Clinical Guideline

Advanced breast cancer: diagnosis and treatment

Full Guideline

Draft for consultation

Contents

Key priorities

1. PET-CT should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

2. If receptor status (oestrogen receptor and HER2) was not assessed at the time of initial diagnosis, then it should be assessed at the time of tumour recurrence. In the absence of any tumour tissue from the primary tumour a biopsy of a metastasis should be obtained if feasible.

3. For patients with hormone receptor-positive advanced breast cancer, offer endocrine therapy as first-line treatment unless there is a clinical need to achieve a rapid tumour response.

4. For patients with advanced breast cancer who are not suitable for anthracyclines (adjuvant anthracyclines or first-line metastatic anthracyclines, or contraindicated), systemic chemotherapy should be offered in the following sequence:
   - first line: single-agent docetaxel,
   - second line: single-agent vinorelbine or capecitabine,
   - third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

5. Patients who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system.

6. Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in previous NICE guidance documents (‘Improving outcomes in breast cancer: Manual opdate [2002] and ‘Improving supportive and palliative care for adults with cancer [2004]), in particular the following two recommendations:
   - ‘Assessment and discussion of patients’ needs for physical, psychological, social, spiritual and financial support should be undertaken at key points such as diagnosis at commencement, during, and at the end of treatment; at relapse; and when death is approaching.’
   - ‘Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of 'key worker' for individual patients.’

7. A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms.

8. Offer bisphosphonates to patients newly diagnosed with bone metastases, to prevent skeletal-related events and to reduce pain.

9. Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain.

10. Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.

Key research recommendations

1. Clinical trials are needed to investigate the most effective endocrine therapy for post-menopausal women with oestrogen receptor positive tumours who progress on treatment with a third-generation aromatase inhibitor.

2. Randomised clinical trials should evaluate the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.

3. The use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial.

4. Randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should receive further biological response modifiers.

5. The relevant research organisations should be encouraged to address the topic of uncontrolled local disease and devise appropriate research studies. This might include development of a national register.

Methodology

Introduction

What is a Clinical Guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development and before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of seven National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of breast cancer in October 2003 as part of NICE's ninth wave work programme. Because of the size of this topic, the NCC-C used 2 guideline slots (early breast cancer and advanced breast cancer) to fulfil this remit. However, the guideline development process began officially on 22-23 June 2006 when sufficient capacity became available at the NCC-C.

Who is the Guideline Intended For?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of advanced breast cancer. Instead we have tried to focus on those areas of clinical practice that are (i) known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with advanced breast cancer, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of patients.

The Remit of the Guideline

Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's ninth wave programme of work:

'To prepare a guideline for the NHS in England and Wales on the clinical management of breast cancer, to supplement existing service guidance. The guideline should cover:

- *the key diagnostic and staging procedures*
- *the main treatment modalities including hormonal treatments*
- *the role of tumour-specific bisphosphonates.'*

What the Guideline Covers - The Scope

The remit was then translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C. The purpose of the scope was to:

- provide an overview of what the guideline would include and exclude identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit
- inform the development of the clinical questions and search strategy
- inform professionals and the public about the expected content of the guideline.

Prior to the commencement of the guideline development process, the scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE, 2005, NICE 2006, NICE 2007). The full scope is shown in Appendix 4. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP; signed off by NICE and posted on the NICE website.

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2007). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the advanced breast cancer guideline can be found in Appendix 6.2.

Needs Assessment

As part of the guideline development process the NCC-C invited specialist registrars to undertake a needs assessment (see Appendix 6.3). The needs assessment aims to describe the burden of disease and current service provision for patients with breast cancer in England and Wales, which informed the development of the guideline. This document forms a supplement to the full guideline and will also appear on the accompanying CD-ROM to this guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented early in the stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined by the 'NICE guidelines manual'. A team of health professionals, lay representatives and technical experts known as the GDG (see Appendix 6.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, defined the scope which sets the parameters of the guideline
- forming the guideline development group
- developing clinical questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Guideline Development Group (GDG)

The Advanced Breast Cancer GDG was recruited in line with the existing NICE protocol as set out in the 'NICE guidelines manual'. The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were informally interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for nominations were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 6.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms, following nomination from their respective stakeholder organisation. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-

holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1).

Guideline Development Group Meetings

Fourteen GDG meetings were held between 22 and 23 June 2006 and 2 July 2008. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations prior to presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Representatives

Individuals with direct experience of advanced breast cancer services gave an integral user focus to the GDG and the guideline development process. The GDG included three patient/carer representatives. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Expert Advisers

During the development phase of the guideline the GDG identified areas where there was a requirement for expert input on particular specialist clinical questions. The clinical questions were addressed by either the production of a position paper or a formal presentation by a recognised expert who had been identified via the relevant registered stakeholder organisation.

A full list of recognised experts who contributed to the guideline can be found in Appendix 6.4. All relevant position papers are presented as part of the evidence review and will also appear on the accompanying CD-ROM to this guideline.

Developing Clinical Evidence-Based Questions

Background

The scope, as described in Appendix 4, needs to be very clear about which patient groups are included and which areas of clinical care should be considered. But within these boundaries it does not usually specify which topics are considered a priority.

It was recognised by the NCC-C at an early stage that in order to complete the guideline development work to an appropriate standard the GDG needed to restrict its work to approximately 30 clinical questions. Previously this prioritisation would have been carried out by the GDG at its first two meetings but it was clear from some guidelines already published that this approach had resulted in a much larger number of questions than 30 being addressed.

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. It was therefore felt important that the 30 clinical questions should be prioritised into areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

An extensive list of potential topics for the guideline to investigate was compiled by the NCC-C Director and GDG Chair and Lead Clinician in consultation with a small number of breast cancer multidisciplinary teams across England and Wales.

This list was incorporated into a questionnaire which asked respondents to rate each topic as low, medium or high clinical priority as well as low or high economic priority. It was made clear that respondents would be rating the priority for each topic to be included in a clinical guideline to be published in two years' time. The questionnaire also asked respondents to suggest any additional topics they would like to see included with an equivalent assessment of their priority.

Questionnaires were subsequently sent to the Breast Cancer Advisory Groups of all 37 cancer networks in England and Wales with a request for a 4-week turnaround. (A list of all cancer networks can be found on the Cancer Action Team website at the DH). Questionnaires were also sent via the Patient and Public Involvement Programme (PPIP) at NICE to all relevant patient/ carer stakeholder organisations.

