

Diagnosis, staging and treatment of patients with breast cancer

National Clinical Guideline No. 7

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Radiation Oncology Section Reviewed May 2023

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.



Reference of National Clinical Guideline

National Clinical Guideline No. 7 should be referenced as follows:

Department of Health. Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7. June 2015, with Radiation Oncology Section retired May 2023. ISSN 2009-6259.

Update May 2023: Radiation Oncology Section reviewed

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

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

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.

Information on the NCEC and endorsed National Clinical Guidelines is available at:
www.health.gov.ie/patient-safety/ncec.

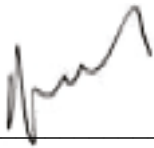
Using this National Cancer Control Programme National Clinical Guideline

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 National Clinical Guideline is available at:
www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer



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1 Background

Cancer is a major healthcare challenge. Each year in Ireland, approximately 19,000 people are diagnosed with malignant cancer. Cancer is the second leading cause of death in Ireland after diseases of the circulatory system (National Cancer Registry in Ireland; NCRI, 2014a). Over 8,000 deaths from cancer are reported in Ireland every year.

Cancer incidence data from the NCRI and population projections from the Central Statistics Office (CSO) have been combined by the NCRI to estimate the number of new cancer cases expected in five year bands from 2015 to 2040. The total number of new invasive cancer cases (including non-melanoma skin cancer) is projected to increase by 84% for females and 107% for males between 2010 and 2040, based only on changes in population size and age distribution (demography). If trends in incidence since 1994 are also taken into account, the number of cases is expected to increase by between 86% and 125% for females (depending on the method of projection used) and by between 126% and 133% for males (NCRI, 2014b).

In Ireland, the annual average incidence for invasive breast cancer was 2,805 cases per annum between 2009 and 2011, which represents 31% of female invasive cancers (excluding non-melanoma skin cancer) (appendix I). The number of cases of female breast cancer is expected to increase by about 130% between 2010 and 2040. However, one Hakulinen/Dyba (HD) model projects a much slower rate of increase for females (NCRI, 2014b). Most cases of breast cancer occur in women aged over 50 years (NCRI, 2014a).

There are eight hospitals designated as cancer centres and one satellite breast unit (Letterkenny General Hospital). As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

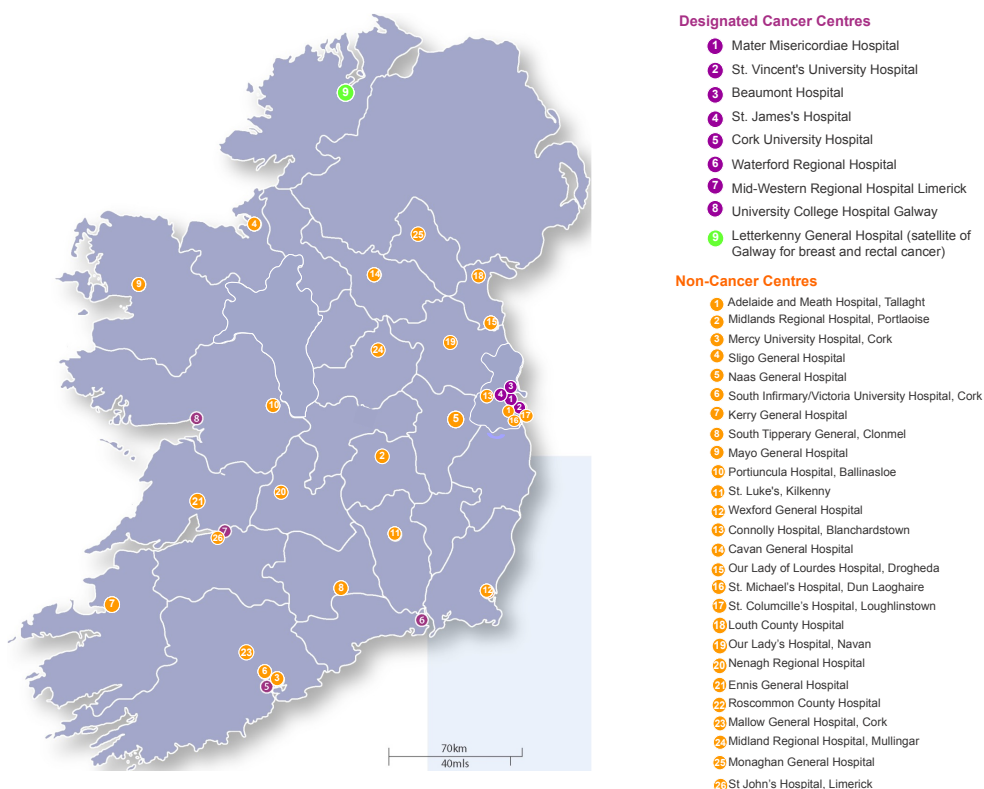


Figure 1 Cancer Services in Ireland

1.1 The rationale for a 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 and financial 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.

A recent population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer is estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). Across the EU, the cost of cancer healthcare was equivalent to €102 per person, but varied substantially from €33 per person in Lithuania to €171 per person in Germany.

In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million. Drug expenditure accounted for a further €127 million, while primary, outpatient and emergency care were estimated at €32 million, €30 million and €13 million, respectively. Across the EU, healthcare costs per person were estimated to cost between €2 and €29 for breast cancer (€15 per person in Ireland) (Luengo-Fernandez et al., 2013). With cancer incidence expected to increase by 99% by 2040 (NCRI, 2014b), there could be a significant increase seen in healthcare costs per person in Ireland. The costs of breast cancer related informal care and productivity losses were estimated at €3.2 billion and €3.25 billion, respectively (Luengo-Fernandez et al., 2013).

1.3 Objectives of the National Clinical Guideline

The overall objectives of the National Clinical Guideline No. 7 'Diagnosis, staging and treatment of patients with breast cancer' 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.

1.4 Scope of the National Clinical Guideline, target population and target audience

1.4.1 Scope

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 and 2.3.9)
- 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. The NCCP has developed general practitioner (GP) referral guidelines, standardised GP referral forms, and GP electronic referral for patients with breast cancer. The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme. The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and their families and healthcare professionals in relation to healthy lifestyle, disease prevention and control. It aims to promote a good quality of life and prolonged survival for people who experience cancer.

The recognition of lymphoedema and intervention at its earliest stage are essential to prevent progression of lymphoedema. Accordingly the NCCP, alongside key stakeholders, have developed a guide for health professionals 'Prevention of clinical lymphoedema after cancer treatment: early detection and risk reduction'. This initiative is part of the NCCP Survivorship Programme.

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 has also set up a Breast National Clinical Leads Network with defined terms of reference. The output of this network includes the following:

- Development and agreement of Key Performance Indicators (KPIs)
- Organising annual multidisciplinary Cancer Quality and Audit Fora
- Focus on cancer specific issues such as the development of information resources for patients and health professionals.

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?

1.4.2 Target population

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.

1.4.3 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with breast cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with breast cancer and their significant others. Cancer specific patient information has already been developed by the NCCP and is available on the NCCP website.

1.5 Governance

Governance of the guideline development process was provided by a multidisciplinary Guideline Steering Group which was chaired by the Director of the NCCP. Membership included representatives from all relevant disciplines and the chairs of each NCCP Guideline Development Group (GDG). Details of GDG members and Guideline Steering Group members are available in appendices 2 and 3. Figure 2 outlines the stages of guideline development.

A GDG was responsible for the development and delivery of this National Clinical Guideline and included representatives from relevant medical groups (radiologists, pathologists, surgeons, medical oncologists, and radiation oncologists) with expertise in the diagnosis, staging and treatment of patients with breast cancer. The GDG also included a project manager, a methodologist and clinical librarians.

1.5.1 Conflict of interest statement

A conflict of interest form (see NCCP Methodology Manual: Appendix II) was signed by all GDG members and reviewers. Members of the GDG declared no conflicts of interest.

The GDG was managed by the chair to promote the highest professional standard in the development of this guideline. Where funding had been obtained to attend conferences etc., this was stated and extra care was taken to ensure that no conflict arose from these situations.

1.5.2 Funding body and statement of influence

The guideline was commissioned and funded by the NCCP; however, the guideline content was not influenced by the NCCP or any other funding body. This process is fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.

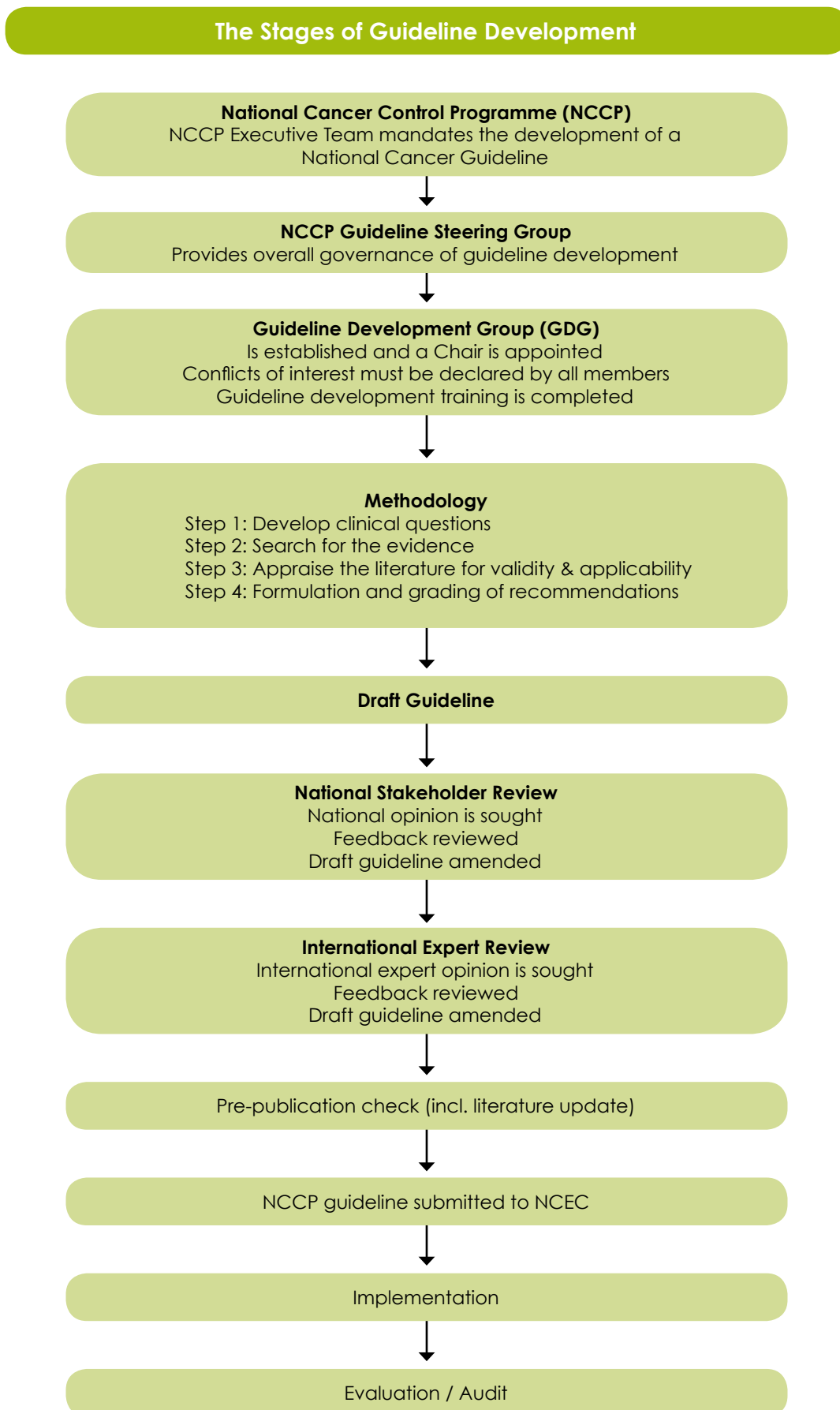


Figure 2 The Stages of Guideline Development

1.6 Guideline methodology

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.

1.6.1 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.

1.6.2 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 (appendix 5). 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.

1.6.3 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).

1.6.4 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 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 documented in appendix 6.

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'.

1.7 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).

1.8 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.

1.9 Procedure for updating the 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.

1.10 Implementation of the 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 (appendix 8).

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.

1.11 Tools to assist the implementation of the National Clinical Guideline

A list of relevant tools to assist in the implementation of the National Clinical Guideline is available in appendix 9.

1.12 Audit

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. For audit criteria see appendix 10.

1.13 Budget impact

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 (appendix 11). In areas where additional resources are required these will be sought through the HSE service planning process.

1.14 Organisational responsibility

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.

1.15 Glossary of terms and abbreviations

A glossary of the terms and abbreviations used throughout the guideline is available in appendix 12.

1.16 Accompanying documents

The following documents are available on the NCCP and NCEC websites:

- Guideline Summary
- NCCP Methodology Manual for guideline development
- Literature search strategies.

2 National Clinical Guideline

2.1 Summary of clinical 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 $\geq 3\text{mm}$ 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

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

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 ≥ 3 mm 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

Clinical question 2.2.7

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-II B 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 ≤ 1 mm, 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
- Anthracycline 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/m² or epirubicin greater than 900mg/m²) 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 amenorrhic 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 exemestane. 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 leucopenia 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 to 1.19, $P = 0.82$) (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

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

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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

2.7 Recommendations for research

There was insufficient evidence to make recommendations on a number of clinical questions. The following areas have been identified that require further research:

- The role of preoperative MRI in invasive breast cancer
- The role of preoperative MRI in invasive lobular breast cancer
- The role of MRI in the setting of pure ductal carcinoma in situ
- The role of MRI in the setting of breast skin dimpling/puckering
- The role of MRI in the clinical context of suspicious nipple discharge
- The role of MRI in the setting of nipple inversion
- The role of contralateral risk reducing mastectomy in non genetic mutation carriers
- A comparison of the efficacy of specific aromatase inhibitors
- The optimal duration of therapy with aromatase inhibitors
- The efficacy of adjuvant bisphosphonates.

In addition, a number of international clinical trials are ongoing, and the guideline will be updated as required, based on the publication of new evidence.

3 Appendices

Appendix 1: Epidemiology of breast cancer

Incidence

The annual average incidence for invasive breast cancer in Ireland between 2009 and 2011 was 2,805 cases per annum (table 1), which represents 31% of female invasive cancers (excluding non-melanoma skin cancer). The incidence rate per 100,000 females was 123.7. The 2012 estimated incidence rates of female breast cancer in Ireland (122.4) was 5% lower than in the UK (129.2) but 13% higher than the European average (108.8). Most cases of breast cancer occur in women aged over 50 years (NCRI, 2014a). On average, 23 men are diagnosed with breast cancer in Ireland every year.

Table 1 Annual average incidence for breast cancer in Ireland, 2009-2011 (NCRI, 2014a)

BREAST CANCER	CASES		
	Females	Males	Total
Breast C50** invasive	2,781	23	2,805*
Breast D05** in situ	340	1	341

*as annual averages have been rounded up to whole numbers, slight discrepancies occur
 **C50 – Malignant neoplasm of breast; D05 – Carcinoma in situ of breast (ICD-10)

Figure 3 shows the relative frequencies of the most common invasive cancers diagnosed in females in Ireland from 2009–2011, including non-melanoma skin cancer. Breast cancer made up 22% of all female invasive cancers.

