral breast tumour recurrence (IBTR) or contralateral breast cancer (CBC) in this low-risk group. Cumulative incidence or IBTR at eight years was 16.5% with tamoxifen, 9.3% with adjuvant RT and 2.8% with both treatments. Survival was 93%–94% in the three groups. The use of tamoxifen resulted in a significant decrease in the risk of CBC when compared with RT alone. The authors conclude that tumours <1cm recur with enough frequency after lumpectomy to justify considering RT, regardless of tumour ER status. (Fisher et al., 2002)

The CALGB trial recruited 636 women at least 70 years of age who had a clinical stage T1N0M0, oestrogen receptor positive breast carcinoma treated by lumpectomy. Participants were randomised to receive tamoxifen and RT or tamoxifen alone. Median follow-up is now 12.6 years. At 10 years, freedom from locoregional recurrence was significantly improved in women receiving RT and tamoxifen compared to tamoxifen alone (98% versus 90%, 95% CI, 85% to 93%). There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer–specific survival, or overall survival between the two groups. Ten-year OS was 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%) in the tamoxifen and RT and tamoxifen groups, respectively. Of the 636 women in this study, only 21 (3%) have died as a result of breast cancer, whereas 313 (49%) have died as a result of other causes (only 6% of deaths attributed to breast cancer). The authors conclude that, depending on the value placed on local recurrence, tamoxifen alone remains a reasonable option for women age ≥70 years with ER positive early-stage breast cancer. (Hughes et al., 2013)

Fyles et al. (2004) in a Canadian study recruited women at least 50 years of age with node negative breast cancer <5cm in size who had undergone lumpectomy. Participants were randomised to receive RT plus tamoxifen or tamoxifen alone. At five years, only 0.6% of the women in the group given tamoxifen plus irradiation had a local relapse, whereas 7.7% of the women in the group given tamoxifen alone had had a recurrence in the breast. There was no difference in overall survival between groups, although the trial was underpowered to detect small differences in survival. (Fyles et al., 2004)

Adjuvant RT reduces risk of recurrence in all subgroups; however in some cases the benefit may be small. There may be very low-risk patients in whom RT can safely be avoided and tamoxifen therapy alone considered. Age, tumour size, lymphovascular invasion status, hormone-receptor status, tumour grade, comorbid conditions and performance status need to be considered in individual cases.

Recommendation 2.5.4.1	**Grade**
In patients who have undergone breast conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations.	A

> **Good practice point**
> Although there is a benefit across all subpopulations, there may be a justification for avoiding adjuvant radiotherapy in certain patients with low-risk breast cancer, following discussion at a multidisciplinary team meeting.

Clinical question 2.5.5

In patients with breast cancer who have undergone breast conserving surgery, what is the evidence that a radiotherapy boost improves outcome?

Evidence statement

Current guidelines (SIGN, 2013) and two RCTs (Bartelink et al., 2007, Romestaing et al., 1997) addressed this question.

Bartelink et al. (2007) recruited 5,318 women undergoing BCS followed by adjuvant RT (50Gy in 25 fractions over five weeks). Participants were randomised to receive either no extra radiation or a boost dose of 16Gy in eight fractions to the original tumour bed. Addition of a boost significantly reduced risk of local recurrence (10.2% versus 6.2%, $P<0.0001$). The hazard ratio for local recurrence was consistent across all age groups at 0.59. The absolute risk reduction was greatest in younger women (i.e. 23.9% to 13.5% in women ≤40 years of age). Late radiation side effects were increased in the boost group, with severe fibrosis increasing from 1.6% to 4.4% ($P<0.0001$). Survival was equivalent in both arms.