The scores from each completed questionnaire were aggregated by NCC-C staff and ranked. These results together with information on identifiable practice variation (see needs assessment) were presented to the GDG at its first meeting. The list of prioritised topics produced via the questionnaire survey was in no way definitive and the GDG used these results to agree their final priorities for the clinical questions.

For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the patients (the population under study - P), the interventions (what is being done - I), the comparisons (other main treatment options - C) and the outcomes (the measures of how effective the interventions have been - O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in Appendix 5.

Care Pathway

Early in the development process the GDG drafted an outline care pathway (or algorithm) in order to explore how patients with advanced breast cancer might access and be treated by the NHS.

Review of Clinical Literature

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG, provided it was relevant to the agreed list of clinical questions.

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work, for example modelling (see section on 'Incorporating Health Economic Evidence').

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded
- (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards
- National Research Register (NRR)
- Current Controlled Trials.

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 30 June 2008 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and will also appear on the accompanying CD-ROM to this guideline).

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers were generated for each question and the rationale for the exclusion was presented to the GDG when required.

The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction.

The researcher assessed the quality of eligible studies by referring to the SIGN quality checklist for systematic reviews/meta-analyses and randomised control trials (Table A). Evidence relating to clinical effectiveness was classified using this established hierarchical system. However this checklist is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated hierarchy for this type of test, NICE suggests levels of evidence that take into account the factors likely to affect the validity of these studies.

Table A Levels of evidence for intervention studies. Data source: 'NICE guidelines manual' (NICE 2007).

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs 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, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

For all the relevant appraised studies for a particular question, data on the type of population, intervention, comparator and outcomes (PICO) was recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All the evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual'.

In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Incorporating Health Economics Evidence

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to advanced breast cancer. It is important to investigate whether health services are both clinically effective and cost effective, i.e. are they 'value for money'.

The health economist helped the GDG by identifying priority topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting economic analysis. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible.

In order to assess the cost-effectiveness of each priority topic, a comprehensive systematic review of the economic literature was conducted. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics and quality of life filter.

Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards.

Economic Modelling

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should be investigated. After the clinical questions were decided, the GDG agreed which topics were an 'economic priority' for modelling. These 'economic priorities' were chosen on the basis of the following criteria, in broad accordance with the 'NICE guidelines manual:

Overall Relevance of the Topic

- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient:* interventions that that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost:* interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice:* priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty

- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues):* when there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

Once the economic priority clinical questions had been chosen, the next task was to perform a systematic review of the cost-effectiveness literature. When relevant published evidence was identified and considered to be of sufficient quality, this information was used to inform the recommendation for that specific clinical question. When no relevant cost-effectiveness evidence was identified, or when it was not considered to be of reasonable quality, consideration was given to building a de novo economic model. This decision was made by the GDG based on an assessment of the available evidence required to populate a potential economic model.

For those clinical questions where an economic model was required, the information specialist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The clinical questions in this guideline selected for modelling was chosen because at the time it was considered likely that the recommendations under consideration could substantially change clinical practice in the NHS and have important consequences for resource use. The details of the model are presented in the evidence review and Appendix 1. During the modelling process the following general principles were adhered to:

- the GDG Chair and Clinical Lead were consulted during the construction and interpretation of the model
- the model was based on the best evidence from the systematic review
- model assumptions were reported fully and transparently
- the results were subject to thorough sensitivity analysis and limitations discussed
- costs were calculated from a health services perspective.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying qualifying statement.

Qualifying Statements

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost-effectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way we have chosen to do this is by writing a 'qualifying statement' to accompany every recommendation and will usually cover:

- the strength of evidence about benefits and harms for the intervention being considered
- the degree of consensus within the GDG
- the costs and cost-effectiveness (if formally assessed by the health economics team).

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed (see pages 18-22 for algorithms). To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders. Registered stakeholders (see Appendix 6.2) had one opportunity to comment on the draft guideline and this was posted on the NICE website between 13 August 2008 and 8 October 2008. The GRP also reviewed the guideline and checked that stakeholder comments had been addressed.

Following the consultation period the GDG finalised the recommendations and the NCC-C produced the final document. This was then submitted to NICE for approval and publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three versions of the advanced breast cancer guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk
- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for patients with advanced breast cancer but may also be useful for family members, advocates or those who care for patients with advanced breast cancer. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 30 June 2008 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the

recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

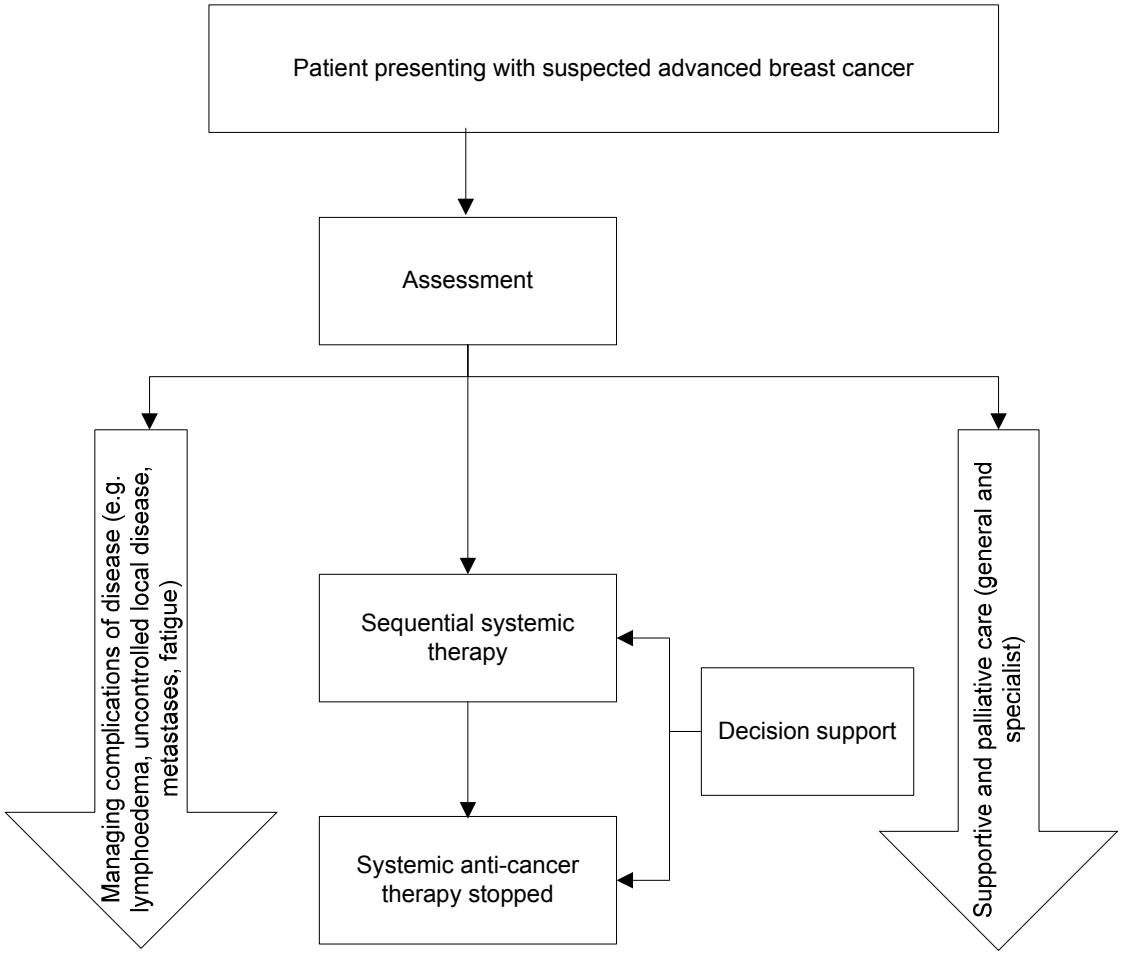
National Institute for Health and Clinical Excellence (2005) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2006) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence.