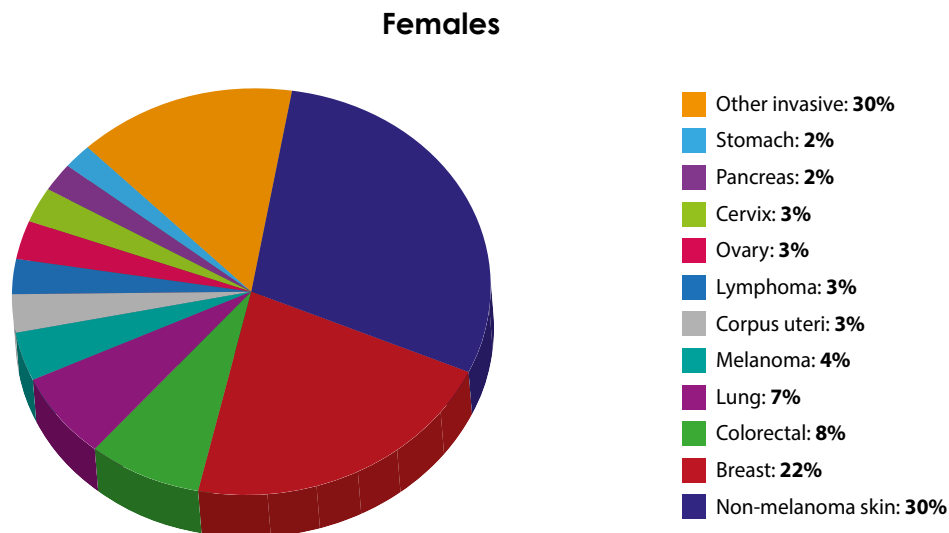


Figure 3 Relative frequencies of the most common invasive cancers diagnosed in females in Ireland, 2009-2011 (NCRI, 2014a)

Table 2 shows the ranking of the most commonly diagnosed invasive cancers in Ireland from 2009–2011, excluding non-melanoma skin cancer. Breast cancer was the most commonly diagnosed invasive cancer among women.

Table 2 Ranking of the most commonly diagnosed invasive cancers in Ireland, 2009-2011 (NCRI, 2014a)

INVASIVE CANCER	Female	
	%	Rank
Breast	31.0	1
Colorectal	11.5	2
Lung	10.1	3

Mortality

Table 3 shows the mortality from invasive breast cancers in Ireland in 2011. The number of deaths from breast cancer was 690 women and seven men (NCRI, 2014a).

Table 3 Number of deaths and mortality rate from invasive breast cancers, 2011 (NCRI, 2014a)

	Deaths		Rate/100,000	
	Female	Male	Female	Male
Breast	690	7	26.5	0.3

Figure 4 shows the relative frequency of the most common cancer deaths in Ireland in 2011. Breast cancer deaths accounted for 17% of the total female deaths from cancer in 2011 (NCRI 2014a), ranking it the second most common cancer death among females (table 4).

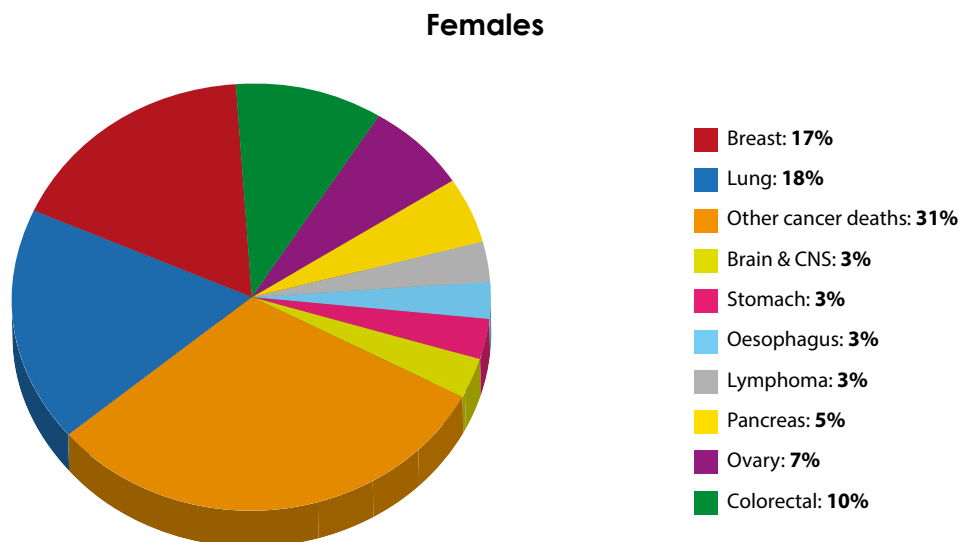


Figure 4 Relative frequency of the most common cancer deaths in Ireland, 2011 (NCRI, 2014a)

Table 4 Ranking of the most common cancer deaths in Ireland, 2011

	Females	
	%	Rank
Lung	18.2	1
Breast	16.6	2
Colorectal	10.3	3

Survival

Breast cancer is now a very treatable disease, which is reflected in the increase in survival rates. According to the latest NCRI statistics, the five year age-standardised estimates of cumulative net survival* for Irish female breast cancer patients has increased from 71.2% in the period 1994–1999 to 81.2% in the period 2006–2011.

*Net survival is an 'improved' version of relative survival which takes better account of competing mortality risks. It represents the cumulative probability of a patient surviving a given time in the hypothetical situation in which the disease of interest is the only possible cause of death.

Cancer projections 2015 – 2040

There was a significant upward trend in breast cancer numbers for females between 1994 and 2010 of 4% annually. Some deviation from this trend can be seen at the time of commencement of BreastCheck (The National Breast Screening Programme) in 2001, and at the time of its extension to the south and west of the country in 2007 but this seems to be overlaid on a steady long-term upward trend. A similar pattern, but with a smaller rate of increase (1.8% annually) can be seen for age-standardised incidence (NCRI, 2014b).

Table 5 shows the projected numbers of incident cases of breast cancer up to the year 2040, estimating a 63% increase in incidence by the year 2040, based on demographic changes only.

Table 5 Projected numbers of incident cases 2015-2040 (with % increase compared to 2010): cancer of the female breast (NCRI, 2014b)

Cancer of the female breast		
Year	Projected numbers of incident cases 2015–2040 (based on demography only)	% increase compared to 2010
2015	3,209	11
2020	3,577	24
2025	3,937	36
2030	4,252	47
2035	4,514	56
2040	4,701	63

Appendix 2: 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 NorthEast

Conflict of Interest

Members declared no conflicts of interest.

NCCP Research Staff

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The NCCP is grateful to the following individuals who have contributed to the development of the guideline:

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Methodology Expert Advisor

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Acknowledgments

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 National Comprehensive Cancer Network® (NCCN®)
 Cancer Care Ontario
 National Cancer Registry in Ireland (NCRI)
 Centre for Behaviour Change, University College London

Appendix 3: 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 4: Clinical questions in PICO format

Radiology

<u>Clinical question 2.2.1</u> In patients with breast cancer, should all patients have pretreatment ultrasound of the axilla to determine node status and treatment options?	
Population:	Patients with diagnosed breast cancer
Intervention:	Ultrasound of the axilla
Comparison:	No ultrasound
Outcome:	To determine node status (node positive or node negative) To determine treatment options Prevention of unnecessary axillary clearance Prevention of morbidity (due to unnecessary axillary clearance) Recurrence Survival/disease free survival
<u>Clinical question 2.2.2</u> 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?	
Population:	Patients with breast cancer who have had ultrasound of the axilla performed
Intervention:	Clinical features on ultrasound which indicate that fine needle aspiration or core biopsy is required (e.g. lymph node cortical thickness, shape and contour, morphologically abnormal lymph nodes)
Comparison:	-
Outcome:	Axillary fine needle aspiration Core biopsy
<u>Clinical question 2.2.3</u> In patients over 35 with a palpable breast lesion with normal imaging (mammography and ultrasound), when should clinical core biopsy be performed?	
Population:	Patients over 35 with a palpable breast lesion with normal imaging (mammography and ultrasound)
Intervention:	Clinical core biopsy (Percutaneous core breast biopsy)
Comparison:	No further intervention
Outcome:	Yield of cancer (cancer detection rate) False negative imaging rate
<u>Clinical question 2.2.4</u> In patients with biopsy proven breast cancer, what is the role of breast MRI in the preoperative staging of: – Patients with biopsy proven ductal carcinoma in situ (DCIS) – Patients with biopsy proven invasive breast cancer • Lobular • Ductal	
Population:	Patients with biopsy proven breast cancer
Intervention:	Breast MRI
Comparison:	No MRI
Outcome:	Planning of treatment To identify/diagnose cancer To rule-out/exclude cancer Sensitivity/specificity of MRI

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?

Population:	Patients with metastatic deposits in axillary nodes with no primary cancer identified clinically or on conventional imaging
Intervention:	MRI
Comparison:	-
Outcome:	Identification of primary cancer Plan treatment Sensitivity/specificity

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?

Population:	Patients with: Nipple discharge/bloody discharge Nipple inversion/nipple changes/nipple retraction Paget's disease/nipple ulceration Breast dimpling
Intervention:	Breast MRI
Comparison:	No MRI
Outcome:	Planning of treatment To identify/diagnose cancer To rule-out/exclude cancer Sensitivity/specificity of MRI

Clinical question 2.2.7

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

Population:	Patients with newly diagnosed breast cancer: Tumours: Stage I Stage II Stage III Stage IV
Intervention:	Staging investigations (CT, Ultrasound, Chest X-ray, Bone Scan, MRI, PET-CT)
Comparison:	No staging investigations
Outcome:	Detection of metastatic disease Sensitivity and specificity False positives False negatives To determine treatment options/change in management

Clinical question 2.2.8

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

Population:	Patients with newly diagnosed breast cancer, in whom staging is indicated.
Intervention:	CT Isotope bone scan Abdominal ultrasound Chest x-ray PET-CT

Comparison:	CT Isotope bone scan Abdominal ultrasound Chest x-ray PET-CT
Outcome:	Detection of metastatic disease Sensitivity and specificity False positives False negatives

Surgery

<u>Clinical question 2.3.1</u> In patients with ductal carcinoma in situ (DCIS), what is the evidence that breast conserving surgery (BCS) and radiotherapy (RT) is more or less effective than mastectomy?	
Population:	Patients with DCIS
Intervention:	BCS and RT
Comparison:	Mastectomy
Outcome:	Local recurrence Disease free survival Overall survival
<u>Clinical question 2.3.2</u> In patients with operable invasive breast cancer, what is the evidence that breast conserving surgery and radiotherapy is more or less effective than mastectomy?	
Population:	Patients with operable invasive breast cancer
Intervention:	BCS and RT
Comparison:	Mastectomy
Outcome:	Local recurrence Disease free survival Overall survival
<u>Clinical question 2.3.3</u> In patients undergoing mastectomy for operable breast cancer (in situ or invasive), what is the evidence for prophylactic mastectomy? a) Those who have had a previous breast cancer and now have a local recurrence/second primary breast cancer in the ipsilateral or contralateral breast b) 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	
Population:	Patients undergoing mastectomy for operable breast cancer (in situ or invasive)
Intervention:	Prophylactic mastectomy
Comparison:	-
Outcome:	Morbidity Contralateral cancer Mortality
<u>Clinical question 2.3.4</u> 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?	
Population:	Patients with breast cancer undergoing breast reconstruction postmastectomy
Intervention:	Immediate reconstruction
Comparison:	Delayed breast reconstruction

Outcome:	Post operative pain Donor site morbidity Postoperative morbidity including capsular contracture, haematoma, flap necrosis, surgical site infections requiring removal of prosthesis Cosmesis Time to delivery of adjuvant treatment Quality of life (social/sexual) Local recurrence Regional (axillary) recurrence Disease free survival Overall survival
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?	
Population:	Patients with operable (invasive) breast cancer
Intervention:	Axillary node clearance Axillary node sampling Sentinel node biopsy
Comparison:	-
Outcome:	Risk of anaphylaxis with blue dye used for SLNB Pain Lymphoedema Upper limb morbidity Regional recurrence Overall survival
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)?	
Population:	Patients with operable (invasive) breast cancer
Intervention:	Axillary node clearance Axillary node sampling Sentinel node biopsy
Comparison:	-
Outcome:	Risk of anaphylaxis with blue dye used for SLNB Pain Lymphoedema Upper limb morbidity Regional recurrence Overall survival
Clinical question 2.3.7	
What is the appropriate management of the axilla in patients with operable (invasive) breast cancer with sentinel node positive isolated tumour cells, micromets or macromets?	
Population:	Patients with operable (invasive) breast cancer
Intervention:	Axillary node clearance Axillary node sampling Sentinel node biopsy
Comparison:	-

Outcome:	Risk of anaphylaxis with blue dye used for SLNB Pain Lymphoedema Upper limb morbidity Regional recurrence Overall survival
<u>Clinical question 2.3.8</u> For patients receiving breast conserving surgery and postoperative radiotherapy for ductal carcinoma in situ, what constitutes an adequate surgical margin?	
Population:	Patients with a primary diagnosis of DCIS receiving BCS and postoperative/ adjuvant RT
Intervention:	Extent of margins/Clear surgical margins
Comparison:	Surgical margins not clear
Outcome:	Ipsilateral breast tumour recurrence (IBTR) related to surgical margins Local recurrence in the preserved breast
<u>Clinical question 2.3.9</u> For patients receiving BCS and postoperative RT for invasive breast cancer, what constitutes an adequate surgical margin?	
Population:	Patients with a primary diagnosis of invasive cancer receiving BCS and postoperative/adjuvant RT
Intervention:	Extent of margins/clear surgical margins
Comparison:	Surgical margins not clear
Outcome:	Ipsilateral breast tumour recurrence (IBTR) related to surgical margins Local recurrence in the preserved breast

Medical oncology

<p><u>Clinical question 2.4.1</u> In patients with breast cancer: a) What is the evidence that adjuvant chemotherapy is effective? b) What is the optimal chemotherapy regimen?</p>	
Population:	<p>Patients with breast cancer (including men, premenopausal women and postmenopausal women) who are:</p> <ul style="list-style-type: none"> - Lymph node positive (+) or lymph node-negative (-) - Oestrogen receptor (ER) + or (ER) - - Human Epidermal Growth Factor Receptor 2 (HER2) + or (HER2) -
Intervention:	<p>Non-anthracycline containing regimens Anthracycline containing regimens Taxane containing regimens Trastuzumab containing regimens</p>
Comparison:	-
Outcome:	<p>Disease free survival Overall survival Toxicity</p>
<p><u>Clinical question 2.4.2</u> In premenopausal women 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?</p>	
Population:	<p>Premenopausal women with breast cancer Oestrogen receptor (ER) + Progesterone receptor (PR) +</p>
Intervention:	<p>Tamoxifen Ovarian suppression/ablation</p>
Comparison:	<p>Ovarian suppression/ablation plus tamoxifen vs. tamoxifen alone 5 years of endocrine therapy vs. longer</p>
Outcome:	<p>Disease free survival Overall survival Adverse events (include venous thromboembolism, menopausal symptoms, endometrial cancer)</p>
<p><u>Clinical question 2.4.3</u> In postmenopausal women 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?</p>	
Population:	<p>Postmenopausal women with breast cancer Oestrogen receptor (ER) + Progesterone receptor (PR) +</p>
Intervention:	<p>Tamoxifen Aromatase inhibitors</p>
Comparison:	<p>Aromatase inhibitors vs. tamoxifen in postmenopausal women Sequential therapy with tamoxifen and an aromatase inhibitor in postmenopausal women 5 years of endocrine therapy vs. longer</p>

Outcome:	Disease free survival Adverse events (including venous thromboembolism, menopausal symptoms, endometrial cancer) Overall survival
<u>Clinical question 2.4.4</u> For women with breast cancer, what subgroups of patients would benefit from neoadjuvant systemic therapy and what is the optimum regimen?	
Population:	Patients with breast cancer
Intervention:	Neoadjuvant chemotherapy Neoadjuvant trastuzumab Neoadjuvant endocrine therapy
Comparison:	-
Outcome:	Pathological complete response (pCR) Rates of BCS (i.e. inoperable to operable) Overall survival Local/regional recurrence Disease free/recurrence free survival Local/regional recurrence Toxicity

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

Palliative care

<u>Clinical question 2.6.1</u> When should palliative care be introduced for patients with cancer?	
Population:	Patients with metastatic cancer
Intervention:	Timing of palliative care
Comparison:	-
Outcome:	Quality of Life

Appendix 5: Systematic literature review protocol



HSE Library Services
NCCP Guideline Development

www.hselibrary.ie



SYSTEMATIC LITERATURE REVIEW PROTOCOL

Literature searches to answer clinical questions identified by the relevant tumour group will be conducted using the following procedure. Questions should only be submitted if they have not been adequately answered in the guidelines adopted by the tumour group, or where guidelines need to be updated. Guidelines should be identified in consultation with library services.