The relative benefit in reducing risk exists in all age groups. Absolute benefit is highest in patients aged <50 years, with a reduction in local recurrence from 19.4% to 11.4% ($P=0.0046$; HR 0.51) (Jones et al., 2009). For all patients with high grade invasive ductal carcinoma, boost reduced recurrence from 18.9% to 8.6% ($P=0.01$; HR 0.42) (Jones et al., 2009). (SIGN, 2013)

Romestaing et al. (1997) recruited 1,024 women in France with breast carcinoma ≤3cm in size treated with local excision and whole breast RT (50Gy in 25 fractions over five weeks). Participants were randomised to receive either no additional radiation or a boost of 10Gy in five fractions to the tumour bed. Local recurrence was significantly reduced by the addition of the boost (3.6% versus 4.5%, $P=0.04$). The boost group had a higher rate of telangiectasia but no difference in self-reported cosmesis outcomes. However, the event rate in this trial is low and further follow-up is necessary to confirm these findings.

Vrieling et al. (1999) demonstrated that the higher radiation dose (boost) was associated with a limited but statistically significant worsening of the cosmetic result. However, the boost dose was not the sole factor that affected the cosmetic outcome negatively: the location of the primary tumour in the lower quadrants of the breast, the volume of the excision, breast infection and/or haematoma, and clinical T2 stage were all independent predictors of worse cosmetic results, in addition to the boost treatment (Bartelink et al., 2007).

A boost should be considered in women <50 years of age receiving whole breast RT after lumpectomy. For the patient group >50 years of age, a boost should be considered in the presence of other risk factors (e.g. high grade). The risk for increase in long term effects with this increased dose should be taken into account, and patients should be counselled, allowing them to judge the balance of benefits and harms in context.

Recommendation 2.5.5.1	Grade
In patients who have breast conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis.	A

Recommendation 2.5.5.2	Grade
Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high grade invasive cancers).	A

Clinical question 2.5.6

In patients who have undergone surgery for breast cancer, what evidence is there that time from final surgery to starting adjuvant radiotherapy influences outcome?

Evidence statement

There were no randomised trials identified comparing different time intervals between surgery and commencement of RT. Current guidelines (Cancer Care Ontario, 2011), two systematic reviews (Chen et al., 2008, Huang et al., 2003) and three retrospective studies (Livi et al., 2009, Olivotto et al., 2009, Hershmann et al., 2006) addressed this question. However, none of these produced strong evidence to support the recommendation.

A systematic review by Chen et al. (2008) identified 44 relevant studies of which 24 were for breast cancer. A meta-analysis of 11 high quality studies of local control in breast cancer demonstrated a significant increase in the risk of local failure with increasing waiting time ($RR_{local recurrence/month}$=1.11, 95% CI: 1.04 -1.19). There was little evidence of any association between waiting time and risk of distant metastasis or survival. (Chen et al., 2008)

In a second systematic review, Huang et al. (2003) showed that the five year local recurrence rate was significantly higher in patients commencing adjuvant RT more than eight weeks after surgery when compared with those treated within eight weeks of surgery (odds ratio [OR]=1.62, 95% CI: 1.21 to 2.16). Both authors conclude that delays in starting adjuvant RT should be as short as reasonably achievable.

In a retrospective Canadian study (Olivotto et al., 2009), women commencing RT more than 20 weeks after BCS had inferior distant recurrence free survival and breast cancer specific survival when compared to women commencing adjuvant RT within four to eight weeks of surgery. Outcomes were statistically similar for surgery-to-RT intervals up to 20 weeks, but there were inferior for intervals beyond 20 weeks.

Multivariate analysis of retrospective data has demonstrated that local recurrence is mainly related to prognostic factors such as age at presentation, surgical margin status and the use of a radiotherapy boost, rather than the timing of RT (Livi et al., 2009). For women treated with adjuvant RT alone (n=1,935) or with adjuvant RT and hormonal therapy (n=1,684), timing of RT had no impact on local recurrence rates. Only in the group of patients treated with adjuvant RT and chemotherapy (n=672) did multivariate analysis show RT timing as an independent prognostic factor (hazard ratio, 1.59; 95% confidence interval, 1.01–2.52; *P*=0.045). Analysing this group of patients, the authors found that most patients included had worse prognostic factors and had received chemotherapy consisting of cyclophosphamide, methotrexate, and 5-fluorouracil before undergoing RT. (Livi et al., 2009)