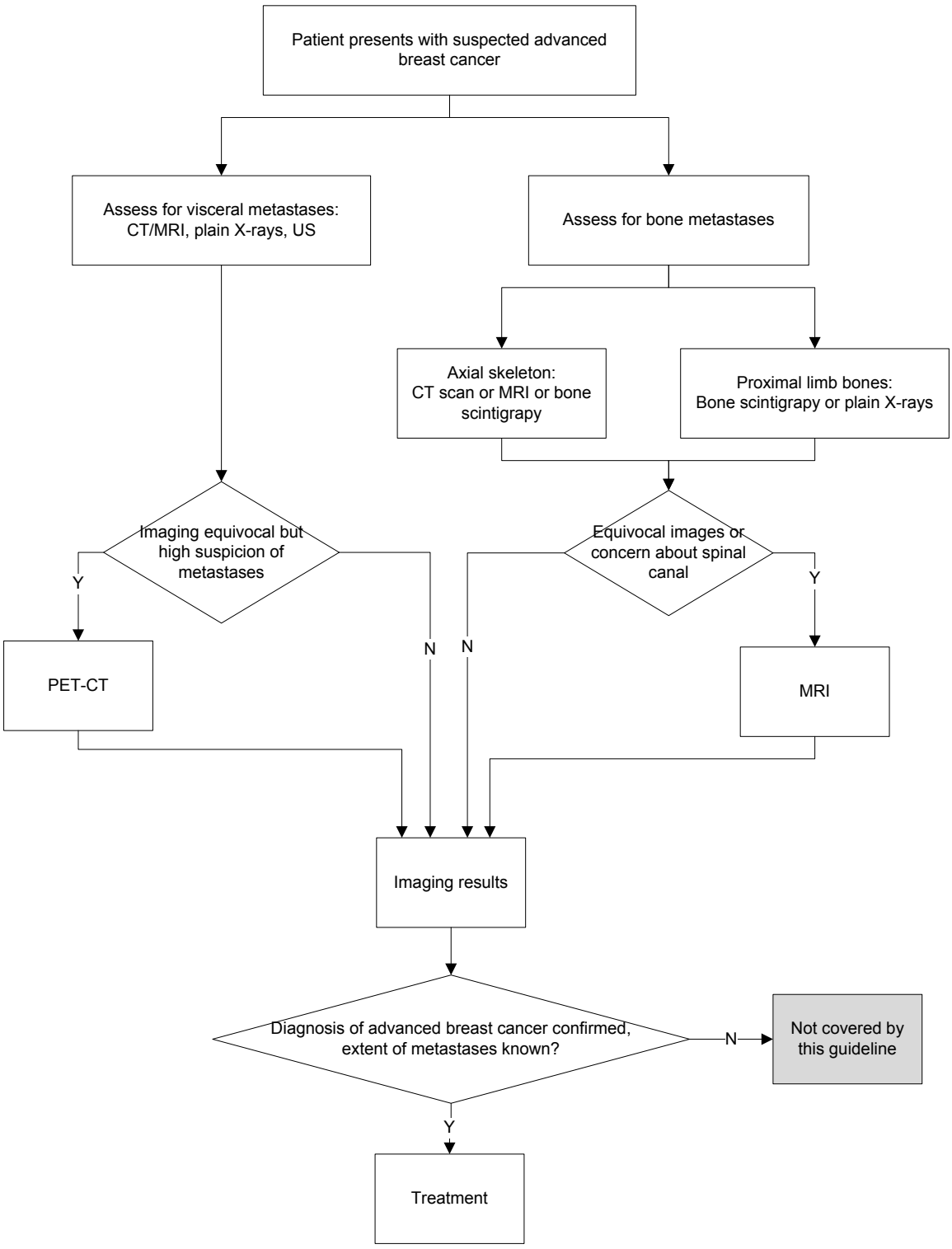
Algorithms

Overview of pathway

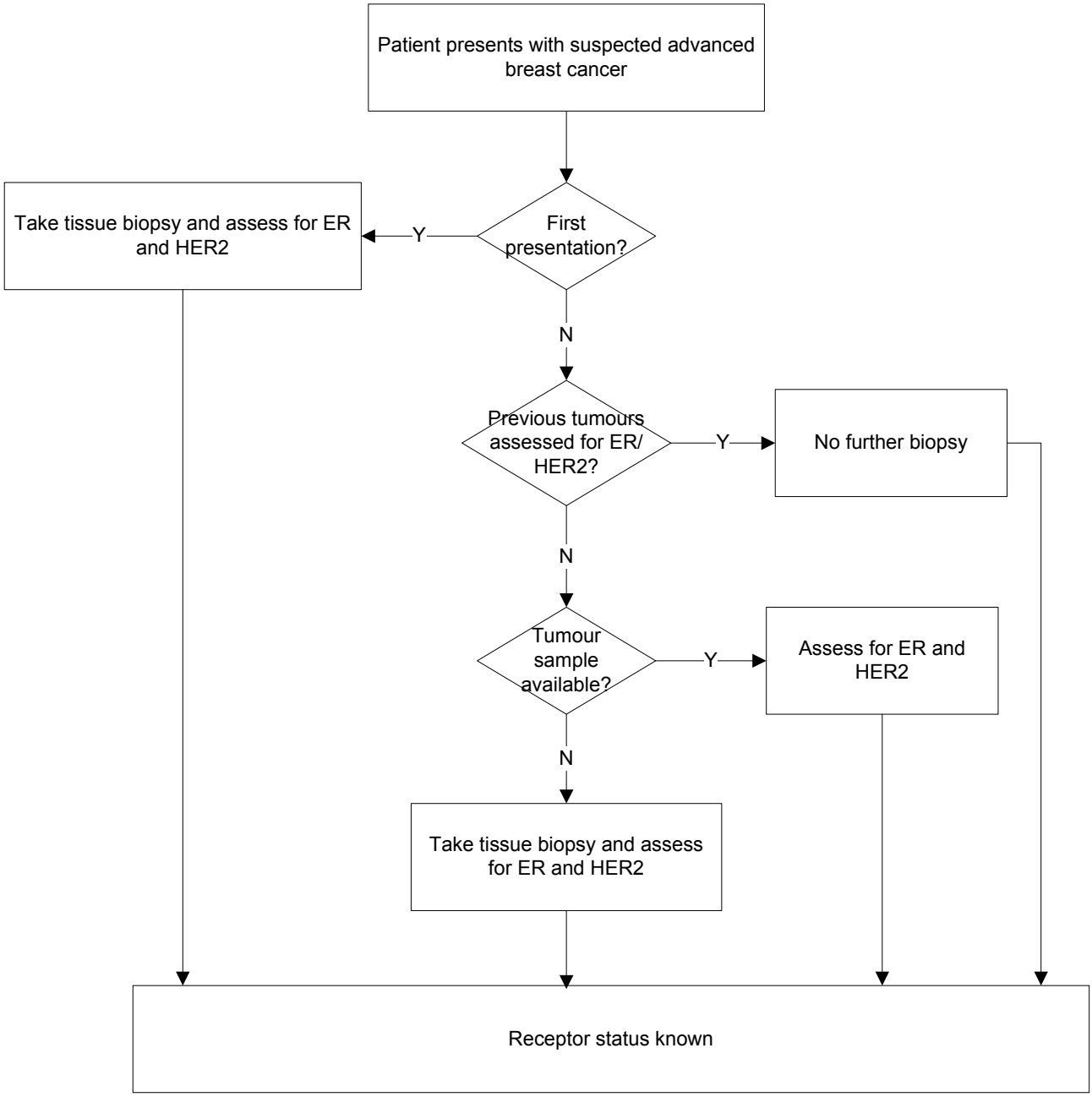


Diagnosing Advanced Breast Cancer

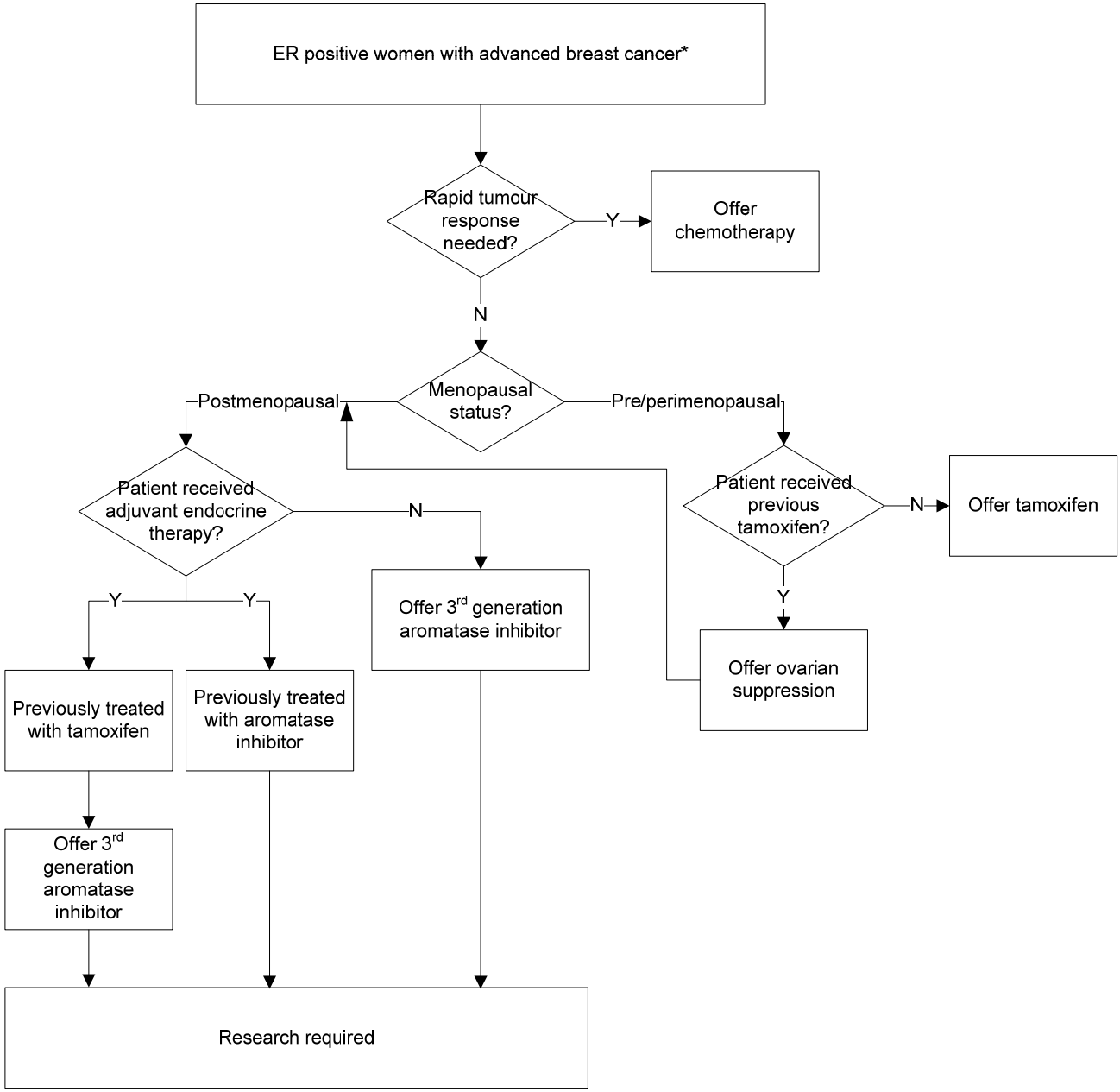
Imaging assessment



Assessing receptor status

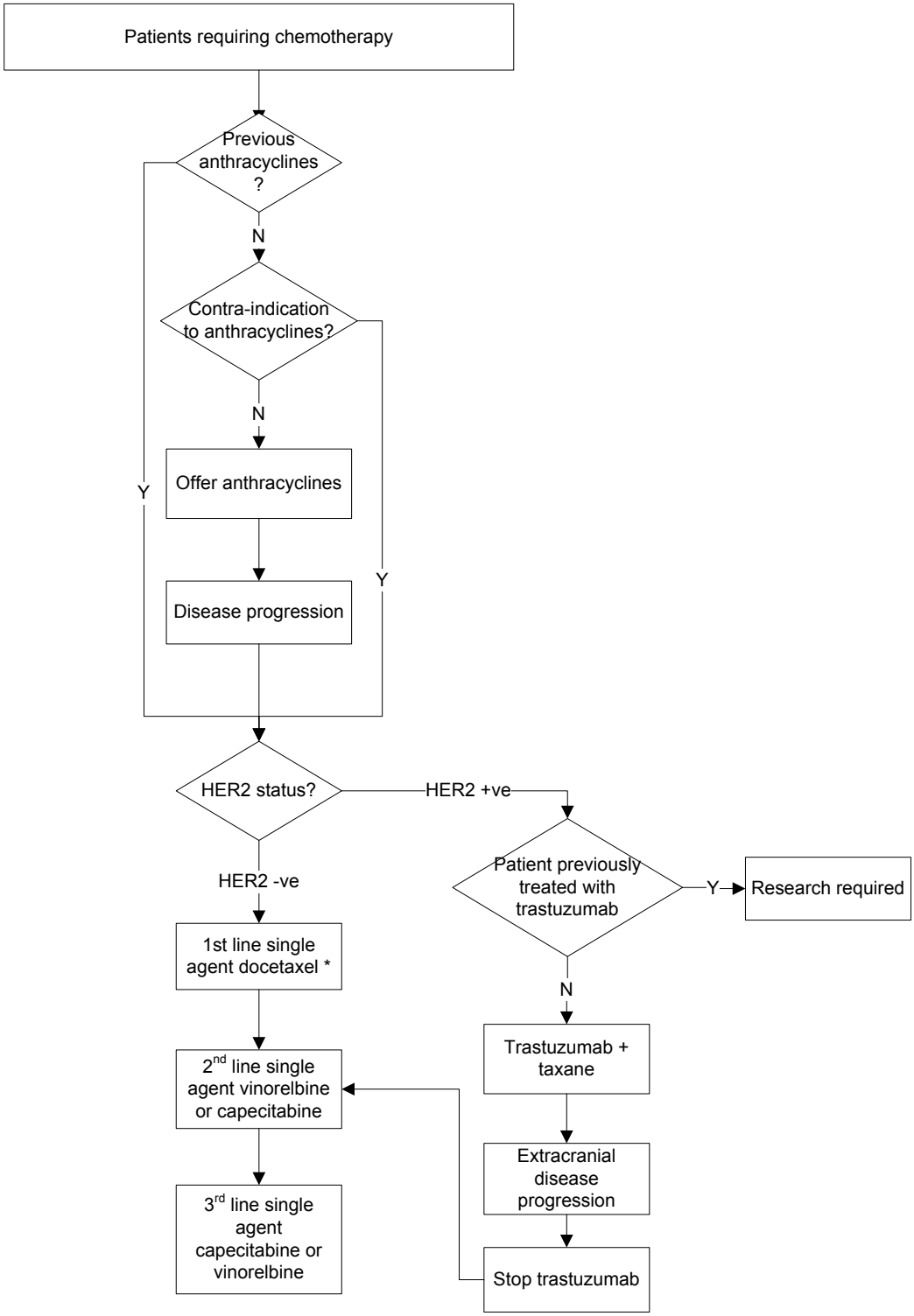


Endocrine therapy



* for ER positive men with advanced breast cancer offer tamoxifen as the first-line treatment

Chemotherapy



* Consider combination therapy for patients in whom a greater probability of response is important and who understand/are likely to tolerate the additional toxicity

1 Epidemiology

1.1 Introduction

The following needs assessment provides a summary of the current information available regarding the epidemiology of breast cancer regionally, nationally and internationally. Its purpose is to provide the context for this guideline, providing an overview of the size of the problem and disease burden, and assessing whether variation in epidemiology or service utilisation exists.