Tumour Group	1	PICO(T)	Analyse the clinical question using PICO(T) and complete a Clinical Query Request form. See below Annex 1: Clinical Query Request.
Tumour Group/ Library Services	2	Question Category	Assign a question category, if appropriate: Therapy/Intervention <input type="checkbox"/> Aetiology/Risk Factors <input type="checkbox"/> Diagnosis <input type="checkbox"/> Prognosis/Prediction <input type="checkbox"/> Frequency/Rate <input type="checkbox"/> Phenomena <input type="checkbox"/> Other <input type="checkbox"/>
Library Services	3	Literature Search	Conduct searches of the following bibliographic databases in the order specified below using keywords implicit in the PICO(T) strategy and any identified subject headings:
		Cochrane	<p>3.1 Cochrane Library Comprising: the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials (Central); the Database of Abstracts of Reviews of Effects; the Health Technology Assessment Database; the NHS Economic Evaluation Database. Use MeSH and keyword searches to identify systematic reviews and other relevant studies.</p>
		Point-of-Care	<p>3.2 Point-of-Care Reference Tools One or more of the following point-of-care reference tools: BMJ Best Practice; DynaMed; UpToDate.</p>
		Medline	<p>3.3 Medline Use MeSH and keyword searches. Limit results using the 'Human' search filter. Unless otherwise specified by the tumour group or warranted by the specific clinical question, limit results to studies from the previous five years. Where appropriate, limit intervention questions according to the following priority: Medline clinical queries; Cochrane systematic reviews; other systematic reviews or meta-analyses; RCTs; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources. Where appropriate, limit diagnosis, prognosis or aetiology questions according to the following priority: Medline clinical queries; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources.</p>
		Embase	<p>3.4 Embase Repeat the Medline search strategy above using Embase, if available.</p>
		Other Databases	<p>3.5 Other Bibliographic Databases Repeat the Medline search strategy above using the Cumulative Index to Nursing and Allied Health Literature and/or PsycINFO, as appropriate.</p>
		Other Sources	<p>3.6 Other Sources Use any other sources for background or additional information, as appropriate. Other sources may include: PubMed, particularly for in-process or ahead-of-print citations; quality-assured, subject-specific Internet resources; clinical reference books; patient information materials; etc.</p>

Trial Registers

3.7 Trial Registers

When a relevant trial is identified through searching the bibliographic databases, a search of trial registers should be carried out to identify any related trials which have been completed but whose findings have not been published or made available. The tumour group should be alerted to the presence of these unpublished trials. The following sources may be included:

3.7.1 ClinicalTrials.gov: <http://clinicaltrials.gov/>

3.7.2 Cochrane Central Register of Controlled Trials (Central): <http://www.thecochranelibrary.com/>

3.7.3 EU Clinical Trials Register: <https://www.clinicaltrialsregister.eu/>

3.7.4 International Prospective Register of Systematic Reviews (Prospero): <http://www.crd.york.ac.uk/prospero/search.asp>

3.7.5 WHO International Clinical Trials Registry: <http://apps.who.int/trialsearch/>

3.8 For questions relating to economic evaluations, use the SIGN economic studies filter for Medline as a basis for the search strategy: <http://www.sign.ac.uk/methodology/filters.html#econ>. The following source may also be consulted, if available: **HEED: Health Economic Evaluations Database:** <http://onlinelibrary.wiley.com/book/10.1002/9780470510933>.

Library Services

4

Reference Management

Retain an electronic record of the search strategy and all search results using the Zotero reference management utility.

Library Services

5

Search Results

Respond to the tumour group using the Clinical Query Response form to include:

- a copy of the search strategy
- bibliographic details of all search results identified
- optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question

See below Annex 2: Clinical Question Response.

Library Services

6

Retracted Publications

6.1 Set up an alert to review results lists returned to the tumour group to rapidly capture any articles that are subsequently retracted or withdrawn, and notify the tumour group accordingly.

Tumour Group/
Library Services

Retracted Publications

6.2 Review all articles included in recommendations of the completed guideline to confirm that they have not been subsequently retracted or withdrawn.

Library Services

7

Summary of Search Strategy

A summary of the search strategy is included as an addendum to the completed guideline. Complete the Clinical Question: Summary of Search Strategy form and return to the tumour group.

See below Annex 3: Clinical Question: Summary of Search Strategy.

Library Services

8

[Pre-External Review] Update of Literature Search

Once internal review of the guideline has been completed, literature searches for all clinical questions should be updated to capture articles published in the interim between the original literature search and the final draft of the guideline. Updated literature searches should be conducted prior to submission of the guideline for external review.

Respond to the tumour group as previously using the Clinical Query Response form to include:

- a copy of the search strategy
- bibliographic details of all search results identified
- optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question

See below Annex 2: Clinical Question Response.

ANNEX 1 CLINICAL QUESTION REQUEST TO LIBRARY

Your Contact Details		
Name		
Job Title		
Work Address		
Telephone		
Email		
Employee Number		
Please state your clinical question		
... and list any relevant keywords		
... or (optional) enter keywords under the following headings (PICO)		
PICO		
Population/Problem		
Intervention/Indicator		
Comparator/Control		
Outcome		
Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male <input type="checkbox"/> Female <input type="checkbox"/>	Infant (0 – 23 months) <input type="checkbox"/> Child (2 – 12 years) <input type="checkbox"/> Adolescent (13 – 18 years) <input type="checkbox"/> Adult (19 – 65 years) <input type="checkbox"/> Aged (> 65 years) <input type="checkbox"/>	Current year only <input type="checkbox"/> 0 – 5 years <input type="checkbox"/> > 5 years <input type="checkbox"/>
Question Type		
Therapy/Intervention <input type="checkbox"/> Aetiology/Risk Factors <input type="checkbox"/> Diagnosis <input type="checkbox"/> Prognosis/Prediction <input type="checkbox"/> Frequency/Rate <input type="checkbox"/> Phenomena <input type="checkbox"/> Other <input type="checkbox"/>		
Additional Information		

ANNEX 2 CLINICAL QUESTION RESPONSE FROM LIBRARY

Dear _____,

Thank you for your email. Please see attached in response to your clinical query and, below, details of the search strategy applied to your question. If you wish to source any of the references contained in these results, or to search further, please do not hesitate to contact us.

Best wishes,

_____.

[ATTACH CLINICAL QUESTION REQUEST HERE]

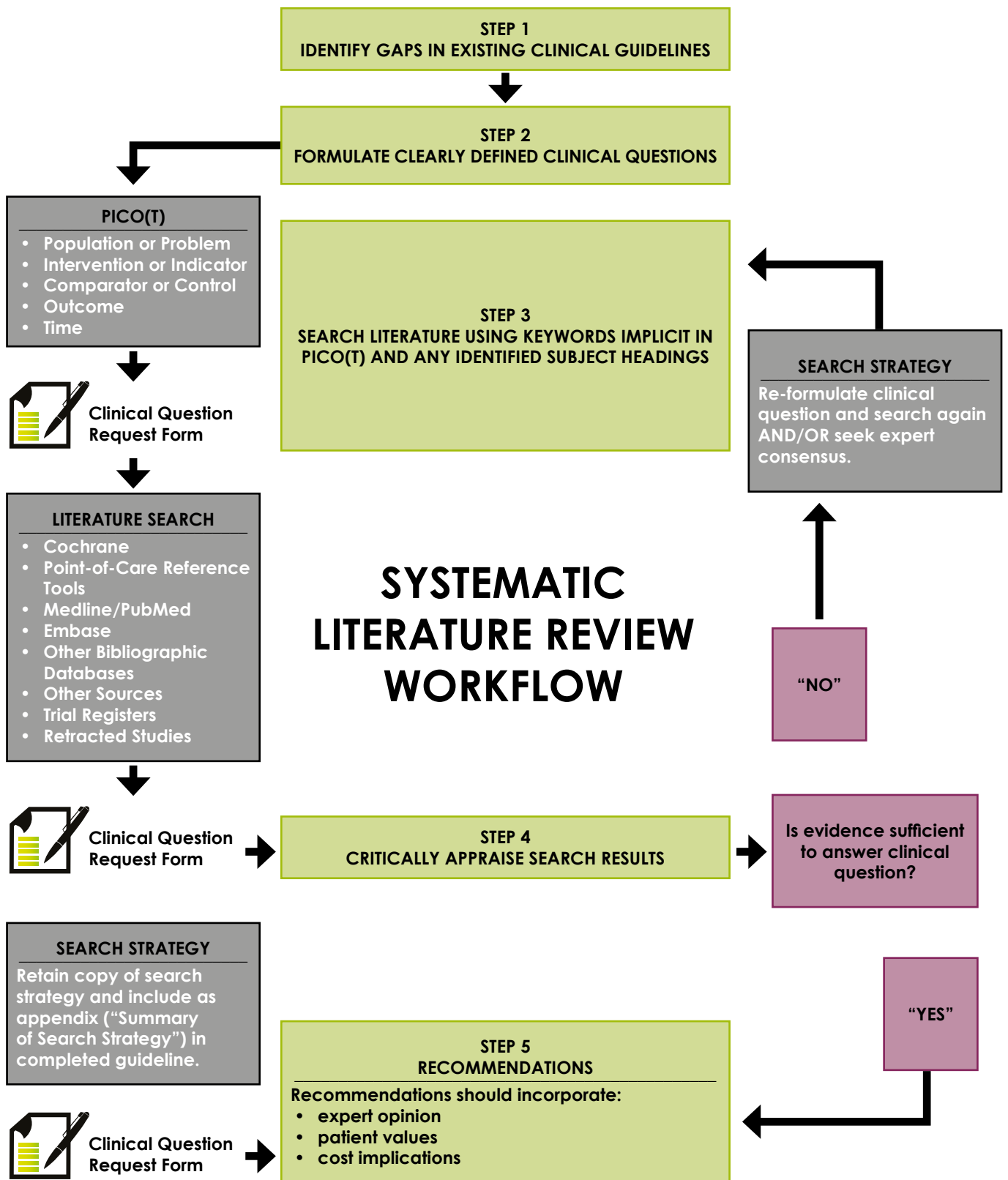
Search Strategy	
Primary Database(s) Searched	
Search Strategy	
Other/Secondary Resources Searched	
Comments	
Contact	
Your Library Staff Contact	
Date	

ANNEX 3

CLINICAL QUESTION: SUMMARY OF SEARCH STRATEGY

Clinical Question		
PICO		
Population/Problem		
Intervention/Indicator		
Comparator/Control		
Outcome		
Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male <input type="checkbox"/> Female <input type="checkbox"/>	Infant (0 – 23 months) <input type="checkbox"/> Child (2 – 12 years) <input type="checkbox"/> Adolescent (13 – 18 years) <input type="checkbox"/> Adult (19 – 65 years) <input type="checkbox"/> Aged (> 65 years) <input type="checkbox"/>	Current year only <input type="checkbox"/> 0 – 5 years <input type="checkbox"/> > 5 years <input type="checkbox"/>
Question Type		
Therapy/Intervention <input type="checkbox"/>		
Aetiology/Risk Factors <input type="checkbox"/>		
Diagnosis <input type="checkbox"/>		
Prognosis/Prediction <input type="checkbox"/>		
Frequency/Rate <input type="checkbox"/>		
Phenomena <input type="checkbox"/>		
Other <input type="checkbox"/>		
Search Strategy		
Primary Database(s) Searched		
Search Strategy	[Copy of base Medline and/or PubMed search strategy HERE. Include subject headings and search hits].	
Other/Secondary Resources Searched		
Search Strategy: Other Resources	[Copy of other search strategies HERE. Include subject headings and search hits].	
Comments	[Short paragraph describing search].	
Date		

ANNEX 4 SYSTEMATIC LITERATURE REVIEW WORKFLOW*



* Based in part on "Figure 10: Systematic Literature Review" of SIGN 50: A Guideline Developer's Handbook. – Scottish Intercollegiate Guidelines Network (SIGN). 2011. A Guideline Developer's Handbook. Edinburgh: SIGN; 2011. (SIGN publication no. 50). [cited 01 Nov 2014]. Available: www.sign.ac.uk

Appendix 6: Levels of evidence and grading systems

Table 6 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 7 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 8 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 9 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.

Appendix 7: National stakeholder and international expert reviewers

Clinical leaders and healthcare managers	National Clinical Leads group (Symptomatic Breast Disease) HSE Clinical Programme in Surgery HSE Clinical Programme in Radiology HSE Clinical Programme in Palliative Care HSE Clinical Programme in Primary Care HSE Clinical Programme in Medicines Management CEOs of the designated Cancer Centres BreastCheck teams; Eccles, Merrion, Galway & Cork Participants at previous SBD Audit Quality & Risk Forum 2010-2013
National groups, organisations, faculties and committees	National Cancer Registry of Ireland (NCRI) Faculty of Surgery, RCSI Faculty of Radiology, RCSI Hospital Pharmacists Association of Ireland Oncology Pharmacists Special Interest Group All Ireland Institute of Hospice and Palliative Care The Irish Hospice Foundation The Irish Association for Palliative Care Irish Society for Medical Oncologists (ISMO) Irish Association for Nurses in Oncology (IANO) Irish College of General Practitioners (ICGP) Irish Association of Directors of Nursing and Midwifery
Patient support and advocacy groups	HSE Patient Forum Irish Cancer Society Cancer Care West Marie Keating Foundation Gary Kelly Cancer Support Centre Bray Cancer Support Centre
International Expert Review	Scottish Intercollegiate Guideline Network (SIGN), Scotland European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services (EUREF)

The following organisations and individuals responded to the stakeholder review and submissions were discussed with the members of the GDG in July 2014:

- Dr John Kennedy (Consultant Medical Oncologist)
- Dr Patrick Morris (Consultant Medical Oncologist)
- Mr Malcolm Kell (Consultant Surgeon)
- Mr Mark Corrigan (Consultant Surgeon)
- Professor Frank Keane (National Clinical Programme in Surgery)
- Ms Sinéad Fitzpatrick (National Clinical Programme for Palliative Care)
- Ms Aisling Heffernan (National Clinical Programme for Radiology)
- Dr Margaret O'Riordan (Irish College of General Practitioners)
- Ms Veronica O'Leary (Bray Cancer Support Centre)
- Dr Marie Staunton (Consultant Histopathologist).

The GDG is also very grateful to Mr Glyn Neades (SIGN), Ms Ailsa Stein (SIGN) and Dr Nicholas Perry (EUREF) for sharing their expertise. We appreciate the time commitment that was involved in reviewing this guideline.

A log was recorded of all submissions and amendments from the National Stakeholder Review and International Expert Review Process.

Appendix 8 Implementation plan

The guideline implementation plan is based on the COM-B model of behaviour change (Michie et al., 2011). Changing clinical behaviour with clinical guidelines is more likely if the behaviour is specified in the implementation plan (Michie et al., 2004). The Behaviour Change Wheel (Michie et al., 2011) was developed in 2011 as a tool for designing and evaluating behaviour change interventions. This model is based around the three conditions which influence behaviour: capability, opportunity and motivation. Each component can be mapped onto one of nine different intervention functions (education, training, enablement, persuasion, incentivisation, coercion, modelling, restrictions and environmental restructuring). This model has been used to assess barriers and facilitators to guideline development and implementation and is outlined in detail in the NCCP Guideline Methodology Manual. Identification of barriers and facilitators is carried out during recommendations meetings with consultants and is recorded in the 'considered judgement forms'. The table below outlines the possible intervention functions for each recommendation in the guideline. Where the recommendation is already current practice, intervention functions are not required.