Hershman et al. (2006) conducted a retrospective study using Surveillance, Epidemiology, and End Results (SEER) data for women over 65 years of age not receiving chemotherapy. Early initiation of RT was not associated with survival. Although delays of more than 3 months were uncommon, they were associated with poor survival. It was not possible to say whether this association is causal or due to confounding factors, such as poor health behaviours and the authors suggest initiating RT in a timely fashion until further data becomes available.

Data from the four randomised trials comparing radiation versus no radiation following BCS (Fisher et al., 1995, Liljegren et al., 1994, Clark et al., 1992, Veronesi et al., 1993), six randomised trials comparing lumpectomy plus radiation versus mastectomy, two large cohort studies, an ongoing randomised trial of chemotherapy followed by RT versus RT followed by chemotherapy,

and five cohort studies examining the effect of the sequencing of chemotherapy and RT were reviewed. Based on the available evidence, the maximum interval between surgery and commencement of RT was defined as 12 weeks. (Cancer Care Ontario, 2011)

Recommendation 2.5.6.1	Grade
Women who have undergone surgery for breast cancer should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery.	C

Clinical question 2.5.7

In patients with invasive breast cancer with node positive disease who have undergone axillary lymph node dissection, who should receive regional nodal radiation?

Evidence statement
Current guidelines (SIGN, 2013), a meta-analysis (Clarke et al., 2005), a systematic review (Overgaard et al., 1999) and nine RCTs (Hennequin et al., 2013, Poortmans et al., 2013, Rutgers et al., 2013, Matzinger et al., 2010, Ragaz et al., 2005, Veronesi et al., 2005, Louis-Sylvestre et al., 2004, Overgaard et al., 1997, Kaija and Maunu, 1995) addressed this question.

Irradiation of all regional lymph nodes
A systematic review (Overgaard et al., 1999) and prospective RCTs (Ragaz et al., 2005, Overgaard et al., 1997) have shown an overall survival benefit and improved disease free survival with the addition of comprehensive locoregional RT after mastectomy and ALND.

The EBCTCG have published a meta-analysis including 8,500 women with node positive breast cancer treated with mastectomy and axillary dissection with or without adjuvant RT (generally to the chest wall and regional lymph nodes), demonstrating improved overall survival and breast cancer survival at 15 years with the addition of locoregional RT (Clarke et al., 2005).

Irradiation of internal mammary nodes
The question of whether irradiation of internal mammary nodes improves outcome has been addressed in three prospective randomised controlled trials (Hennequin et al., 2013, Poortmans et al., 2013, Matzinger et al., 2010 Kaija and Maunu, 1995). Hennequin et al. (2013) randomised 1,334 patients with positive axillary nodes or central/medial tumours with or without positive nodes to receive internal mammary node radiation or not. At a median survival of over 11 years, no survival benefit was demonstrated; 10 year overall survival was 59.3% versus 62.6% with RT, (*P*=0.8) (Hennequin et al., 2013).

The EORTC 22922/10925 trial investigated the potential survival benefit and toxicity of elective irradiation of the internal mammary and medial supraclavicular (IM-MS) nodes. A total of 4,004 women with involved axillary nodes and/or a medially located primary tumour were randomised between 1996 and 2004. Outcome at 10 years was presented at ECCO 2013. Women who received RT to IM-MS nodes had a trend towards improved overall survival (82.3% versus 80.7%, *P*=0.056) significantly improved disease free survival (72.1% versus 69.1%, *P*=0.044) and metastasis free survival (78% versus 75%, *P*=0.02) (Poortmans et al., 2013). A published paper is awaited. In addition, an earlier report on this trial described minimal toxicity and good tolerance to treatment (Matzinger et al., 2010).