The full report covers both early and advanced breast cancer and is available as a supplement to the full guidelines. Although the disease is the same in both cases, the issues differ markedly. This executive summary relates to advanced breast cancer, breast cancer with metastases. For those with advanced breast cancer the focus is inevitably upon palliation of symptoms, dealing with the longer term side effects of treatment and improving the quality of life. The process of producing this summary has highlighted the lack of routine data available to assess the burden of advanced breast cancer on individuals, society and the NHS.

1.2 Availability of Routine Data

Cancer registries

Information on the incidence, mortality and survival of breast cancer for the UK is published by the Office of National Statistics (UK Statistics Authority 2007). It is based on data collated by 11 registries covering Northern Ireland, Scotland, Wales and 8 regional registries in England (Department of Health 2008). The registries are the only source of reliable population level data for the UK.

Most registries are designed to record information about cancers apparent at the time of diagnosis of the primary neoplasm. Whereas there are some data available on the occurrence of secondary breast cancer at the time of primary diagnosis, most registries do not collect information on the occurrence and distribution of secondary breast cancer occurring *after* the primary diagnosis. A recent survey found that only one registry (West Midlands Cancer Intelligence Unit) collects information on all cases of secondary breast cancer within their area (Secondary Breast Cancer Taskforce 2007). Reasons that other registries do not collect this information relate to various problems of systems, process and capacity – both within registries and amongst the institutions from which they collect data. Similar problems exist in other countries, including those contributing to the European Network of Cancer Registries, Australia, and the USA (Secondary Breast Cancer Taskforce 2007).