Radiology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.2.1 In patients with breast cancer, should all patients have pretreatment ultrasound of the axilla (to determine node status and treatment options)?	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.	Current practice. (no intervention required)	Current practice.	N/A	N/A
Q.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?	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 $\geq 3\text{mm}$ or if the node demonstrates abnormal morphological features.	3mm correlates with current practice.	Current practice.	N/A	N/A
Q.2.2.3 In patients over 35 with a palpable breast lesion with normal imaging (mammography and ultrasound), when should clinical core biopsy be performed?	In patients with a clinically suspicious examination (S4, S5) and normal imaging (mammography and ultrasound), clinically guided core biopsy should be performed.	Current practice. Very small population have clinically suspicious palpable lesion with negative imaging.	Current practice.	N/A	N/A
Q.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	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. 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. In patients with invasive lobular cancer, MRI can be considered to assess tumour size, if breast conserving surgery is a treatment option.	The number of MRIs may increase for some subgroups (e.g. invasive lobular, occult primary breast cancer) and decrease for others (e.g. preoperative assessment of patients with biopsy proven breast cancer or DCIS).	Access to MRI. Training and equipment may be required for MR biopsy.	Capability (physical) Opportunity (physical)	Training Enablement Environmental restructuring

***Capability** Psychological or physical ability to enact the behaviour.

Opportunity Physical and social environment that enables behaviour.

Motivation Reflective and automatic mechanisms that activate or inhibit behaviour.

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.2.5 In patients with metastatic deposits in axillary nodes where no primary cancer has been identified, what is the role of breast MRI?</p>	<p>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.</p>	<p>Number of MRIs may increase.</p>	<p>Resources required.</p>	<p>Opportunity (physical)</p>	<p>Enablement Environmental restructuring</p>
<p>Q.2.2.6 In patients with breast dimpling, nipple discharge, inversion, or Paget's disease, who have normal ultrasound and mammography, what is the role of breast MRI?</p>	<p>In the setting of negative conventional imaging, MRI can facilitate treatment planning for patients with Paget's disease.</p>	<p>Number of MRI may increase. Small numbers for Paget's disease.</p>	<p>Resources required.</p>	<p>Opportunity (physical)</p>	<p>Enablement Environmental restructuring</p>
<p>Q.2.2.7 In women with breast cancer, who/what subgroups should have staging investigations performed (to detect metastases)?</p>	<p>In newly diagnosed patients with breast cancer who have symptoms suggestive of metastases, appropriate imaging investigations should be performed, regardless of tumour stage. 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. In newly diagnosed asymptomatic patients with breast cancer, use of staging imaging for metastatic disease is recommended for stage III and IV disease.</p>	<p>Represents a change to current practice with regard to imaging – unnecessary investigations potentially being carried out currently. Briefing/update sessions may be required for clinicians. Imaging should be reduced. Current practice.</p>	<p>Knowledge/implementation of EBM.</p>	<p>Motivation (reflective) Capability (psychological)</p>	<p>Education Persuasion Coercion Enablement Environmental restructuring</p>
<p>Q.2.2.8 In women with breast cancer who are being staged, what investigations should be performed?</p>	<p>In patients with newly diagnosed breast cancer who require staging, contrast enhanced CT (chest-abdomen-pelvis) and whole body isotope bone scan are recommended. PET-CT is not routinely recommended. However, it may be considered in specific cases.</p>	<p>Current practice.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>

Surgery

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.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?</p>	<p>Women with ductal carcinoma in situ who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy.</p> <p>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 dissection.</p>	<p>Current practice – trend for more BCS for patients with DCIS.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>
<p>Q.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?</p>	<p>Women with invasive breast cancer who are undergoing breast surgery should be offered the choice of breast conserving surgery and radiotherapy or mastectomy.</p>	<p>Current practice.</p> <p>Mammoplasty – contralateral procedure, additional admission required, small numbers.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>
<p>Q.2.3.3 In patients undergoing mastectomy for operable breast cancer (in situ or invasive), what is the evidence for prophylactic mastectomy?</p>	<p>In the general population, there is no evidence that a contralateral risk-reducing mastectomy (CRRM) improves a patient's prognosis. However, a CRRM 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.</p> <p>There are subsets of patients who may benefit from a CRRM, such as genetic mutation carriers.</p>	<p>Current practice in general.</p> <p>More extensive surgery. However, no follow-up imaging surveillance required (decrease in imaging).</p>	<p>Physician decision making using EBM.</p> <p>Social/media portrayal.</p>	<p>Opportunity (physical)</p> <p>Opportunity (social)</p> <p>Motivation (reflective)</p>	<p>Enablement</p> <p>Restrictions</p> <p>Education</p> <p>Environmental restructuring</p>

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.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?</p>	<p>A discussion regarding breast reconstruction should be undertaken with all patients undergoing mastectomy for breast cancer.</p>	<p>Current practice. Physician to discuss options with patients, however delayed reconstruction will result in two operations. Expander implants will result in two operations.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>
<p>Q.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 node metastases at initial diagnosis?</p>	<p>Patients with operable (invasive) breast cancer with no clinical or radiological evidence of axillary lymph node metastases at initial diagnosis should be considered for sentinel node biopsy. Q.2.3.6 – Good practice point only</p>	<p>Reduction in the need for second surgical procedure. Reduced ALND. Reduced upper limb morbidity. Less surgery and lymphoedema. Lower cost.</p>	<p>Change in physician surgical practice to newer less invasive surgical techniques.</p>	<p>Capability (physical) Motivation (reflective)</p>	<p>Education Training Enablement Persuasion</p>
<p>Q.2.3.7 What is the appropriate management of the axilla in patients with operable (invasive) breast cancer with sentinel node positive isolated tumour cells, micromets or macromets?</p>	<p>Patients with isolated tumour cells and micrometastases do not require an axillary clearance. 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.</p>	<p>Z0011 trial – if adopted – less burden on patient and on health system, less ALND.</p>	<p>Physician decision making using EBM.</p>	<p>Motivation (reflective) Capability (Psychological)</p>	<p>Education Persuasion</p>

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.3.8 For patients receiving breast conserving surgery and postoperative radiation therapy for ductal carcinoma in situ, what constitutes an adequate surgical margin?</p>	<p>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.</p>	<p>When surgical margins are not clear, surgical re-excisions may be required, necessitating additional admissions. Reduction in more radical surgery such as mastectomy and therefore also decrease in length of stay (LOS).</p>	<p>Physician decision making using EBM. Surgical technique.</p>	<p>Capability (physical) Motivation (reflective) Capability (Psychological)</p>	<p>Education Training Enablement Persuasion</p>
<p>Q.2.3.9 For patients receiving breast conserving surgery and postoperative radiotherapy for invasive breast cancer, what constitutes an adequate surgical margin?</p>	<p>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.</p>	<p>New evidence on surgical margins. Briefing/update sessions may be required for clinicians.</p>	<p>Change in surgical methods.</p>	<p>Motivation (reflective)</p>	<p>Education</p>

Medical oncology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.4.1 In premenopausal women with breast cancer: a) What is the evidence that adjuvant chemotherapy is effective? b) What is the optimal chemotherapy regimen?</p>	<p>Adjuvant chemotherapy should be considered for all patients with breast cancer whose disease is at moderate/high risk of recurrence.</p> <p>Adjuvant trastuzumab should be considered in all patients with HER2 positive breast cancer who receive adjuvant chemotherapy.</p> <p>The standard duration of treatment with trastuzumab is one year.</p> <p>Adjuvant trastuzumab should preferably be given concurrently with taxane based regimens. It should not be given concurrently with anthracyclines.</p>	<p>Current practice.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>
<p>Q.2.4.2 In premenopausal women 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, and d) What is the optimum duration of therapy?</p>	<p>Premenopausal women with hormone receptor positive breast cancer should be treated with tamoxifen.</p> <p>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.</p> <p>Currently, the routine use of adjuvant ovarian ablation/suppression is not considered standard practice.</p>	<p>Current practice in general. Demand led service.</p> <p>Increase in duration of medication to 10 years to be standardised.</p> <p>Patient adherence for longer duration.</p>	<p>Current medication, but duration may change for those not already on extended regimen.</p>	<p>Opportunity (physical)</p>	<p>Enablement Environmental restructuring</p>

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.4.3 In post-menopausal women with breast cancer that is ER+ and/or PR+:</p> <ol style="list-style-type: none"> What is the evidence that adjuvant hormone therapy is effective, What is the optimum endocrine agent, What is the optimum strategy of endocrine therapy, and What is the optimum duration of therapy? 	<p>Postmenopausal women with hormone receptor positive breast cancer should be treated with hormonal therapy for at least five years. The options include:</p> <ul style="list-style-type: none"> Tamoxifen for five years followed by five years of an aromatase inhibitor. An aromatase inhibitor as initial adjuvant therapy for five years. 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. <p>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.</p>	Current practice.	Current practice.	N/A	N/A
<p>Q.2.4.4 For women with breast cancer, what subgroups of patients would benefit from neoadjuvant systemic therapy and what is the optimum regimen?</p>	<p>Any patient who is a candidate for adjuvant systemic therapy can be considered for neoadjuvant systemic therapy.</p> <p>Neoadjuvant chemotherapy can be considered as part of a multimodal treatment approach for patients with stage IIa, IIb, & III breast cancer.</p> <p>For patients with locally advanced or inflammatory breast cancer, preoperative chemotherapy is the preferred option.</p> <p>Patients with HER2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab.</p> <p>Neoadjuvant endocrine therapy is an option for patients with ER positive breast cancer considered unsuitable for neoadjuvant chemotherapy or primary surgery.</p>	<p>Current practice.</p> <p>Results of neoadjuvant trials in HER2 positive disease have demonstrated improved pathological response rates using dual-targeted agents. This may alter clinical practice in the future.</p>	Current practice.	Opportunity (physical)	<p>Enablement</p> <p>Environmental restructuring</p>

Radiation oncology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.5.1 In breast cancer patients who have undergone a mastectomy (and axillary staging), what is the evidence that radiotherapy to the chest wall improves outcome?</p>	<p>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).</p> <p>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.</p>	Current practice.	Current practice.	N/A	N/A
<p>Q.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?</p>	<p>All patients with ductal carcinoma in situ having breast conserving surgery should be considered for adjuvant radiotherapy.</p>	Current practice.	Current practice.	N/A	N/A
<p>Q.2.5.3 In breast cancer patients who have undergone breast conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome and what is the optimal dose regimen?</p>	<p>Radiotherapy is recommended for all patients undergoing breast conserving surgery for early breast cancer.</p> <p>Hypofractionation schedules are recommended for patients with early breast cancer.</p>	<p>Currently being implemented.</p> <p>Shorter fractionation is as effective and also more convenient for patients. With shorter fractionation schedules, there is a potential for up to 30% decrease in usage of radiotherapy for breast.</p>	Physician decision making using (EBM)	<p>Motivation (reflective)</p> <p>Capability (Psychological)</p>	<p>Education</p> <p>Persuasion</p> <p>Coercion</p>
<p>Q.2.5.4 In otherwise healthy breast cancer patients 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? What are the outcomes for these patients?</p>	<p>In patients who have undergone breast conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations.</p>	Current practice.	Current practice.	N/A	N/A

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
<p>Q.2.5.5 In patients with breast cancer who have undergone breast conserving surgery, what is the evidence that a radiotherapy boost improves outcome?</p>	<p>In patients who have breast conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis.</p> <p>Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high grade invasive cancers).</p>	<p>Current practice.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>
<p>Q.2.5.6 In patients who have undergone surgery for breast cancer, what evidence is there that time from final surgery to starting a first adjuvant radiation therapy influences outcome?</p>	<p>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.</p>	<p>Current practice.</p> <p>A shorter defined time-to-treatment (<12 weeks) would have significant resource implications with no demonstrated benefits.</p>	<p>Current practice.</p>	<p>N/A</p>	<p>N/A</p>

***Capability** Psychological or physical ability to enact the behaviour.

Opportunity Physical and social environment that enables behaviour.

Motivation Reflective and automatic mechanisms that activate or inhibit behaviour.

Appendix 9: Summary of tools to assist in the implementation of the National Clinical Guideline

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

[Information for Health Professionals and Patient Information](#)

[NCCP GP Resources](#)

[NCCP Chemotherapy Protocols](#)

[NCCP Symptomatic Breast Service: Quality Assurance for Safer Better Healthcare](#)

The above literature is available on the NCCP website

[Health Information and Quality Authority \(HIQA\). National Standards for Safer Better Healthcare \(www.hiqa.ie\)](#)

[Centre for Evidence Based Medicine \(www.cebm.net\)](#)

[Improving Health: Changing Behaviour – NHS Health Trainer Handbook](#)

[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 10: 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:

<p>Radiology – axillary ultrasound (Clinical question 2.2.1)</p>
<p>Patients with a diagnosis of primary operable breast invasive cancer shall have an ultrasound of the axillary nodes</p>
<p>Numerator: The number of patients who were operated on for a primary invasive breast cancer and who had ultrasound of the axillary nodes</p>
<p>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</p> <ul style="list-style-type: none"> • 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]
<p>Surgery (Clinical question 2.3.8)</p>
<p>For patients having breast conserving surgery, the number of therapeutic interventions shall be recorded</p>
<p>Data variables</p> <ol style="list-style-type: none"> 1. Record all patients with a primary breast cancer (invasive or in situ) 2. Record all surgical procedures
<p>For patients with primary breast cancer who have breast conserving surgery, the number of therapeutic operations undertaken on the patient.</p> <p>Therapeutic interventions include</p> <ul style="list-style-type: none"> • 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
<p>Radiation Oncology – access (Clinical question 2.5.6)</p>
<p>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</p>
<p>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</p>
<p>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</p>

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 11: Budget impact assessment

Key message

This review of the literature on the economic evaluation of the diagnosis, staging and treatment of breast cancer and the budget impact analysis highlights potential economic consequences of the clinical guideline recommendations.

The report was compiled by:

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Economic literature review results

The Guideline Development Group (GDG) undertook a literature search for evidence of clinical and cost effectiveness, cost and resource impact, including primary (research studies) and secondary (reviews) sources. The literature sources searched are specified in the literature search strategy and include relevant resources, such as trial/guideline registries and relevant citation databases. The economic literature review was undertaken using the same search terms as derived from the clinical literature review (available as a separate document) but with an economic filter applied.

The results of this search were then filtered by focusing on studies carried out in countries where the population, costs and treatment were considered similar to the Irish setting. All papers included were subject to appraisal by a health economist and are deemed of acceptable quality unless otherwise stated.

Budget impact of National Clinical Guideline

For recommendations which affect resource requirements, the budget impact was calculated. Additional resources where required will be sought through the HSE service planning process.

The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed countries. In 2008, the worldwide cost of cancer due to premature death and disability (not including direct medical costs) was estimated to be US\$895 billion. This is not simply due to an increase in absolute numbers, but also the rate of increase of expenditure on cancer. Several drivers of cost, such as over-use, rapid expansion, and shortening life cycles of cancer technologies (such as medicines and imaging modalities), and the lack of suitable clinical research and integrated health economic studies, have converged with more defensive medical practice, a less informed regulatory system and a lack of evidence-based socio-political debate. (Sullivan et al., 2011)

"The cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost." (Sullivan et al., 2011)

Sullivan et al. (2011) believe that value and affordable cancer care can be introduced into the cancer policy lexicon without detracting from quality, and that the management tools,

evidence, and methods are available to affect this transformation across all developed countries.

A recent population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer was estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million. Drug expenditure accounted for a further €127 million, while primary, outpatient and emergency care were estimated at €32 million, €30 million and €13 million, respectively. Across the EU, healthcare costs per person were estimated to cost between €2 and €29 for breast cancer (€15 per person in Ireland) (Luengo-Fernandez et al., 2013). With cancer incidence expected to increase by 99% by 2040 (NCRI, 2014b), there could be a significant increase seen in healthcare costs per person in Ireland. The cost of breast cancer related informal care and productivity losses were estimated at €3.2 billion and €3.25 billion, respectively (Luengo-Fernandez et al., 2013).