Irradiation of axillary nodes
Veronesi et al. (2005) randomised 435 women with clinically T1N0 breast cancer to breast conservation with or without axillary RT. At five years, disease free survival was equivalent in both arms. Axillary metastases occurred in 1.5% of those receiving no axillary treatment and 0.5% of those in the axillary RT group. Louis-Sylvestre et al. (2004) randomised 658 women with breast tumours <3cm in size and clinically negative axilla to BCS and breast RT with either axillary dissection or axillary RT. At 15 years, survival rates were equivalent in both groups. Axillary recurrence was reduced in the group undergoing axillary dissection (1% versus 3%, *P*=0.04).

The AMAROS trial is a large multinational phase III non-inferiority trial which includes 4,806 women with cT1N0 primary breast cancer, comparing axillary dissection and axillary radiation in those after a positive SLNB. Results were presented at ASCO 2013 and are available in abstract format only. With a median follow-up of six years, axillary recurrence occurred in 0.54% after axillary dissection versus 1.03% after axillary radiation. The trial was underpowered due to the

unexpectedly low event rate. Overall survival and disease free survival were equivalent. Axillary RT was associated with significantly reduced risk of lymphoedema. (Rutgers et al., 2013)

Irradiation of supraclavicular nodes

No RCTs were identified to guide the use of supraclavicular fossa (SCF) RT after axillary clearance in patients with positive lymph node involvement. Retrospective observational data suggest that it may be of benefit in patients with ≥4 positive lymph nodes (Tai et al., 2007, Strom et al., 2005, Wang et al., 2007). Participation in clinical trials should be encouraged. (SIGN, 2013)

Recommendation 2.5.7.1	Grade
Recommend adjuvant radiation to the supraclavicular fossa in patients with four or more positive axillary nodes.	C

Recommendation 2.5.7.2	Grade
Consider adjuvant radiation to the supraclavicular fossa in selected patients with 1-3 positive axillary nodes.	C

Recommendation 2.5.7.3	Grade
Consider irradiation to the internal mammary chain in patients with positive axillary nodes and/or inner quadrant tumours.	B

Recommendation 2.5.7.4	Grade
Consider adjuvant radiation to the axilla in patients with positive axillary nodes who have not had an axillary dissection.	B

Good practice point

The Guideline Development Group do **not** recommend adjuvant radiotherapy to the axilla for early breast cancer after axillary lymph node dissection.

2.6   Palliative care

There is a HSE Clinical Programme for Palliative Care and a Needs Assessment Guide was published in 2014. Palliative care recommendations are included as a generic set of recommendations for NCCP National Clinical Guidelines

Clinical question 2.6.1

When should palliative care be introduced for patients with cancer?

Evidence statement

Palliative care is an approach that improves the quality of life of people and their families facing the problems associated with life-limiting illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (World Health Organisation, 2014). It is a vital and integral part of all clinical practice.

When combined with standard cancer care or as the main focus of care, palliative care leads to better patient and caregiver outcomes. These include improvement in symptoms, quality of life (QOL), and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care (Smith et al., 2012).

No trials to date have demonstrated harm to patients and caregivers from early involvement of palliative care (Smith et al., 2012).

A 2013 literature review on the cost and cost-effectiveness of palliative care found that despite wide variation in study type, characteristics and study quality, there are consistent patterns in the results. Palliative care is most frequently found to be less costly relative to comparator groups, and in most cases, the difference in cost is statistically significant. (Smith et al., 2014)

Good clinical practice dictates that assessment of palliative care needs should be an ongoing process throughout the course of a patient's illness; assessments should be carried out at key transition points in the patient pathway, for example:
- At diagnosis of a life-limiting condition
- At episodes of significant progression/exacerbation of disease
- A significant change in the patient's family/social support
- A significant change in functional status
- At patient or family request
- At end of life. (HSE, 2014)

Palliative care services should be structured in three levels of ascending specialisation according to the expertise of the staff providing the service (Department of Health, 2001):
- Level one (Palliative Care Approach): Palliative care principles should be appropriately applied by all healthcare professionals.
- Level two (General Palliative Care): At an intermediate level, a proportion of patients and families will benefit from the expertise of healthcare professionals who, although not engaged full time in palliative care, have had some additional training and experience in palliative care.
- Level three (Specialist Palliative Care): Specialist palliative care services are those services whose core activity is limited to the provision of palliative care.