One implication of this is that population level data for describing the epidemiology of secondary breast cancer are relatively sparse. The data available tend to be framed in terms of the start and end of the illness. The argument has been made that such data are more descriptive for women with

early stage breast cancer than they are for women with secondary breast cancer (Musa 2004). The lack of data available regarding secondary breast cancers (cancers which occur after the initial diagnosis) has recently been raised as an issue by the Secondary Breast Cancer Taskforce and Breast Cancer Care (2007) These data are not collected nationally or internationally and this leads to great difficulties in estimating the burden of secondary disease.

Where there is a lack of comprehensive national data, there may be alternative sources available. For example, the Breast Cancer Clinical Outcome Measures (BCCOM) project has audited a cohort of more than 16,000 individuals diagnosed in 2004, providing data on the management of symptomatic breast cancer across the UK (BCCOM 2007). In some instances, regional data provide the best indicator of the national position. Data on secondary breast cancers are a good example of this.

Hospital activity

Information regarding every hospital admission commissioned by the NHS, including details of the patient, diagnosis and procedures performed are recorded in England (Hospital Episode Statistics) and Wales (Patient Episode Database Wales). This relates to episodes of care rather than individuals and also relates to procedures performed rather than the indication, whether early or advanced breast cancer, or the outcome of treatment. These data are processed and 'cleaned' nationally, removing duplicates and obvious errors, to provide the most robust data possible. The purpose of including these data in the full report is to give an estimate of the level of inpatient activity within secondary care, and so emphasise the importance of breast cancer as a resource issue. However, as these data are not relevant to advanced breast cancer it has not been included in this summary. There is work currently under way to combine the HES data with the cancer registry data in England. This will enable analysis at an individual level and also allow the assessment of repeat procedures and outcomes. This work will be an extension of a previous cohort analysis performed by the West Midlands Cancer Intelligence Unit.

Outpatient data have also been collected through the hospital activity data since 2003. However, these data record the speciality associated with the appointment but not the diagnosis or reason for referral. These data have therefore not been examined for this assessment.

Primary care

The majority of contacts in primary care are now recorded on electronic systems. There are several sources of these data, which fall into two main groups. The first are the routinely available sources tailored to collect monitoring information for a specific purpose. An example is the monitoring of disease registers and treatment of individuals with certain health conditions through QOF (Quality and Outcomes Framework). Breast cancer is not a condition monitored through the QOF system. The second main source is a group of primary care research databases that represent a sample of practice activity but are not routinely accessible.

There are issues regarding how primary care contacts are recorded, entries for patient contacts may be coded with the reason for attendance, underlying diagnosis or left uncoded. A survey in 2003, of practice information systems, found that although 96% of paper and 94% of computerised records recorded the reason for a patient contact episode in primary care, only 48% of paper records and 34% of computerised records contained a diagnosis (Hippisley-Cox et al. 2003). Systems will also not detect contacts which are related to breast cancer, for example psychological problems related to a diagnosis or treatment, unless specifically coded.

Surveys of the population have been conducted in the past to provide information on the level of activity in primary care. Morbidity survey information is available from the Royal College of General Practitioners Annual Prevalence Report (2007) and has been included.

Socioeconomic status

Information regarding socioeconomic status was obtained from the literature as it is not routinely available from cancer registry data (Sloggett et al. 2007). Studies have examined socioeconomic status by individual measures, place of residence or country of residence. Status is defined by indicators which mark material deprivation. These markers are socially constructed by judgements which may not be appropriate for all cultures, for example overcrowding may be a choice rather than a sign of poverty in some cultures (Farooq et al. 2005). There are also difficulties in assessing the socioeconomic status of women (Coleman et al. 2001).

Ethnicity

Ethnicity is poorly recorded in NHS data. It is part of the dataset for cancer registries (Farooq et al. 2005) but remains an optional field and country of birth, not ethnicity, is currently the method of recording used in UK death registrations (Wild et al. 2006). NHS providers are required to collect ethnicity monitoring data for outpatients and inpatients (Farooq et al. 2005), but the recording remains incomplete and the use of the ‘not known’ category remains high. The Quality and Outcomes Framework (QOF) has begun to encourage recording of ethnicity but only for new registrations with a practice. Information was obtained from the literature as no routine data are available, but there were no specific findings for the advanced breast cancer guideline.

Prescribing

Primary care prescribing data are collected nationally, through PACT (Prescribing Analysis and Cost) by prescriber, but it is not possible to make conclusions relating to breast cancer from the prescriptions of particular medications. The data are collected for budgetary reasons and are not allocated to individual patients or to the diagnosis or reason for prescription.

National data are not available for hospital based prescribing. However, the National Cancer Director (2004) published an audit of the usage of cancer drugs approved by NICE. The data used for the audit were taken from the IMS Health Hospital Pharmacy Audit, collected in 2005 from hospitals

covering 93% of acute beds in the UK. The audit reviewed the use of 6 drugs for cancers that included breast cancer, and for trastuzamab used for breast cancer alone. These data indicate the presence of variation across the country, but do not include information regarding the type of cancer, stage of disease, particularly if early or advanced breast cancer, or outcome of treatment.

Radiotherapy

Radiotherapy centres currently collect information regarding the site of treatment and the dose and number of fractions of radiotherapy delivered, but this may not include the primary site of the cancer or the indication for treatment. There has been voluntary national reporting of these data, but the completeness and quality is questionable and so this is not included in the report. Agreement has been reached to introduce a core data set and mandatory reporting for radiotherapy data which will enable separation of doses given for treatment and for palliation, but this was not available at the time of this report.

Work has been undertaken by the National Cancer Services Analysis Team (NATCANSAT) to examine travel distances to radiotherapy centres. These data are included to highlight some of the geographical issues that impact upon patient access to treatment.

1.3 Epidemiology of Advanced Breast Cancer

There are no national data on the incidence[1] of advanced breast cancer. Regional data from the West Midlands Cancer Intelligence Unit indicate that about 5% of women and men diagnosed with breast cancer between 1992 and 1994 had metastases at the time of their primary diagnosis (Secondary Breast Cancer Taskforce 2007). The data also suggest that a further 35% of all those with a primary diagnosis went on to develop metastases in the 10 years following diagnosis. Currently there are few data to quantify the number of cases of secondary breast cancer developing after the 10-year time period.