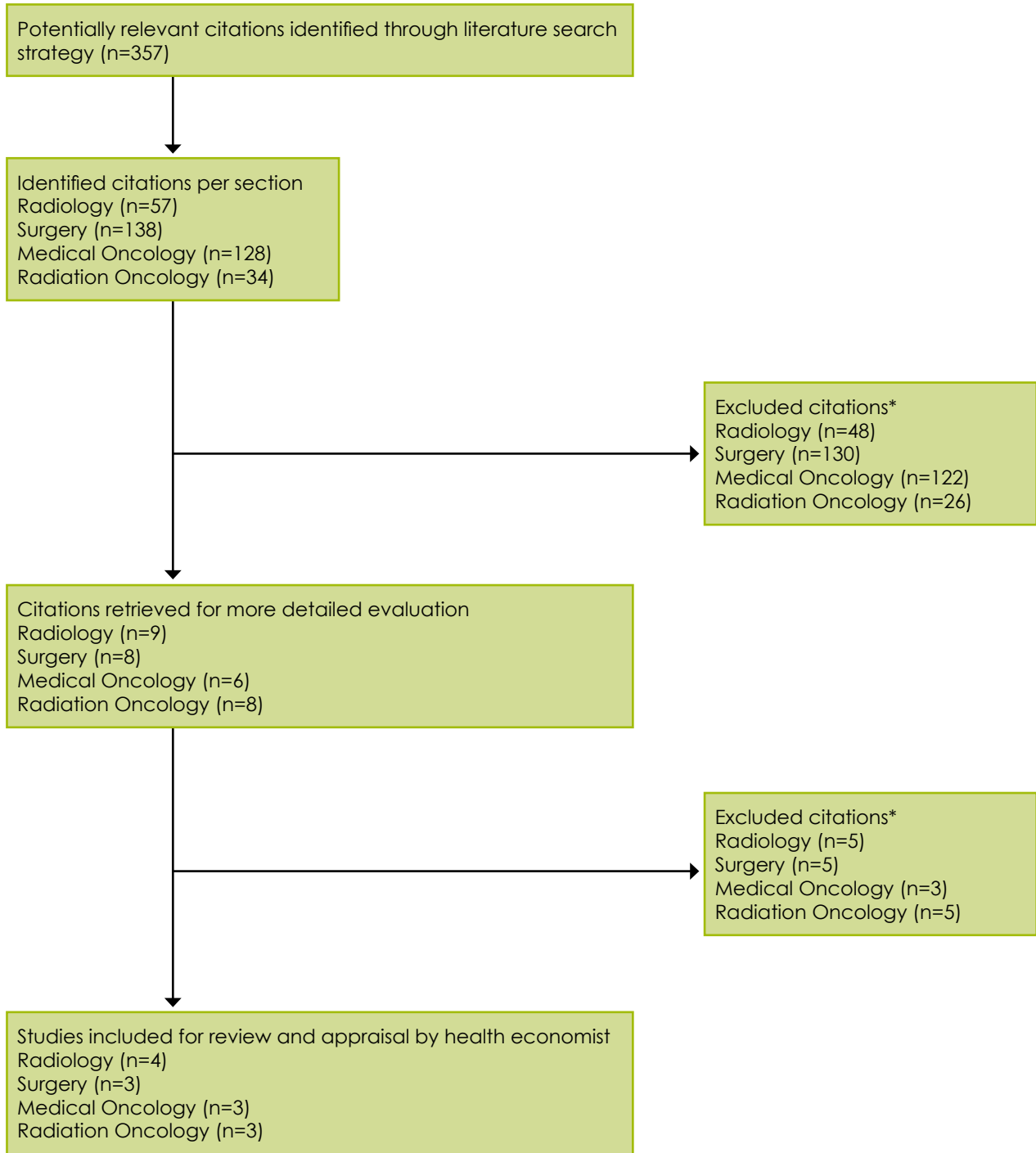
Methods

The search strategy for economic literature is based on the search used in the clinical literature review, with the addition of a SIGN economic studies filter for Medline (Table 10) including the Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database (EED), Health Technology Assessment Database, the Cochrane Library, and Google Scholar.

The estimated costs per quality adjusted life year (QALY) or life years gained (LYG) given in the following summaries are those reported within each study for the given year and national currency. These cost-effectiveness ratios have been complemented in brackets by euro estimates to correct for the exchange rate, purchasing power parity (PPP) between countries and health inflation to 2013 costs as per the Health Information and Quality Authority's Economic Evaluation Guidelines (HIQA, 2014).

The following summaries report the conclusions regarding cost-effectiveness made by the authors of the reviewed literature. It is important to note that the thresholds of cost-effectiveness in other countries differ from that in Ireland and that statements of cost-effectiveness made in another context therefore may not be applicable to Ireland. While Ireland has no explicit cost-effectiveness threshold for non-drug interventions, cost-effectiveness ratios falling within the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland.

Despite the conversion of the reported costs to PPP-adjusted 2013 euro values it is also important to remember that there may still be a number of other factors which mean that cost-effectiveness ratios from other countries are not necessarily directly applicable to the Irish setting. For example, Ireland's discount rate is higher than that applied in the UK, so many interventions assessed in the UK would have less favourable ratios if the Irish discount rate was applied. Similarly, some analyses are conducted from the societal perspective and may account for more benefits than are considered in Irish cost-effectiveness analyses (CEAs), which only account for costs to the health sector. Accordingly, the euro-adjusted ratios reported here should be only be considered broadly indicative of the level of cost-effectiveness rather than precisely adjusted estimates for the Irish health system.



***Inclusion criteria**

- Cost utility model
- Applicable to the Irish healthcare system
- Applicable to patient population
- English Language
- Clinically relevant outcomes
- Relevant to guideline recommendations

***Exclusion criteria**

- Not a cost effectiveness study
- Not in English language
- Methodological or quality issues
- Not applicable to Irish healthcare system
- Applicable to patient population
- Not relevant to guideline recommendations

Figure 5 Economic literature review results

Table 10 Economic literature review protocol (SIGN)

ID	Search
1	Economics/
2	"costs and cost analysis"/
3	Cost allocation
4	Cost-benefit analysis/
5	Cost control/
6	Cost savings/
7	Cost of illness/
8	Cost sharing/
9	"deductibles and coinsurance"/
10	Medical savings accounts/
11	Health care costs/
12	Direct service costs/
13	Drug costs/
14	Employer health costs/
15	Hospital costs/
16	Health expenditures/
17	Capital expenditures/
18	Value of life/
19	Exp economics, hospital/
20	Exp economics, medical/
21	Economics, nursing/
22	Economics, pharmaceutical/
23	Exp "fees and changes"/
24	Exp budgets/
25	(low adj cost).mp.
26	(high adj cost).mp.
27	(health?care adj cost\$).mp.
28	(fiscal or funding or financial or finance).tw.
29	(cost adj estimate\$).mp.
30	(cost adj variable).mp.
31	(unit adj cost\$).mp.
32	(economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw.
33	Or/1-32

Section I Economic literature appraisals**Radiology****PET and MRI for the assessment of axillary lymph node metastases in early breast cancer**

A high quality study (Cooper et al., 2011) considered the use of MRI and PET both with and without CT as adjuncts or alternatives to SLNB or four node sampling (4-NS) for the identification of axillary metastases in women with breast cancer. The analysis is conducted from the perspective of the UK NHS. The report features an extensive systematic review of test performance of the alternative strategies. It also features a cost-effectiveness model, the specification and results of which are reported to a very considerable level of detail.

The level of detail in the literature search and model description conveys an impression of a high quality analysis that is well informed by a broad range of data sources. As such this appears to offer a very good standard of evidence.

The cost-effectiveness analysis considers PET and MRI alternatives to SLNB and 4-NS in two separate analyses using SLNB and 4-NS as the base case in each, rather than considering all alternatives together in one comparison. The results present an interesting finding that PET alone or MRI alone would both outperform SLNB and 4-NS in terms of both costs and effects. The analysis indicates that from a solely cost-effectiveness perspective MRI alone would clearly be the preferred strategy, as it is markedly more effective than any of the other strategies considered and less expensive than any strategy involving SLNB or 4-NS.

Despite the apparently clear evidence in favour of MRI over SLNB or 4-NS, the report notes that replacing surgical node examination with imaging is not likely to be clinically acceptable. The principal benefit of imaging in this context is that it leads to fewer adverse events, including those with long lasting effects, but that this has to be traded-off against inferior test sensitivity and specificity, resulting in both more false positives and negatives. This inferior test performance increases the chance of both the disease being missed and unnecessary interventions being performed due to false negatives. So although imaging is expected to have a lower health burden on the whole population on aggregate, as some individuals will have markedly worse clinical outcomes this leads the authors to exclude both MRI and PET only strategies from their primary analysis.

The primary analysis considered MRI and PET in conjunction with SLNB or 4-NS as opposed to SLNB or 4-NS alone. In the imaging plus node sampling diagnostic pathway patients initially receive MRI or PET imaging. If positive they proceed directly to axillary lymph node dissection (ALND). If negative they then receive either SLNB or 4-NS.

The results of the restricted cost-effectiveness analysis in which the imaging only strategies are included find only very small additional clinical benefit of using MRI or PET. Adding MRI may be a cost-effective strategy, as additional MRI before SLNB has an incremental cost-effectiveness ratio (ICER) of £2,500/QALY (€3,900). However, adding MRI before 4-NS does not appear cost-effective with an ICER of £49,000/QALY (€77,800/QALY). Adding PET to SLNB or 4-NS clearly appears not cost-effective with ICERs of £647,000/QALY (€1,028,000/QALY) and £1,200,000/QALY (€1,905,700/QALY) respectively. The interpretation of the likely cost-effectiveness of these strategies does not change when if the euro adjusted estimates are compared to the Irish threshold range.

Although there is mixed evidence regarding the use of MRI in addition to surgical sampling it should be recognised that the estimated difference in costs and effects of adding MRI are small and subject to considerable uncertainty. Consequently, it is not possible to reach strong conclusions positive or negative regarding the cost-effectiveness of MRI as an adjunct to

surgical sampling. Despite this, the estimated difference in cost per patient is small, so even if adjunctive MRI is cost-ineffective it is unlikely to waste a large amount of resources.

A second study (Meng et al., 2011) also from a UK NHS perspective demonstrated that the use of all four alternative imaging strategies (replace SLNB with MRI, replace SLNB with PET, add MRI before SLNB, add PET before SLNB) is expected to bring improved health benefits relative to the use of SLNB alone. The four imaging strategies are to either complement or replace SLNB with either MRI or PET imaging. The health gains are estimated to be small for the most part, although the gains of replacing SLNB with MRI are greater. Adding imaging to SLNB will increase costs, while replacing SLNB with imaging will reduce costs. Like the changes in health effects, the changes in costs are small relative to overall costs.

Overall, the preferred strategy on the basis of cost-effectiveness is that MRI should replace SLNB, as this is the most effective and least costly strategy of all. Furthermore, it generally seems that using imaging instead of SLNB will be more efficient than using it as well as SLNB. However, the modest differences in costs and health effects between the strategies and the uncertainty in the results mentioned by the authors indicate that there is a lack of strong evidence to consider any one strategy to be far more efficient than another. Consequently, the study quite reasonably suggests that the choice of the diagnostic pathway could be determined by clinical concerns rather than cost-effectiveness considerations.

As disaggregated model predictions are not presented or explained, there is a lack of clarity on how alternative strategies impacted on the costs and health effects. In particular, how the reduction in lymphoedema is traded off against increased risk of metastatic disease when imaging is used to replace SLNB is unclear. Similarly, it is not sufficiently clear whether the primary health burden of SLNB is from the intervention itself or subsequent ALND for positive cases. It is not fully clear where the health benefits of replacing SLNB by MRI are realised. This issue is relevant, as much of the possible benefits of adding MRI or PET imaging to diagnostic strategies may not be realised if many MRI or PET negative women still receive SLNB. Furthermore, the study emphasises the degree of uncertainty in the results of the analysis, but the presentation of the uncertainty analysis is insufficiently clear to illustrate this. This lack of disaggregation of the results does not necessarily indicate that the study is of low analytic quality, but rather is it possibly of limited usefulness to decision makers wishing to weigh up the consequences of alternative forms of treatment.

Although the evidence suggests that replacing SLNB with MRI imaging would be an improvement in cost-effectiveness, there does not appear to be very strong evidence for changing clinical practice. That the replacement of SLNB with MRI imaging is likely to lead to more women developing metastatic disease due to lower test sensitivity means more evidence may be required to justify such a change in the diagnostic pathway.

PET and PET-CT for the diagnosis of breast cancer recurrence

A high quality study (Auguste et al., 2011) investigated the cost-effectiveness of diagnostic strategies for women with a prior history of breast cancer who are at risk of disease recurrence. Conventional diagnostic work-up used in the study setting of the UK NHS includes conventional radiography, computed tomography, ultrasonography and bone scintigraphy. This study investigates the use of three alternatives of conventional workup alone of PET, PET-CT and combined conventional workup and PET-CT. The study includes a systematic review of the literature and a model based CEA reporting the costs per QALY.

The systematic review found no relevant studies directly relating to breast cancer. The CEA model used in the analysis combined existing estimates of the test performance of the diagnostic alternatives with the anticipated treatment outcomes of the detection of disease and diagnostic and treatment costs. The estimates of costs and effects of treatment used in this

analysis are taken from a prior study under the assumption that the most cost-effective treatment strategy is followed. These treatment costs and effects are applied to women anticipated to be either true or false positive and true or false negative after diagnostic work-up.

The results find that conventional work up, PET, PET-CT and PET-CT + conventional work-up combined all lie on the cost-effectiveness efficient frontier, meaning that all are possibly rational strategies and that the optimal choice depends on the willingness to pay for health gain. In ascending order of costs and effectiveness, the strategies are as follows; conventional work-up, PET, PET-CT and PET-CT + conventional work-up. The ICERs of PET, PET-CT and PET-CT + conventional work-up are £29,300/QALY (€37,800/QALY), £31,000/QALY (€40,000/QALY), and £42,100/QALY (€54,300/QALY). The report interprets these ICERs relative to a threshold of £20,000 and concludes that the strategies involving PET are not cost-effective.

Overall this report provides a relatively clear modelling demonstration of the anticipated cost-effectiveness of alternatives to conventional work-up in the detection of breast cancer recurrence. The authors interpret their ICER results relative a cost-effectiveness threshold of £20,000/QALY. NICE has an explicit threshold range of £20-30,000/QALY and so some of the PET strategies could justifiably be considered cost-effective or marginally so at the upper bound. Furthermore, although the combined PET-CT + conventional work-up strategy has an ICER exceeding the upper bound of the threshold, it does not exceed it greatly. Accordingly, none of the PET strategies considered are grossly cost-ineffective given the UK threshold. Similarly, interpreting the euro adjusted ICER estimates with respect to the Irish threshold of €45,000/QALY indicates that the first two efficient strategies or PET and PET-CT would be cost-effective and the third strategy of PET-CT + conventional workup would not exceed the threshold by a gross margin.

An important caveat to note is that the cost-effectiveness estimates are made on the basis of the assumption that subsequent treatment is itself cost-effective. These results could change if post-diagnostic treatment is not cost-effective. It is difficult to anticipate how the cost-effectiveness of diagnostics would change in response to down-stream cost-ineffective treatment. In particular, the cost-effectiveness of some diagnostic strategies could improve, while others could diminish. Consequently, there are difficulties in extrapolating the results from the UK setting to Ireland where treatment may be different from what was assumed in this analysis.

Contrast-enhanced high field MRI in women with primary breast cancer scheduled for wide local excision

A high quality study (Turnbull et al., 2010) of a trial using MRI to guide the localisation of breast cancer tumours with an aim of improving wide local excision (WLE) to reduce the reoperation rate was identified. The trial analysis also features an economic evaluation based on the trial results. This economic evaluation is based on the health related quality of life and cost differences of using MRI to aid WLE and not using MRI. The randomised trial involving approximately 1,600 participants at 45 UK hospitals found no difference in the primary end point of the reoperation rate. The economic analysis found no difference in the health related quality of life between the MRI and no MRI arms and no statistically significant difference in costs. Consequently, the authors concluded that the use of MRI as an additional procedure to aid tumour localisation for WLE was likely to impose extra health costs for little or no benefit and so the additional imaging is not necessary.