All patients should be able to engage easily with the level of expertise most appropriate to their needs.

Recommendation 2.6.1.1	Grade
For patients with cancer, early provision of palliative care can improve patient outcomes.	C

Recommendation 2.6.1.2	Grade
Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	D

3 National Clinical Guideline development process

3.1 Aim of National Clinical Guideline

The overall objectives of this National Clinical Guideline are:
- To improve the quality of clinical care,
- To prevent variation in practice,
- To address areas of clinical care with new and emerging evidence,
- Be based on the best research evidence in conjunction with clinical expertise,
- Be developed using a clear evidence-based internationally used methodology.

3.2 Methodology and literature review

The full methodological processes for this guideline are available in the full guideline version, which is available on the NCEC and NCCP websites.

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

Step 1: Develop clinical questions

The first step in guideline development was to identify areas of new and emerging evidence or areas where there was variance in practice. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:
- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time.

This process was carried out by discipline specific sub-groups. The GDG signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 22 clinical questions are listed in appendix 4 of the full National Clinical Guideline.

Step 2: Search for the evidence

The first step in searching for the evidence is the identification of international guidelines. Searches of the primary literature were only conducted if the answers to the clinical questions were not found in up to date evidence based guidelines.

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (see appendix 5 of the full National Clinical Guideline). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:
- Cochrane Library
- Point-of-Care Reference Tools

- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to September 2014. A full set of literature search strategies is available on the NCCP and NCEC websites.

Details of the search strategy undertaken for the budget impact assessment are available in appendix 11 of the full National Clinical Guideline.

Step 3: Appraise the literature for validity and applicability

International guidelines were appraised using the international, validated tool; the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising all the research evidence:
- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of the guideline? (external validity).

Step 4: Formulate and grade the recommendations

The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN; see NCCP Methodology Manual: Appendix VII) was completed for each clinical question.

The following items were considered and documented:
- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
  - What is the potential impact on the health system?
- What is the potential benefit and potential harm to the patient?
- Are there resource implications?

The evidence statements and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are in section 1.4.

Good practice points were based on the clinical expertise of the GDG.

For the economic literature, key messages are presented in boxes entitled 'relevance to the guideline recommendations'.

3.3 Financial impact of condition/disease

Many recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG has identified the areas that require change to ensure full implementation of the guideline. The potential resource implications of applying these recommendations have been considered. In areas where additional resources are required these will be sought through the HSE service planning process.

The complete budget impact assessment to support the recommendations of this National Clinical Guideline is described in the full version National Clinical Guideline, Appendix 11.

3.4 External review

3.4.1 Patient advocacy

A collaborative approach is used in the development of the NCCP patient information, clinical guidelines and other national projects. All NCCP booklets are submitted to the National Adult Literacy Agency (NALA) (www.nala.ie) for the Plain English Award. This is to ensure comprehension and readability are in line with health literacy best practice standards. Service user testing is a key part of the process, and includes liaising with the HSE Patient Forum, online surveys, and engaging with other relevant patient groups e.g. Irish Cancer Society, Marie Keating Foundation.

The views and preferences of the target population were sought by inviting patient advocacy groups (HSE Patient Forum, Irish Cancer Society, Cancer Care West, Marie Keating Foundation, Gary Kelly Cancer Support Centre and Bray Cancer Support Centre) to engage in the National Stakeholder Review process (appendix 7).