Mortality[2] data may be considered as a proxy measure for the incidence of advanced breast cancer. For example, a trend in mortality may indicate an underlying trend in incidence of advanced breast cancer. However, there are important cautions to consider in making these assumptions. Mortality from breast cancer may include those who die from complications of treatment, rather than advanced metastatic disease. Also the mortality in a particular year cannot be related to the incidence of new cases in that year, as those who die from breast cancer will have been diagnosed over a range of years.

Mortality from breast cancer follows the same socioeconomic gradient as incidence (Gage et al 1997; Faggiano et al 1997). Women in higher socioeconomic groups are more likely to have breast cancer recorded as their

[1] Incidence – the number of new cases occurring in a period of time in a defined population.
[2] Mortality - the number of deaths attributed to breast cancer in a specified period of time in a defined population.

cause of death than those in lower socioeconomic groups. However, the survival[3] in more deprived groups is worse at every stage of the disease (Garvican et al. 1998). Studies have shown that women from lower socioeconomic backgrounds are more likely to be diagnosed with more advanced disease (Downing et al. 2007), with differences being more pronounced in the 50-69 age group (Schrijvers et al. 1995), and are more likely to have a poorer prognosis[4] than affluent women (Garvican et al. 1998). This relates to the fact that women from deprived groups are less likely to have their breast tumours diagnosed by screening (Robinson et al. 2006).

Based on numbers of women diagnosed up to the end of 1992, and historical survival patterns it has been estimated that in 2003 there were approximately 172,000 women in the UK who have a history of breast cancer. This number is likely to be an underestimate in view of the increases in incidence and survival experienced in the UK since the early 1990s. The proportion of these living with advanced breast cancer is not known (Micheli et al. 2002).

Primary Care Activity

Primary care provides a great deal of healthcare to individuals with a current diagnosis or past history of breast cancer. This includes contacts for physical problems associated with the cancer and its treatment, plus social and psychological support. Survey estimates reveal that an average practice of 10,000 will have around 25 registered patients who consult their GP regarding their breast cancer diagnosis each year (Royal college of General Practitioners 2007).

Variation in Use of Chemotherapeutic Drugs

The audit of the use of NICE approved cancer drugs by the National Cancer Director (2004) included the use of trastuzamab. These data are assumed to apply mainly to the use of trastuzamab in advanced breast cancer as the review was prior to the start of its use in early breast cancer. Although there was a nearly threefold difference in the level of its use by Acute Trusts across England in 2005, this had reduced from an over fourfold variation in 2003. A similar pattern was seen for the other cancer drugs reviewed.

Distance from Radiotherapy Centres

Distance from radiotherapy centres is a significant factor in the equity of provision of radiotherapy services. It has a more marked impact in early breast cancer with this particular therapy as patients are often required to travel daily for treatment. Palliative radiotherapy is usually delivered as a single dose, but several visits may be required, and the variation in distance to travel will still impact upon patients and carers. Pure distance does not capture all the variables which affect equity of access in this case but gives one method of assessing the access. This may also be affected by the availability of public transport in the area and the time to travel on these

[3] Survival – in this case refers to relative survival - the proportion of people diagnosed with breast cancer who are living at the end of a defined period of time (for example, after five or ten years) when compared to similar people of the same age who do not have breast cancer. This measure takes into account deaths from other causes.

[4] Prognosis - a prediction of the probable course and outcome of a disease.

roads. There are large areas that are over 50km by road from their local radiotherapy centre. These are rural areas with low levels of population, but 7% of the population of England and Wales do live more than 50km from their radiotherapy centre. 15% of the Welsh population live more than 50km away from their local centre.

Summary

There is little information available regarding advanced breast cancer. Up to 40% of those diagnosed with breast cancer will develop advanced disease within 10 years. This means that we have very little information with which to plan services for the future or to estimate resource use and better information is needed for this purpose.

Variation in outcomes does not appear to vary geographically. However, mortality from breast cancer is highest in those from higher socioeconomic groups, and survival is poorest in those from lower socioeconomic groups. Information is insufficient to assess variations in most treatments and services for advanced breast cancer, but evidence shows that access to NICE approved drugs and physical access to radiotherapy centres does vary across the country.

1.4 Summary of findings from breast cancer teams peer review in England 2004–2007

Following the publication of the updated NICE guidance on 'Improving outcomes in breast cancer' (NICE 2002) a process was put in place in England (as for other cancer sites covered by service guidance from NICE or the Department of Health) to monitor progress made in implementing the changes in service organisation and delivery which had been recommended.

Breast cancer care was the first to be managed by multidisciplinary teams (MDTs), starting in the early 1990s. All these MDTs were reviewed in the first round of cancer peer review carried out in 2001 and many had been reviewed in predecessor systems too.

Between November 2004 and May 2007 each cancer network in England and all the designated breast cancer MDTs were reviewed by a team of clinical peers. A total of 174 breast cancer MDTs were included as part of this 2004-2007 peer review round. Of these, 88% had a full core team membership in place (a figure exceeded only by specialist urology cancer teams) although only half of the teams met the updated guidance requirement (NICE 2002) to have two core members in all the key disciplines.

For breast cancer teams alone, core members are required to spend at least half of their clinical time on breast cancer management. Only half of the teams reviewed complied with this measure, the most frequent source of non-compliance being histopathologists.

Compliance to attend MDT meetings (at the 50% minimum attendance level) was high at 77% and exceeded only by specialist teams in gynaecological and urological cancer.

The extant NICE Guidance (2002) requires hospital-based follow-up (after treatment of early breast cancer) to be limited to a maximum of three years. A total of 40% of cancer networks did not consent to this and several others, despite having guidelines to that effect, did not expect them to be followed. The 2002 guidance also seeks movement towards harmonisation and alignment of screening services with symptomatic services. Less than half of the cancer networks had carried out the required review and only a third had actually developed an action plan.

There is high compliance with patient experience measures (e.g. patient surveys) in most breast cancer teams but only 69% of teams were allocated a key worker.

As many as 16 (9%) of the breast cancer teams had workload volumes of less than 100 patients a year. Most of these teams had low overall compliance levels with all breast cancer measures.