This study offers good evidence of the lack of additional effectiveness of adding MRI to aid WLE. In addition to this directly observed trial finding of no reduction in the reoperation rate the report also finds no health related quality of life benefits either. Although the report does not find a statistically significant difference in costs between the two arms it can be expected that using MRI will impose additional costs in actual use. Consequently, the conclusion is clear from a cost-effectiveness perspective that MRI is not justified.

Relevance to the guideline recommendations

In summary, it is not possible to reach strong conclusions, either positive or negative, regarding the cost-effectiveness of MRI as an adjunct to surgical sampling (Question 2.2.4).

The evidence suggests that replacing SLNB with MRI imaging would be an improvement in cost-effectiveness. However, there does not appear to be very strong evidence for changing clinical practice (Question(s) 2.2.4, 2.2.5).

None of the PET strategies for the detection of breast cancer recurrence considered above are grossly cost-ineffective (Question(s) 2.2.7, 2.2.8).

Use of MRI to aid tumour localisation for WLE is likely to impose extra health costs for little or no benefit and so the additional imaging is not necessary (Question 2.2.4).

Implementation of the guideline recommendations on staging investigations will result in an overall reduction in imaging. A reduction in staging investigations for stage I and II represents 71% of breast cancers (approx 1,991 cases/yr). This represents a potential saving of up to €940,757.50 per annum.

Surgery

Sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer

One high quality study (Verry et al., 2012) was identified. This paper compared two diagnostic procedures for women with suspected breast cancer; sentinel lymph node biopsy and axillary lymph node dissection from the perspective of the Australian health system. SLNB carries a lower burden of morbidity both immediately due to less invasive surgery and in the longer term due to reduced incidence of lymphoedema. However, SLNB carries a higher risk of false positives in the detection of disease. Consequently, using SLNB instead of ALND trades-off reduced intervention-induced morbidity against increased risk of excess morbidity and mortality due to the recurrence of disease. The study uses a cost-utility simulation model to explore the differences between the two methods. They find the less invasive procedure of SLNB yields greater QALYs and has less overall cost, and so dominates ALND. However, the authors note that the per-woman difference in terms of costs and effects is small, SLNB yields an additional 0.0082 QALYs over 20 years of model follow-up and a cost saving of AUS \$880 (€570).

The study is a well written analysis with a comprehensive description of the model. The authors conducted a comprehensive sensitivity analysis to see what factors influence the choice of which strategy is optimal.

The authors are correct to draw attention to the small differences in costs and quality of life estimated between the two procedures. The additional QALY gain of SLNB equates to just an additional 3 days of good health per patient over 20 years of analysis. Similarly, the cost savings of SLNB are small in both absolute terms and proportional to overall treatment costs. Consequently, if the results of the analysis are correct, there is virtually nothing to choose between these two interventions on the grounds of cost-effectiveness. Accordingly, there appears to be no substantial concerns from a cost-effectiveness perspective of the choice of diagnostic procedure to remain a choice for patients and clinicians. Indeed, the appropriate choice may largely depend on each individual patient's risk preference in the choice in the trade-off between reduced morbidity and increased risk of mortality implied by choosing SLNB over ALND.

Contralateral risk reducing mastectomy

Zendejas et al. (2011) used a simulation model to compare contralateral risk reducing mastectomy (CRRM) and annual mammographic surveillance for women with a prior breast cancer in the setting of the US.

The study reports cost-effectiveness estimates for 7 age subgroups starting at age 45 and increasing by 5 year increments to age 75. It finds that CRRM is both more effective (21.22 vs. 20.93 QALYs) and, for most age groups, is cost-effective (ICER \$4,900/QALY) compared to annual mammography. It finds the cost-effectiveness of CRRM declines with age, with the ICER estimate for women aged 45 being \$4,900/QALY (€4,900/QALY), rising to \$28,200/QALY (€28,100/QALY) for women aged 65 and \$62,800/QALY (€62,500/QALY) for women aged 70. As such, the ICERs for women under 65 are well within a notional cost-effectiveness threshold of \$50,000/QALY, but the ICERs for women aged 70 and 75 exceed this threshold. The same conclusion that CRRM is cost-effective for women aged 65 and under but not for those 70 and over applies if the Irish threshold range is applied to the euro adjusted estimates. In a subgroup analysis the study also finds that CRRM is likely to dominate mammographic surveillance (i.e. be more effective and less costly) in higher risk women who carry BRCA 1/2 genes.

Overall, this appears a good quality study compromised by one key methodological defect. The study applies discounting to costs but not to health effects. It is widely recognised in cost-effectiveness analysis that discounting should be applied to both costs and effects. The

application of discounting means that the present value of costs and health effects that occur in the future is less than if they occurred in the present. Undiscounted cost-effectiveness results are generally more favourable, as the value of future health gains have not been adjusted downwards by discounting. Therefore the failure to discount appropriately in this case is a considerable weakness of the analysis. It is difficult to anticipate exactly how the results would change had the discounting been applied appropriately, but it can at least be safely assumed that cost-effectiveness would be worse than reported. However, the ICERs of prophylactic mastectomy are so low (below \$20,000/QALY or €15,000/QALY) for women aged under 60 it is quite possible that the intervention would still be cost-effective if discounting was applied to health effects. Had the discounting been done correctly the age at which breast removal is no longer cost-effective is likely to be younger than the age of 70 reported.

A notable limitation of this study is acknowledged in the discussion that it does not consider the costs (or health benefits) of breast reconstruction in the case of removal. This appears a considerable omission from the model, as it is likely that a not inconsiderable portion of women will opt for reconstruction following mastectomy. How the inclusion of the additional costs and potential QALY gains of breast reconstruction would change the study's conclusions is not clear.

A finding not explored by the authors in the discussion is that the cost of the two interventions is not greatly different (\$35,594 CRRM, \$35,182 surveillance). Consequently, based on this analysis there is unlikely to be a considerable difference in budget impact between the two alternatives. Therefore, it seems there is unlikely to be any grave consequences for healthcare resources if the decision to opt for CRRM over mammography surveillance remains the choice of patients in consultation with their clinicians. However, this conclusion may well be different if the surveillance strategy adopted in practice is more intensive than that modelled here. For example, surveillance strategies involving MRI in addition to mammography are likely to be more expensive, which would make CRRM more cost-effective.

Alternative methods of breast reconstruction surgery

One study (Grover et al., 2013) was identified which compared five alternative methods of breast reconstruction. This analysis only considered costs and effects over a one year period, which was considered too short to account for the consequences of the intervention, and so this paper was rejected from this review.

Relevance to the guideline recommendations

In summary, there appears to be no substantial concerns from a cost-effectiveness perspective, if the option of ALND and SLNB as diagnostic procedures remains a choice for patients and clinicians (Question(s) 2.3.5, 2.3.6, 2.3.7).

Similarly, there is unlikely to be any substantial consequences for healthcare resources if the decision to opt for CRRM over mammography surveillance remains the choice of patients in consultation with their clinicians (Question 2.3.3).

Implementation of the guideline recommendations will result in a decrease in annual imaging. While the cost of CRRM and annual mammography has been shown to be similar in the USA, Zendejas et al. (2011) found that CRRM is cost-effective with better patient outcomes when compared to annual mammography.

Medical oncology

Adjuvant trastuzumab for HER2/neu-positive T1bN0 breast cancer

One analysis was identified (Skedgel et al., 2013) which aimed to estimate the probability that trastuzumab (Herceptin®) is cost-effective in HER2 positive women with small node negative tumours in a Canadian setting. They use a simulation model to estimate the probability of cost-effectiveness of different trastuzumab treatment regimens in different age groups of women over a range of disease recurrence risk rates. The study considers concurrent and sequential trastuzumab and chemotherapy treatment, whereby trastuzumab is delivered at the time of chemotherapy or afterward respectively.

The findings indicate that the probability of cost-effectiveness increases with the rate of disease recurrence and diminishes with age. For women aged 40, 50 or 60 there was a probability of cost-effectiveness greater than 50% at higher rates of disease recurrence relative to a threshold of CAN\$100,000/QALY (€73,000/QALY). Women over 70 did not achieve a 50% or greater probability of cost-effectiveness relative to the threshold over all the incidence rates considered in the analysis. In all cases the probability of cost-effectiveness was lower with sequential rather than concurrent treatment.

The model description in this study is satisfactory, but the presentation of results makes interpretation difficult. The study does not report the estimated costs and effects of the treatment strategies or the resulting cost-effectiveness ratios. Rather, it reports the outcome of a probabilistic sensitivity analysis (PSA) of the probability of cost-effectiveness at one cost-effectiveness threshold. The reporting of the probability of cost-effectiveness gives little insight into what the cost-effectiveness might be and whether it would be cost-effective at thresholds lower than the relatively high threshold of CAN\$100,000/QALY used in the analysis. Furthermore, it is not clear how the reported probabilities relate to an appropriate cost-effectiveness decision rule. While it is implied within the study that a 50% probability of reaching the threshold is evidence of cost-effectiveness this is not explained or justified.

The study presents the results of the PSA over a range of probabilities of disease recurrence. Since it is not clear what range of rates of recurrence might be most representative the study provides little clear indication whether or not the treatment is likely to be cost-effective. Consequently, applying the findings to other settings would require careful judgement on the risk of disease recurrence in that context.

The findings that the cost-effectiveness of trastuzumab declines with age and that it is less likely to be cost-effective when delivered sequentially than concurrently are reasonably clear findings. However, it is not clear if sequential treatment is more or less costly than concurrent therapy. Overall, while this study presents a reasonable model, the unusual presentation of the results precludes it as being a useful guide to the likely cost-effectiveness or otherwise in other settings.

Endocrine therapy in the adjuvant setting for postmenopausal patients with hormone receptor-positive breast cancer

A high quality study (Lux et al., 2011) used a model simulation to compare anastrozole and letrozole, two aromatase inhibitor treatments as alternatives to tamoxifen for the treatment of hormone receptor positive breast cancer in the context of the German healthcare system. The study not only considers the two treatments at their full market price but also considers three price reductions of 75%, 50% and 25% to anticipate how cost-effectiveness might change as patents expire and the drugs become cheaper.

The simulation analysis finds that both anastrozole and letrozole are more effective than tamoxifen, with letrozole being considerably more effective relative to anastrozole. The results

show that at the full market price letrozole has an ICER of €29,400/QALY (€27,100/QALY) relative to tamoxifen. Although there is no explicit cost-effectiveness threshold in Germany the authors conclude that letrozole is cost effective. The PPP adjusted ICER falls within the Irish threshold range and so would be considered cost-effective in an Irish context.

The report's consideration of price changes of the two treatments indicates that letrozole will be increasingly cost-effective as its price falls. The report indicates that the price of anastrozole would have to fall to 25% of its full price before it would be considered cost-effective when compared to tamoxifen. As such, the report is a clear endorsement of letrozole and a strong indication that anastrozole is an inferior treatment that would require significant price reductions to be considered cost-effective.

Letrozole is estimated to be the most effective treatment and is likely to be cost-effective too.

John-Baptiste et al. (2013) performed a review of published CEAs of aromatase inhibitors (AIs) in the treatment of early stage breast cancer. Accordingly, this addresses a similar research question as that of Lux et al., although this review is not looking at the cost-effectiveness in the context of any one particular country and is specifically looking at treatment for early stage disease. The review assessed 18 relevant studies in depth. The primary comparisons were between either anastrozole or letrozole compared to tamoxifen. The authors extracted the costs and effects from the reviewed studies, converted costs to a common currency in a common year (2010 US dollars).

The review considered interventions with ICERs of less than \$100,000/QALY (€75,000/QALY) to be cost-effective. All but one of the reviewed studies reported ICERs for both AIs to be within this threshold. Ten of the 18 studies found at least one of the AIs to have ICERs under a threshold of \$50,000/QALY (€37,500/QALY). The evidence from the reviewed studies provide some indication that letrozole is more cost-effective than anastrozole. The reported evidence also indicates that both treatments are roughly equivalent in effectiveness. Overall, the reported cost-effectiveness estimates of the reviewed studies indicate that AIs have good potential for being cost-effective relative to tamoxifen. At the very least, the reported estimates indicate that AIs are not likely to be grossly cost-ineffective.

The authors note that that the reviewed CEAs assume an overall survival benefit for AIs that has not been demonstrated in trials. Furthermore, they note that both tamoxifen and AIs can have adverse effects. They raise the concern that the adverse effects particular to AIs have not been adequately assessed in the reviewed CEAs. Consequently, they raise the concern that the cost-effectiveness estimates may be unjustifiably favourable to AIs. Similarly, they raise the concern that the lack of subgroup analyses in the reviewed studies may limit the applicability of the findings.

This review appears to be a high quality and comprehensive assessment of the cost-effectiveness of AIs for the treatment of early stage breast cancer. The review process is well described. A wide range of quality indicators are recorded. The authors have demonstrated what appears to be a good understanding of the clinical context of the disease and what factors are relevant to the correct assessment of the intervention. The results of the review are well presented and the possible limitations of the existing literature are clearly explained.

One possible shortcoming of the review is the failure to consider the incremental cost-effectiveness of the two AIs in analyses that assessed both letrozole and anastrozole. An incremental comparison between both AIs and tamoxifen might not always conclude that both AIs are cost-effective.

Regarding the relevance for the provision of AIs in Ireland, the review shows that more than half of the published CEAs find ICERs that are likely to be cost-effective given the upper bound of

the Irish threshold range of €45,000/QALY. Moreover, the published evidence suggests that AIs are not likely to be grossly cost-ineffective, as all but one of the reviewed studies reported ICERs within the \$100,000/QALY (€75,000/QALY) threshold. However, the review indicates that there are fundamental concerns regarding the assumed survival estimates, raising considerable doubt over the validity of the published ratios. Therefore, the evidence showing AIs to be cost-effective cannot be considered undisputed.

Routine Oncotype DX[®] testing of women with node negative or pN1mi, ER positive breast cancer

A high quality study (Holt et al., 2013) was identified by the economic literature search. This study was inadvertently included in the literature sent to the health economist for appraisal. As this guideline does not cover the use of 21 gene recurrence score, this study has been omitted.

The use of Oncotype DX[®] for gene expression profiling to support chemotherapy decision making was recommended by the NCCP Technology Review Committee in August 2011 in line with eligibility guidelines drafted by the Irish Society of Medical Oncology.

Information on Oncotype-DX[®] gene expression profile and chemotherapy decision-making in patients with early stage breast cancer is available on the NCCP website.

Relevance to the guideline recommendations

In summary, the findings that the cost-effectiveness of trastuzumab declines with age and that it is less likely to be cost-effective when delivered sequentially rather than concurrently are reasonably clear findings. However, it is not clear if sequential treatment is more or less costly than concurrent therapy (Question 2.4.1).

As an alternative to tamoxifen and compared with anastrozole, letrozole is estimated to be the most effective treatment and is likely to be cost-effective (Question 2.4.3).

Regarding the relevance for the provision of AIs in Ireland, more than half of the published CEAs find ICERs are likely to be cost-effective given an Irish cost-effectiveness threshold of €45,000/QALY. However, there are fundamental concerns regarding the assumed survival estimates, raising considerable doubt over the validity of the published ratios. The evidence showing AIs to be cost-effective cannot be considered undisputed (Question(s) 2.4.2, 2.4.3).

Some costs of treatment could be reduced if patients were prescribed the most cost-effective treatment (tamoxifen).

Radiation oncology

Internal mammary and medial supraclavicular lymph node radiotherapy

Lievens et al. (2005) compared the costs and effects of post-operative radiotherapy (RT) of the internal mammary and medial supraclavicular lymph node chain (IM-MS) for women with breast cancer in a Belgian context. The study notes that at the time of the analysis there was no statistically significant trial evidence of the effectiveness of RT of the IM-MS. While a large trial had been commissioned to determine any differences, the results were not yet available, so a modelling approach was used instead.

The model simulates women following surgery for stage I to III breast cancer. The model accounts for the side effects of RT, including cardiovascular morbidity. The costs in the model include societal costs of patient travel, but no costs for foregone wages or lost economic productivity have been included. The modelled effectiveness of IM-MS RT is informed by assumptions based on the results of previous RT trials, although not specifically trials comparing IM-MS RT to RT restricted to other relevant anatomical sites. The model uses a 20 year time horizon to capture long term costs and effects.