3.4.2 National stakeholder and international expert review

The draft guideline was signed off by the entire GDG and the NCCP Guideline Steering Group before going to national stakeholder review. It was circulated to relevant organisations and individuals for comment between 3rd June and 18th July 2014. A full list of those invited to review this guideline is available in appendix 7.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided (NCCP Methodology Manual: Appendix VIII) along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.

All feedback received was reviewed by the project manager and research team. Suggested amendments and supporting evidence were reviewed by the discipline specific sub-group and consensus reached to accept or reject the amendments. Amendments were rejected following discussion between members of the relevant subgroup(s) and in instances where no superior evidence was provided or no conflict of interest form was provided. All modifications were documented.

The amended draft guideline was then submitted for international expert review. The GDG nominated two international bodies to review the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the national stakeholder review. The guideline was circulated for comment between 11th August and 19th September 2014.

A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process.

3.5   Procedure for update of National Clinical Guideline

This guideline was published in June 2015 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

3.6   Implementation of National Clinical Guideline

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual. The implementation plan outlines facilitators and barriers to implementation (see appendix 8 of the full National Clinical Guideline).

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available on the NCCP and NCEC websites.

A multidisciplinary clinical team is responsible for the implementation of the guideline recommendations and a Lead Clinician for Breast Cancer has been nominated in each Breast Unit in the designated cancer centres. Recommendations have been divided into the key clinical areas of radiology, surgery, medical oncology, radiation oncology and palliative care.

All priorities in relation to breast cancer care are agreed annually by the NCCP and are submitted to the annual HSE Service Plan, which is published on the HSE webpage.

A list of relevant tools to assist in the implementation of the National Clinical Guideline is available in appendix 3.

3.7   Roles and responsibilities

This National Clinical Guideline should be reviewed by the multidisciplinary clinical team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline. A Clinical Lead for Symptomatic Breast Cancer has been appointed in each Breast Unit in the designated cancer centres. A Cancer Network Manager from the NCCP meets with each cancer centre on a quarterly basis for performance monitoring and service planning.

All clinical staff with responsibility for the care of patients with breast cancer are expected to:
- Comply with this National Clinical Guideline and any related procedures or protocols,
- Adhere to their code of conduct and professional scope of practice as appropriate to their role and responsibilities, and
- Maintain their competency for the management and treatment of patients with breast cancer.

3.8   Audit criteria

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care.

The following audit criteria will be monitored as KPIs:

Radiology – axillary ultrasound (Clinical question 2.2.1)
Patients with a diagnosis of primary operable breast invasive cancer shall have an ultrasound of the axillary nodes
Numerator: The number of patients who were operated on for a primary invasive breast cancer and who had ultrasound of the axillary nodes
Denominator: The number of patients who were operated on for a primary invasive breast cancer and who had surgery defined as any of the following procedures • Excision of lesion of breast [31500-00] • Subcutaneous mastectomy, unilateral [31524-00] • Subcutaneous mastectomy, bilateral [31524-01] • Simple mastectomy, unilateral [31518-00] • Simple mastectomy, bilateral [31518-01]

Surgery (Clinical question 2.3.8)
For patients having breast conserving surgery, the number of therapeutic interventions shall be recorded
Data variables 1. Record all patients with a primary breast cancer (invasive or in situ) 2. Record all surgical procedures
For patients with primary breast cancer who have breast conserving surgery, the number of therapeutic operations undertaken on the patient. Therapeutic interventions include • 31500-00 – excision of lesion of breast • 31524-00 – subcutaneous mastectomy, unilateral • 31524-01 – subcutaneous mastectomy, bilateral • 31518-00 – simple mastectomy, unilateral • 31518-01 – simple mastectomy, bilateral • 31515-00 – re-excision of breast lesion

Radiation Oncology – access (Clinical question 2.5.6)
For primary invasive or in situ tumours, following surgery, patients who require radiation therapy alone shall commence treatment within 12 weeks (less than or equal to 84 days) of the final surgical procedure
Numerator: The number of patients with primary invasive or in situ tumours who have undergone surgical treatment and require radiation therapy alone and commenced treatment within 12 weeks (less than or equal to 84 days) of the final therapeutic surgical procedure
Denominator: The total number of patients with primary invasive or in situ tumours who have undergone surgical treatment and require radiation therapy alone and commenced treatment

The following patient outcomes can also be monitored through National Cancer Registry (NCRI) data:

- Survival, by stage (summary stage) and tumour type (invasive, in situ)
- Breast conserving surgery: Comparison of breast conserving surgery and mastectomy: rates, outcomes by stage (summary stage) and tumour type (invasive, in situ)
- Management of the axilla: ALND vs. SLNB
- Absence or presence of residual tumour after treatment (micro/ macro).

The following recommendations have been identified as key areas for audit:

Radiology
Staging (Question 2.2.7)
In newly diagnosed asymptomatic breast cancer patients, evidence does **not** support the use of routine imaging for metastatic disease in pathological stage I and II disease.

Surgery
Margins (Question 2.3.9)
For patients receiving breast conserving surgery and post operative radiotherapy for invasive breast cancer, the excision should have a clear margin; the tumour should not be touching ink.

Radiation oncology
Hypofractionation (Question 2.5.3)
Hypofractionation schedules are recommended for patients with early breast cancer.

Appendix 1: NCCP Guideline Development Group membership

Terms of reference
To develop a national evidence-based clinical guideline for the diagnosis, staging and treatment of patients with breast cancer. Full terms of reference are available in the NCCP Methodology Manual for guideline development.

Membership of the Guideline Development Group

Chair
Dr. Ann O'Doherty   Consultant Radiologist, SVUH

Members

Radiology
Dr. Fidelma Flanagan   Consultant Radiologist, MMUH
Dr. Ronan McDermott   Consultant Radiologist, SJH
Dr. Sorcha McNally   Consultant Radiologist, SVUH
Dr. Angela O'Brien   Consultant Radiologist, MMUH
Dr. Ann O'Doherty   Consultant Radiologist, SVUH

Pathology
Dr. Margaret Sheehan   Consultant Pathologist, GUH
Dr. Cecily Quinn   Consultant Pathologist, SVUH

Surgery
Mr. Mitchel Barry   Consultant Surgeon, MMUH (from May 2012)
Prof. Tom Gorey   Consultant Surgeon, MMUH
Ms. Anne Merrigan   Consultant Surgeon, ULH (to April 2012)

Medical Oncology
Dr. Cathy Kelly   Consultant Medical Oncologist, MMUH
Dr. Miriam O'Connor   Consultant Medical Oncologist, WRH
Dr. Janice Walshe   Consultant Medical Oncologist, SVUH/Tallaght

Radiation Oncology
Dr. Clare Faul   Consultant Radiation Oncologist, SLRON
Dr. Joseph Martin   Consultant Radiation Oncologist, GUH
Dr. Orla McArdle   Consultant Radiation Oncologist, SLRON

Nursing
Ms. Mary Dowd   Clinical Nurse Specialist, GUH

NCCP
Ms. Niamh O'Rourke   Project Manager Breast Tumour Group
Dr. Eve O'Toole   Guideline Methodologist

Librarians
Mr. Anthony Linnane   Librarian, HSE West
Ms. Jean Harrison   Librarian, HSE North East

Conflict of Interest
Members declared no conflicts of interest.

Appendix 2: NCCP Guideline Steering Group membership

Terms of reference

To set strategic direction regarding the development of multidisciplinary/interdisciplinary evidence-based clinical practice guidelines for the diagnosis, staging and treatment of cancer. Full terms of reference are available in the NCCP Guideline Methodology Manual for guideline development.

Membership of the NCCP Guideline Steering Group

The NCCP Guideline Steering Group provided governance for the development of the guideline. The members of the steering group are listed below. The GDG project managers were also present at meetings as observers.