The primary results of the study are that RT of the IM-MS is more effective and cost saving. As such, it dominates no intervention and would be cost-effective at any threshold. This result that RT is cost-saving stems from the model assumption that the initial costs of RT are more than offset by reduced costs of care through avoided relapse cases. A sensitivity analysis finds this result to be robust under a range of alternative parameter assumptions. While the primary result of dominance could change if the costs of RT and relapse rate are varied, these costs would have to vary widely from what are considered plausible estimates.

Overall, this study appears well researched and written. The model description is largely clear and the assumptions and data sources are justified for the most part. However, there is one significant weakness of this study which calls its results into question. The improved survival and reduced relapse of IM-MS RT are based on assumptions justified by data from trials not specifically assessing IM-MS RT. The relevance of trials of RT not specifically directed at the IM-MS region is unclear. The methods used to extract relevant assumptions from this trial were also not clear. Since the primary findings of the model of improved effectiveness and reduced cost rely on these assumptions the results of this study cannot be considered reliable evidence.

Hypofractionation

There is currently a paucity of evidence on the cost effectiveness of the emerging area of hypofractionation in breast cancer. One study (Min et al., 2014) was identified which gave a brief cost analysis based on US Medicare reimbursement data. The study considered the clinical outcomes and treatment costs of a cohort of women with early stage breast cancer offered a hypofractionated radiotherapy regimen. The authors identified previous trial evidence comparing the effectiveness of 16 daily radiotherapy doses relative to a standard regimen of 25 daily doses with follow-up over ten years. This previous study found no difference in effectiveness. This study assesses the same hypofractionated regimen in a patient cohort on the basis of 3 years of observation.

While the study did not include a control arm undergoing the standard treatment, the study states the outcomes were comparable with historical controls, indicating that hypofractionated radiotherapy is not less effective. The study also reports the estimated costs of radiotherapy for both the hypofractionated regimen provided and an estimate had the standard regimen been applied. The cost estimate of the hypofractionated treatment is markedly lower than standard regimen. Thus, the report concludes that hypofractionated radiotherapy appears to have promising outcomes and favourable costs.

This analysis does not present a full cost-effectiveness or cost-minimisation analysis, but does present some evidence on the likely cost reduction that the authors anticipate to realise from hypofractionated radiotherapy. The report does not contain a controlled comparison of effectiveness or costs between alternatively fractionated regimens. Notably the report does not make strong claims of equal effectiveness between the regimens, but rather makes qualified statements on the likely relative performance. Accordingly, this study cannot be considered strong evidence that hypofractionated radiotherapy will necessarily be equally effective and cost saving. Despite this, the evidence both from the study's own findings and those cited within its literature review indicates that hypofractionated radiotherapy may be equally effective and is likely to have lower treatment costs in a US context. While we should be cautious about assuming that findings regarding the US health system apply equally to Ireland, it might be reasonable to assume that any costs savings in an Irish system would be more modest, as the overall cost of care is generally expected to be lower in Ireland. This study should be considered broadly supportive of hypofractionated radiotherapy from a cost-effectiveness perspective.

Radiation therapy among older women with favourable-risk breast cancer

Sen et al. (2014) notes that while radiation therapy has proven survival benefits it is less clear how great these benefits are to older women with breast cancer, in part because disease is more likely to be indolent. Consequently, there have been recommendations that older women with lower risk disease could be spared radiation therapy. Despite this, radiation therapy remains widely used in older age groups, prompting concerns of overuse. In light of this, Sen et al. considers the cost-effectiveness of external beam radiation therapy (EBRT) and newer intensity modulated radiation therapy (IMRT) in a US context. The study considers three age bands of women aged 70-74, 75-79 and 80-94. The study considered the ICERs of the two strategies relative to the two threshold values commonly cited in the US of \$50,000 and \$100,000/QALY (€37,500 and €75,000/QALY respectively).

The results show that EBRT is estimated to be beneficial to women of all ages considered in the analysis and that IMRT is considered to be even more effective in all age groups. The ICER of EBRT in women aged 70-74 is \$38,300/QALY (€28,300/QALY), rising to \$55,800/QALY (€37,700/QALY) for women aged 80-94. The ICERs of IMRT for the same two age groups are \$77,100/QALY (€71,400/QALY) and \$110,500/QALY (€76,400/QALY). Thus the results indicate that the cost-effectiveness of both modalities deteriorates with age and that EBRT is likely to be considered a cost-effective intervention and that IMRT is only cost-effective in younger groups and at the higher threshold. However, the results indicate that neither intervention would be grossly cost-ineffective given a maximum willingness to pay of \$100,000/QALY. Using the Irish threshold of €45,000/QALY and the euro adjusted estimates, EBRT appears cost-effective for both age groups, while IMRT does not.

This study appears to be a well-documented model based analysis. The clarity of reporting and sound model description lends confidence to the results. Considerable effort has been made to use real population data in the estimation of costs and health effects. One aspect of the model that is noted in the analysis is the inclusion of only a ten year model horizon. While this is unlikely to make a difference for the oldest cohort of women considered in the study, it could mean that the estimates for younger women are somewhat conservative and both interventions may be somewhat more cost-effective than estimated.

The analysis does mention that brachytherapy is another treatment alternative that could be considered. While the analysis does consider the cost of brachytherapy, its cost-effectiveness is not presented. It notes that trials are still ongoing to determine the relative effectiveness of brachytherapy compared to EBRT. The report also notes that there is still some uncertainty regarding the health related quality of life impact of IMRT and that the results are rather sensitive to utility assumptions regarding this intervention. Consequently, there is a degree of uncertainty regarding the benefits of choosing IMRT over EBRT.

Relevance to the guideline recommendations

In summary, while RT of the IM-MS has been shown to be more effective and cost saving, this relies on several assumptions and as such, cannot be considered reliable evidence (Question 2.5.7).

Hypofractionation is likely to be cost saving, but as this is an emerging area there is insufficient evidence on its cost effectiveness to make any conclusions at present (Question 2.5.3).

Based on the clinical evidence, there is no significant difference in local recurrence rate, overall survival and cosmetic outcome between standard fractionation and hypofractionation schedules (James et al., 2010, Whelan et al., 2010, Haviland et al., 2010). When compared to standard fractionation schedules (50/25), use of a hypofractionated schedule (40/15 or 42.5/16) would lead to a ~40% decrease in RT sessions for those patients eligible for hypofractionation schedules with an overall reduction in RT costs for breast cancer (Question 2.5.3).

Table 11 Economic literature evidence table

All monetary values given in the table below are those which are detailed in the original paper, adjusted euro equivalents of these can be found in the main text above.

Study	Intervention	Analysis Details	Clinical & QALY Outcomes	Costs	Results
Cooper et al., 2011	PET and MRI for the assessment of axillary lymph node metastases in early breast cancer. The baseline and scenarios considered were: baseline 1: 4-NS baseline 2: SLNB scenario 1: replace sampling with MRI scenario 2: replace sampling with PET scenario 3: add MRI before 4-NS scenario 4: add PET before 4-NS scenario 5: add MRI before SLNB scenario 6: add PET before SLNB.	Country: United Kingdom Discount rate: 3.5% p/a Perspective: NHS Time Horizon: Lifetime Model Type: Probabilistic discrete-event simulation	When 4-NS is used as the baseline, the most cost-effective strategy is to replace sampling with MRI (scenario 1), which has the highest net benefits under all willingness-to-pay thresholds tested. The next most cost-effective strategy is to replace sampling with PET (scenario 2). The baseline 4-NS strategy is dominated by both scenario 1 and scenario 2, as they have lower total costs and higher total QALYs. When SLNB is used as the baseline, the most cost-effective strategy is still to replace sampling with MRI (scenario 1), which has the highest net benefits under all willingness-to-pay thresholds tested. The next most cost-effective strategy is also to replace sampling with PET (scenario 2). The baseline SLNB strategy is dominated by both scenarios 1 and 2, as they have lower total costs and higher total QALYs.	The costs of clinical examination, ultrasound, and ultrasound-guided biopsy are £86, £53 and £147, respectively. ALND when carried out as a stand-alone procedure costs £2448. The cost of MRI is £232.56 The cost of PET is £978 according to a study based on UK hospital. ⁶⁶ All costs have been adjusted to 2007 prices.	Decision modelling based on these results suggests that the most cost-effective strategy may be MRI rather than SLNB or 4-NS. This strategy reduces costs and increases quality-adjusted life-years (QALYs) because there are fewer adverse events for the majority of patients. However, this strategy leads to more FN cases at higher risk of cancer recurrence and more false positive (FP) cases who would undergo unnecessary axillary lymph node dissection. Results of the decision modelling suggest that the MRI replacement strategy is the most cost-effective strategy and dominates the baseline 4-node sampling (4-NS) and sentinel lymph node biopsy (SLNB) strategies in most sensitivity analyses undertaken. The PET replacement strategy is not as robust as the MRI replacement strategy, as its cost-effectiveness is significantly affected by the utility decrement for lymphoedema and the probability of relapse for false-negative (FN) patients.
Meng et al., 2011	PET and MRI for the assessment of axillary lymph node metastases in early breast cancer. (Four different strategies compared: replace SLNB with MRI, replace SLNB with PET, add MRI before SLNB, add PET before SLNB)	Country: United Kingdom Discount rate: 3.5% p/a Perspective: (not stated, probably NHS) Time Horizon: Model Type: Individual patient discrete-event simulation	The strategy of replacing SLNB with MRI has the highest total quality-adjusted life years (QALYs). However, clinical evidence for MRI is based on a limited number of small studies and replacing SLNB with MRI or PET leads to more false-positive and false-negative cases.	The strategy of replacing SLNB with MRI has the lowest total costs.	Based on the analysis the baseline SLNB strategy is dominated by the strategies of replacing SLNB with either MRI or PET. The strategy of adding MRI before SLNB is cost-effective, but subject to greater uncertainty. Based on this analysis the most cost-effective strategy is to replace SLNB with MRI. However, further large studies using up-to-date techniques are required to obtain more accurate data on the sensitivity and specificity of MRI.

Study	Intervention	Analysis Details	Clinical & QALY Outcomes	Costs	Results
Auguste et al., 2011	PET and PET-CT for the diagnosis of breast cancer recurrence. (Strategies compared: conventional workup alone, PET, PET-CT and combined conventional workup and PET-CT)	Country: United Kingdom Discount rate: Not applied Perspective: NHS Time Horizon: Lifetime Model Type: Decision Tree	Clearly, for each additional diagnostic test that is added to PET, the more effective it becomes in terms of QALYs gained.	Clearly, for each additional diagnostic test that is added to PET, the more expensive the package becomes,	The ICER for the strategy of PET compared with conventional work-up was estimated at £29,300 per QALY; the ICER for PET-CT compared with PET was £31,000 per QALY; and the ICER for PET-CT combined with conventional work-up versus PET-CT was £42,100. The probabilistic sensitivity analysis shows that at a willingness-to-pay threshold of £20,000 per QALY, conventional work-up is the preferred option. Based on the current model and given the limitations that are apparent in terms of limited availability of data, the result of the current analysis suggests that the use of PET-CT in the diagnosis of recurrent breast cancer in every woman suspected of having a recurrence is unlikely to be cost-effective given the current willingness-to-pay thresholds that are accepted in the UK by decision-making bodies such as NICE. Our modelling suggests that conventional work-up could be the most cost-effective diagnostic strategy given current data.
Turnbull et al., 2011	Contrast-enhanced high field MRI in women with primary breast cancer scheduled for wide local excision. (MRI vs. no MRI)	Country: United Kingdom Discount rate: Not applied Perspective: NHS Time Horizon: 12 months Model Type: NA (trial based analysis)	In the economic assessment at 12 months after surgery, we identified no statistically significant difference in health related quality of life, as measured by the EQ-5D, between the two groups (p=0.075). Results show that addition of MRI to conventional triple assessment has no benefit on reduction of re-operation rate.	Results of this assessment suggested that a cost difference between the two trial groups might exist, with the MRI strategy having a larger mean resource cost per patient than the no MRI strategy (£5508.40 [US\$8877.36] vs. £5213.50 [\$8402.10]), although the difference was not significant (p=0.075).	In terms of total costs, results suggested a difference between the two trial groups, with the MRI group costing more than the no MRI group, although the difference was not statistically significant. In view of the similar clinical and health-related quality-of-life outcomes of patients in both groups, they conclude that the addition of MRI to the conventional triple assessment might result in extra use of resources at the initial surgery period, with few or no benefits to saving resources or health outcomes, and the additional burden on patients to attend extra hospital visits.
Very et al., 2012	Sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer.	Country: Australia Discount rate: 5% p/a Perspective: Health system Time Horizon: 20 years Model Type: Markov decision model	The SLNB was more effective than the ALND over 20 years, with 8 QALYs gained per 1000 patients. The SLNB was less effective when: SLNB false negative (FN) rate >13%; 5-year incidence of axillary recurrence after an SLNB FN >19%; risk of an SLNB-positive result >48%; lymphoedema prevalence after ALND <14%; or lymphoedema utility decrement <0.012.	The SLNB was less costly than the ALND over 20 years, with \$883 000 saved per 1000 patients	The long-term advantage of SLNB over ALND was modest and sensitive to variations in key assumptions, indicating a need for reliable information on lymphoedema incidence and disutility following SLNB. In addition to awaiting longer-term trial data, risk models to better identify patients at high risk of axillary metastasis will be valuable to inform decision-making.

Study	Intervention	Analysis Details	Clinical & QALY Outcomes	Costs	Results
Zendejas et al., 2011	Contralateral Risk Reducing Mastectomy v.s. Routine Surveillance in Patients With Unilateral Breast Cancer.	Country: USA Discount rate: 3% p/a Perspective: Health care provider Time Horizon: Lifetime Model Type: Markov model	CRRM provides 21.22 mean QALYs compared with 20.93 for surveillance. For BRCA-positive patients, CRRM provides more QALYs.	Mean costs of treatment for women age 45 years are comparable: \$36,594 for the CRRM and \$35,182 for surveillance. For BRCA-positive patients, CRRM is less costly	CRRM compared with surveillance, results in an incremental cost-effectiveness ratio (ICER) of \$4,869/QALY gained for CRRM. To prevent one CBC, six CRRMs would be needed. CRRM is no longer cost-effective for patients older than 70 years (ICER \$62,750/QALY). For BRCA-positive patients, CRRM is clearly cost-effective, providing more QALYs while being less costly. In non-BRCA patients, cost-effectiveness of CRRM is highly dependent on assumptions regarding QOL for CRRM versus surveillance strategy. CRRM is cost-effective compared with surveillance for patients with breast cancer who are younger than 70 years. Results are sensitive to BRCA-positive status and assumptions of QOL differences between CRRM and surveillance patients. This highlights the importance of tailoring treatment for individual patients.
Grover et al., 2013 (Rejected)	Comparing Five Alternative Methods of Breast Reconstruction Surgery	Country: USA Discount rate: Not applied Perspective: Health care provider Time Horizon: 7 years Model Type: Decision Tree	The autologous flap with pedicled tissue method approaches a 40 percent probability of being cost-effective at \$100,000 per quality-adjusted life-year, whereas the autologous flap with free tissue method is less likely to be cost-effective, near 35 percent, for either patient case.	Cost of autologous flaps with pedicled tissue: With RT - \$7768.22 Without RT - \$7358.69	Autologous pedicled tissue was slightly more cost-effective than free tissue reconstruction in irradiated and non-irradiated patients. Implant based techniques were not cost-effective.
Skedgel et al., 2013	Adjuvant trastuzumab for HER-2/neu-positive T1bN0 breast cancer. 4 strategies were considered 1) no adjuvant chemotherapy or trastuzumab (baseline), 2) adjuvant chemotherapy alone, 3) adjuvant chemotherapy plus concurrent trastuzumab 4) adjuvant chemotherapy plus sequential trastuzumab.	Country: Canada Discount rate: 3% p/a Perspective: Healthcare system and patient combined Time Horizon: Lifetime Model Type: Probabilistic, discrete cycle, state transition model	Not stated	The costs of incorporating trastuzumab in the adjuvant setting, including HER-2/neu testing, acquisition costs, drug administration, supportive medications and cardiac monitoring, were taken from previous cost studies conducted by members of the study team.	The primary analysis suggested that concurrent trastuzumab plus adjuvant chemotherapy was likely to meet the \$100 000 threshold at recurrence risks of 29–35%. Sequential trastuzumab was less likely to meet such a threshold. The secondary analysis was more favourable for both trastuzumab strategies, but of limited relevance as clinical benefits were predominantly driven by chemotherapy without trastuzumab. Concurrent trastuzumab plus adjuvant chemotherapy appears to offer favourable value for money at the upper ranges of baseline recurrence risks reported to date, although more precise estimates of underlying risk are required to confirm the cost-effectiveness of adjuvant trastuzumab in T1bN0 breast cancer.