Chair

Dr. Jerome Coffey	Interim National Director, NCCP (since Nov 2014)
Dr. Susan O'Reilly	National Director, NCCP (until Nov 2014)

Members

Dr. Jerome Coffey	NCCP Radiation Oncology Advisor & SLRON
Mr. Justin Geoghegan	Chair Hepatobiliary GI GDG, SVUH
Ms. Noreen Gleeson	Chair Gynaecological GDG, SJH & The Coombe
Dr. Mary Hynes	Deputy Director, NCCP
Prof. Arnold Hill	NCCP Surgical Advisor & BH
Dr. Maccon Keane	NCCP Medical Oncology Advisor & GUH
Dr. Marcus Kennedy	Chair Lung GDG, CUH
Mr. Brendan Leen	Regional Librarian, HSE South-East
Ms. Debbie McNamara	Chair Lower GI GDG, BH
Dr. Deirdre Murray	Health Intelligence, NCCP
Dr. Ann O'Doherty	Chair Breast GDG, SVUH
Dr. Margaret O'Riordan	Medical Director, ICGP (to May 2014)
Dr. Eve O'Toole	Guideline Methodologist, NCCP
Prof. John Reynolds	Chair Gastrointestinal GDG, SJH
Dr. Karen Ryan	Consultant in Palliative Medicine & Clinical Lead Clinical Programme for Palliative Care, SFH
Mr. David Quinlan	Chair Prostate GDG, SVUH

Patients: The views and preferences of the target population were sought by inviting patient advocacy groups to engage in the national stakeholder review process (NCCP Methodology: Appendix VII) and also in the development of information materials.

Management: A Cancer Network Manager from the NCCP meets with each cancer centre (CEO/General Manager) on a quarterly basis for performance monitoring and service planning. A lead clinician for Symptomatic Breast Disease is appointed in each cancer centre.

Appendix 3: Summary of tools to assist in implementation of National Clinical Guideline

National Clinical Guidelines for Cancer – Methodology Manual, National Cancer Control Programme, 2014.

InformationforHealthProfessionalsandPatientInformation NCCPGPResources

NCCPChemotherapyProtocols

NCCPSymptomaticBreastService:QualityAssuranceforSaferBetterHealthcare

The above literature is available on the NCCP website

HealthInformationandQualityAuthority(HIQA).NationalStandardsforSaferBetterHealthcare (www. hiqa.ie)

Centre for Evidence Based Medicine (www.cebm.net)

ImprovingHealth:ChangingBehaviour–NHSHealthTrainerHandbook UCL Centre for Behaviour Change (www.ucl.ac.uk)

Michie, S; Atkins, L; West, R; (2014) The Behaviour Change Wheel: A Guide to Designing Interventions. (1st ed.). Silverback Publishing: London.

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ; 337.

Medical Research Council. (2008). Developing and evaluating complex interventions: new guidance. Available from: www.mrc.ac.uk/complexinterventionsguidance.

Guide for health professionals
Prevention of clinical lymphoedema after cancer treatment: Early detection and risk reduction, NCCP

Patient information booklets/leaflets
Symptomatic Breast Clinic – A Guide for Patients, NCCP

Your follow-up care plan after treatment for breast cancer – A guide for women, NCCP

Breast Pain – A Guide for Women, NCCP

Appendix 4: Glossary of Terms and Abbreviations

Definitions within the context of National Clinical Guideline

Case Control Study   The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (CEBM website)

Case Series   A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)

Cohort study   A research study that compares a particular outcome (such as lung cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke). (NCI dictionary)

External validity   The extent to which we can generalise the results of a study to the population of interest.

Internal validity   The extent to which a study properly measures what it is meant to measure.

Meta-analysis   A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (NCI dictionary)

Randomised trial   An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (CEBM website)

Systematic review   The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results. (CEBM website)

A list of abbreviations and references used throughout this Guideline Summary are available in the full version of the guideline available at: http://health.gov.ie/patient-safety/ncec/.

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DEPARTMENT OF HEALTH