Study	Intervention	Analysis Details	Clinical & QALY Outcomes	Costs	Results
Lux et al., 2011	Endocrine Therapy (5 years of letrozole versus tamoxifen versus anastrozole) in the Adjuvant Setting for Postmenopausal Patients with Hormone Receptor-Positive Breast Cancer.	Country: Germany Discount rate: 3% p/a Perspective: Health system Time Horizon: 20 Years Model Type: Markov model	The cost-benefit model showed a gain of 0.3124 or 0.0659 quality-adjusted life years (QALYs) for letrozole or anastrozole.	Incremental costs of €29,375.15/QALY for letrozole (100% of original price) were calculated and €94,648.03 / QALY for anastrozole (75% of original price). All costs are based on data from the German health care system for the year 2010. The costs of care, diagnosis and treatment were estimated for outpatients on the basis of the 2010 Standard Assessment Criteria (Einheitlicher Bewertungsmaßstab, EBM) (EBM score 3.5048 cents).	Marked increases in cost-effectiveness are observed with further decreases in price (anastrozole: 50% price €54,715.17/QALY, 25% price €14,779.57/QALY; letrozole 75% price €20,988.59/QALY, 50% price €12,602.03/QALY, 25% price €4,215.46/QALY). The present model including the inverse probability of censoring weighted analysis (IPCW) for letrozole and generic prices for both AIs shows that letrozole is cost effective.
Holt et al., 2013 (Inadvertently included and subsequently removed)	Routine Oncotype DX® testing of women with node-negative or pN1mi, ER-positive breast cancer.	Country: United Kingdom Discount rate: 3.5 % p/a Perspective: NHS Time Horizon: 30 Years Model Type: Markov Model	Oncotype DX® testing resulted in changes in chemotherapy decisions in 38 of 142 (26.8%) women, with 26 of 57 (45.6%) spared chemotherapy and 12 of 85 (14.1%) requiring chemotherapy when not initially recommended (9.9% reduction overall). Decision conflict analysis showed that Oncotype DX® testing increased patients' confidence in treatment decision making.	Not stated	Economic analysis showed that routine Oncotype DX® testing costs £6232 per quality-adjusted life year gained. Oncotype DX® decreased chemotherapy use and increased confidence in treatment decision making in patients with ER+ early-stage breast cancer. Based on these findings, Oncotype DX® is cost-effective in the UK setting.
John-Baptiste et al., 2013	Aromatase Inhibitors versus Tamoxifen in Early Stage Breast Cancer.	Country: Canada Discount rate: NA (review) Perspective: NA (review) Time Horizon: NA (review) Model Type: We abstracted ICERs and the ICUR from each study. To allow direct comparison across countries and years we converted the ICERs and ICURs to a common year and currency (2010 US Dollars).	18 studies met inclusion criteria. All CE estimates assumed a survival benefit for aromatase inhibitors. Twelve studies performed sensitivity analysis on the risk of adverse events and 7 assumed no additional mortality risk with any adverse event. Sub-group analysis was limited; 6 studies examined older women, 2 examined women with low recurrence risk, and 1 examined women with multiple comorbidities.	Not stated	Published CEAs comparing AIs to tamoxifen assumed an OS benefit though none has been shown in RCTs, leading to an overestimate of the cost-effectiveness of AIs. Results of these CEA analyses may be suboptimal for guiding policy.

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

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Section II Budget impact of the guidelines for the staging, diagnosis and treatment of breast cancer

Scope of the budget impact assessment

The cost-impact analysis focused on those recommendations on the diagnosis, staging and treatment of breast cancer, considered to have cost implications, as determined by the Guideline Development Group at the recommendation meetings held for each clinical question.

Radiology

Clinical question	Recommendation	Change in resources required	Budget impact
<p>Q.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:</p> <ul style="list-style-type: none"> – patients with biopsy proven ductal carcinoma in situ (DCIS) – patients with biopsy proven invasive breast cancer <ul style="list-style-type: none"> – lobular – ductal 	<p>The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS.</p> <p>In patients with invasive lobular cancer, MRI can be considered to assess tumour size, if breast conserving surgery is a treatment option.</p>	<p>Number of MRI may increase for some subgroups (e.g. invasive lobular cancer, Paget's disease, occult primary breast cancer).</p> <p>MRI may decrease for other subgroups (e.g. preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS).</p>	<p>Costs of MRI: €259.06 (HIQA) Costs for MR guided biopsy: €1,334.50 (HIQA)</p> <p>Small numbers e.g. Paget's disease: There were a total of 32 cases of Paget's disease nationally in 2012 (NCRI). 15% of breast cancer cases were lobular cancers in 2004-2009 (NCRI). Data are not available on the number of cases in each subgroup already receiving MRI.</p> <p>With increases in a number of subgroups and decreases in others, a significant budget impact is not anticipated.</p>
<p>Q.2.2.5 In patients with metastatic deposits in axillary nodes where no primary cancer has been identified, what is the role of breast magnetic resonance imaging (MRI)?</p>	<p>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.</p>		<p>However, access to MRI can be difficult in some centres. The facility to do MR biopsy should be available in any centre doing Breast MRI. (minimum case volume of 25 biopsies/year recommended).</p> <p>Budget requirement to provide increased access to MRI (10% of cases: 280 x €259.06 = €72,537) MRI guided biopsy (5% of cases: 140 x €1334.50 = €186,830.</p> <p>Total annual budget requirement to provide increased access to MRI and MR guided breast biopsy: €260,000</p>
<p>Q.2.2.6 In patients with breast dimpling, nipple discharge, inversion, or Paget's disease, who have normal ultrasound and mammography, what is the role of breast magnetic resonance imaging (MRI)?</p>	<p>In the setting of negative conventional imaging, MRI can facilitate treatment planning for patients with Paget's disease.</p>		

Clinical question	Recommendation	Change in resources required	Budget impact
<p>Q.2.2.7 In women with breast cancer, who/what subgroups should have staging investigations performed (to detect metastases)?</p>	<p>In newly diagnosed patients with breast cancer who have symptoms suggestive of metastases, appropriate imaging investigations should be performed, regardless of tumour stage.</p> <p>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.</p> <p>In newly diagnosed asymptomatic patients with breast cancer, use of staging imaging for metastatic disease is recommended for stage III and IV disease.</p>	<p>Will represent a change to current practice with regard to imaging - unnecessary investigations potentially being carried out currently.</p> <p>Briefing/update sessions may be required for clinicians.</p> <p>Overall imaging should be reduced.</p>	<p>In 2004 - 2009, of breast cancers diagnosed in Ireland Stage I – 29% Stage II – 42% Stage III – 12% Stage IV – 7% Unknown – 10% (NCRI, 2012)</p> <p>With a reduction in staging investigations for Stage I and II, this represents 71% of breast cancers (approx 1,991 cases/yr).</p> <p>Approx cost of staging tests per person (SJH Finance Dept., 2015): Chest X-ray (CXR) (€41.91), Contrast enhanced CT chest-abdomen-pelvis (€131.09), Whole body isotope bone scan (€201.58)</p> <p>Total cost of 3 tests (per person): €374.58</p> <p>This represents a potential saving of up to €745,788 per annum (1,991 cases x €374.58)</p>

Surgery

Clinical question	Recommendation	Change in resources required	Budget impact
<p>Q.2.3.3 In patients undergoing mastectomy for operable breast cancer (in situ or invasive), what is the evidence for prophylactic mastectomy?</p>	<p>In the general population, there is no evidence that a contralateral risk reducing mastectomy improves a patient's prognosis. However a CRRM may be undertaken to address specific patient concerns if it is discussed at a multi-disciplinary team meeting and the benefits, risks and alternatives have been discussed with the patient.</p> <p>There is a subset of patients who may benefit from a CRRM (i.e. genetic mutation carriers).</p>	<p>Current practice in general.</p> <p>More extensive surgery. However, no follow-up imaging surveillance required (decrease in imaging).</p> <p>Approx 5% of breast cancers diagnosed each year are positive for the BRCA gene. This equates to approx. 140 cases annually.</p> <p>It is estimated that the uptake of CRRM in this population is up to 20% (n=28 annually) (HIQA HTA)</p> <p>As genetic testing increases, the known number of BRCA carriers may increase.</p>	<p>Cost of CRRM in Ireland: Double mastectomy €6,699 DRGJ06Z (Case mix)</p> <p>Frequency of CRRM 21 cases of bilateral mastectomy in 2012 (NCRI)</p> <p>Decrease in annual imaging (mammogram €102.50 +/- MRI €259.06 annually)</p> <p>The cost of the two interventions is similar in the US (\$35,594 CRRM, \$35,182 surveillance). Zendejas et al. (2011) found that CRRM is both more effective (21.22 vs. 20.93 QALYs) and, for most age groups, is cost-effective (ICER \$4,869/QALY) compared to annual mammography.</p> <p>Therefore an increase in budget requirements is not envisaged.</p>

Medical oncology

Clinical question	Recommendation	Change in resources required	Budget impact
<p>Q.2.4.2 In pre-menopausal women with breast cancer that is ER+ and/or PR+:</p> <p>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, and d) What is the optimum duration of therapy?</p>	<p>Pre-menopausal women with ER positive breast cancer should be treated with tamoxifen.</p> <p>The standard duration of treatment with tamoxifen for pre-menopausal women with ER positive breast cancer is at least five years, but there is evidence to support up to 10 years of use.</p> <p>Currently, the routine use of adjuvant ovarian ablation/suppression is not considered a standard of care.</p>	<p>Current practice.</p> <p>Demand-led service.</p> <p>Extension to 10 years use recommended internationally in 2013 but level of implementation of best practice and level of patient adherence is not known.</p> <p>Cost of treatment has halved in Ireland but treatment duration may be extended for those not already on extended duration.</p>	<p>Medications unchanged but duration of therapy may change.</p> <p>Estimated population on adjuvant hormone therapy for breast cancer in Ireland in 2013 = 8,554.</p> <p>The full annual cost of adjuvant hormone therapy based on 2013 data is €4.9m. The cost of drugs in 2013 and going forward has reduced due to the IPHA agreement 2012 and also the Health Pricing and Supply of Medical Goods 2013. As a result based on the same data the annual cost for 2015 will be €2.2m. The cost of treatment has halved due to reductions in drug costs.</p> <p>Some costs of treatment could be reduced if patients were prescribed the most cost effective treatment (tamoxifen).</p>

This section has been updated by the National Cancer Control Programme.

For the updated Radiation Oncology section, please visit:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/breast/>

Appendix 12: Glossary of terms and abbreviations

Definitions within the context of this document

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)

Abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AI	Aromatase Inhibitor
ALN	Axillary Lymph Node
ALND	Axillary Lymph Node Dissection
ASCO	American Society of Clinical Oncologists
CAP	College of American Pathologists
BCS	Breast Conserving Surgery
BH	Beaumont Hospital
BI-RADS	Breast Imaging-Reporting and Data System
BM	Bone Metastases
BMI	Body Mass Index
BMJ	British Medical Journal
BS	Bone Scan
CAN	Canadian
CBC	Contralateral Breast Cancer
CEA	Cost Effectiveness Analysis
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CINAHL	Cumulative Index to Nursing and Allied Health Literature database
CGB	Clinically Guided Biopsy
COM-B	Capability, Opportunity and Motivation Behaviour Model
CRRM	Contralateral Risk Reducing Mastectomy
CSO	Central Statistics Office
CT	Computed Tomography
CXR	Chest X-Ray
CYP2D6	Cytochrome P2D6
CUH	Cork University Hospital
DCIS	Ductal Carcinoma in Situ
DFS	Disease Free Survival
DOHC	Dept. of Health and Children
DM	Distant Metastases
DRG	Diagnosis Related Group
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EED	Economic Evaluation Database
EBM	Evidence Based Medicine
EBP	Evidence Based Practice
ER	Oestrogen Receptor
EBRT	External Beam Radiation Therapy
EU	European Union
EUREF	European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services
FDG	Fluorodeoxyglucose
FNA	Fine Needle Aspiration
FSH	Follicle Stimulating Hormone
GDG	Guideline Development Group
GBP	Great British Pound
GI	Gastrointestinal
GP	General Practitioner
GUH	Galway University Hospital
Gy	Gray (unit of radiation)
HD	Hakulinen/Dyba model
HEED	Health Economic Evaluations Database
HER2	Human Epidermal Growth Factor Receptor 2

HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	Health Technology Assessment
IANO	Irish Association for Nurses in Oncology
IBC	Inflammatory Breast Cancer
IBTR	Ipsilateral Breast Tumour Recurrence
ICD-10	International Statistical Classification of Disease and Related Health Problems 10th revision
ICER	Incremental Cost Effectiveness Ratio
ICUR	Incremental Cost Utility Ratio
ICGP	Irish College of General Practitioners
IGR	Institut Gustave-Roussy
ILC	Invasive Lobular Cancer
IM-MS	Internal Mammary and Medial Supraclavicular
IMRT	Intensity Modulated Radiation Therapy
IPHA	Irish Pharmaceutical Healthcare Association
ITC	Isolated Tumour Cell
KPI	Key Performance Indicator
LCIS	Lobular Carcinoma in Situ
LOS	Length of Stay
LR	Local Recurrence
LS:TS	Longitudinal Size:Transverse Size
LH	Luteinising Hormone
LVEF	Left Ventricular Ejection Fraction
LYG	Life Years Gained
MDT	MultiDisciplinary Team
MeSH	Medical Subject Headings
MMUH	Mater Misericordiae University Hospital
MRI	Magnetic Resonance Imaging
NALA	National Adult Literacy Agency
NCCP	National Cancer Control Programme
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Registry Ireland
NHBF	Non-Hilar Blood Flow
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSS	National Screening Service
NST	No Special Type
pCR	Pathological Complete Response
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography - Computed Tomography
PICO	Population/patient; intervention; comparison/control; outcome;
PICO(T)	Population/patient; intervention; comparison/control; outcome; (Time)
PMRT	Postmastectomy Radiotherapy
PPP	Purchasing Power Parity
PR	Progesterone Receptor
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted-Life-Year
QoL	Quality of Life
QUB	Queen's University Belfast
RCSI	Royal College of Surgeons in Ireland
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
RRBSO	Risk-Reducing Bilateral Salpingo-Oophorectomy

RRM	Risk-Reducing Mastectomy
RT	Radiotherapy
SBD	Symptomatic Breast Disease
SCF	Supraclavicular Fossa
SEER	Surveillance, Epidemiology, and End Results
SFH	St. Francis Hospice
SIGN	Scottish Intercollegiate Guidelines Network
SJH	St. James's Hospital
SLN	Sentinel Lymph Node
SLNB	Sentinel Lymph Node Biopsy
SLND	Sentinel Lymph Node Dissection
SLRON	St. Luke's Radiation Oncology Network
SPECT	Single Photon Emission Computed Tomography
SSO	Society of Surgical Oncology
SSRI	Selective Serotonin Reuptake Inhibitor
SVUH	St. Vincent's University Hospital
TCD	Trinity College Dublin
UK	United Kingdom
ULH	University of Limerick Hospitals
US	United States
WHO	World Health Organisation
WLE	Wide Local Excision
WRH	Waterford Regional Hospital
XRM	X-Ray Mammogram

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