Overall compliance with all cancer measures by breast cancer teams was 77% which is amongst the highest for all cancer sites (exceeded only by specialist gynaecological cancer teams). However, 5% of teams had total compliance levels of under 50%.

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2 Presentation and Diagnosis

2.1 Making a diagnosis

Imaging

A new diagnosis of advanced breast cancer may be suspected in patients who have previously been treated for breast cancer, and who present with symptoms such as bone pain, dyspnoea, nausea, abdominal discomfort and general malaise. Occasionally metastatic disease may be suspected at first presentation.

The initial investigation depends on the presenting symptoms, for instance a chest radiograph performed to investigate dyspnoea or radiographs to assess localised bone pain. Once a diagnosis of advanced breast cancer is suspected either clinically or on initial imaging, it is routine practice to confirm the diagnosis and to assess the extent of metastatic disease with more imaging (commonly referred to as staging). This may include assessment of the commoner sites of metastasis including lung, liver and bone. A variety of imaging techniques are available: plain radiography, ultrasound, bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography fused with computed tomography (PET-CT).

Unlike imaging with X-rays or MRI, PET provides functional information by using 18F-deoxyglucose (FDG), a glucose analogue labelled with positron emitting fluorine. Most malignant tumours have a higher glucose metabolism than normal tissue, take up more FDG than the surrounding tissue and emit more positrons, so areas of malignancy show up as areas of increased activity on the scan. When PET is fused with CT functional information can be accurately located anatomically.

Recommendations

- Assess visceral metastases using an appropriate combination of plain radiography, ultrasound, CT scan and MRI.
- Use either bone windows on a CT scan, MRI or bone scintigraphy to assess the presence and extent of metastases in the bones of the axial skeleton.
- Assess proximal limb bones in patients with evidence of bone metastases elsewhere, for the risk of pathological fracture using either bone scintigraphy and/or plain radiographs.
- Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example lytic metastases encroaching on the spinal canal).
- PET-CT should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

Qualifying statement: There was insufficient evidence to support the choice of one imaging modality over another but there was GDG consensus that imaging should still be used to assess the extent of advanced breast cancer.

Clinical Evidence

Two systematic reviews (Isasi et al., 2005 and Shie et al., 2008) and fifteen small comparative studies or case series (Abe et al., 2005, Altehoefer et al., 2001, Bradley et al., 2000, Bristow et al., 2008, Cook et al., 1998, Engelhard et al., 2004, Eubank et al., 2001, Eubank et al., 2004, Fueger et al., 2005, Haubold-Reuter et al., 1993, Kamby et al., 1987, Nakai et al., 2005, Schirrmeister et al., 1999, Schmidt et al., 2008 and Ternier et al., 2006) formed the evidence base for the topic on imaging to determine disease extent. Other than the reviews, papers were generally of poor to medium quality and many were retrospective studies.

MRI and FDG-PET were equal to or better than scintigraphy in visualising bone metastases, other than osteoblastic lesions, but whole body MRI was better than FDG-PET at detecting distant metastases particularly in abdominal organs, brain and bone. MRI also detected previously unidentified metastases, including those that were non-skeletal and, in one study, the treatment plan was changed accordingly in ~43% of patients.

CT had a high diagnostic value in detecting local breast cancer recurrence and, when the field was extended to include the pelvis, also had a higher diagnostic accuracy in detecting bone metastases than scintigraphy.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Pathology

Histological verification of metastatic disease is not needed routinely in patients who have a history of previous breast cancer and in whom the pattern of metastatic disease is consistent with breast origin, but sometimes is appropriate. For example:

- If the imaging findings are equivocal such as a solitary liver lesion not diagnostic of metastatic disease.
- If a patient presents with metastatic cancer of possible breast origin without a history of a previous primary breast cancer.
- If patients have a history of more than one different primary cancer in the past and therefore the source of the metastatic disease may be uncertain.

The treatment of patients with advanced breast cancer is guided by a number of factors including the hormone receptor (oestrogen and progesterone receptor) status and the expression of HER2 of the primary tumour or the metastases. Current practice in some centres is to establish oestrogen and progesterone receptor and HER 2 status on all newly diagnosed breast cancers. However there is no evidence that assessing progesterone receptor

status adds significant information to oestrogen receptor status in predicting response to hormone treatment (see Chapter 4 of the NICE full guideline on Early Breast Cancer: diagnosis and treatment). It is not routine practice to reassess receptor status on recurrence. If the receptor status of the primary tumour is unknown and further analysis is not possible, it may be necessary to biopsy the metastatic disease.

Recommendations

- Patients with tumours of known oestrogen receptor status whose disease recurs should not have a further biopsy to reassess oestrogen receptor status.

Qualifying statement: Although there is some evidence from observational studies that oestrogen receptor status can change on recurrence, there was GDG consensus that there are few clinical situations in which re-biopsy can be justified.

- Patients with tumours of known HER2 status whose disease recurs should not have a further biopsy to reassess HER2 status

Qualifying statement: The evidence about change in HER2 status was poor and there was no evidence about how to manage patients in whom a change was detected.

- If receptor status (oestrogen receptor and HER2) was not assessed at the time of initial diagnosis then it should be assessed at the time of tumour recurrence. In the absence of any tumour tissue from the primary tumour a biopsy of a metastasis should be obtained if feasible.

Qualifying statement: This recommendation is based on the GDG consensus that knowledge of receptor status will significantly affect management.

Clinical Evidence

The evidence for this topic was provided by seventeen observational studies all of which compared paired (from the same patient) biopsy or fine needle aspirate samples from primary and locoregional or metastatic tumour tissue. Her2 (Niehans et al., 1993, Shimizu et al., 2000, Gancberg et al., 2002, Carlsson et al., 2004, Regitnig et al., 2004, Gong et al., 2005, Zidan et al., 2005, Lorincz et al., 2006, Rom et al., 2006, Pectasides et al., 2006, Tapia et al., 2007 and Santinelli et al., 2008) and/or endocrine receptor (Spataro et al., 1992, Johnston et al., 1995, Lower et al., 2005, Rom et al., 2006, Shimizu et al., 2000 and Brankovic-Magic et al., 2002) status was determined by immunohistochemistry or in situ hybridisation. All study participants had advanced breast cancer.

The majority of papers were concerned with identifying the rate of status change but did not address overall survival, time to progression or quality of life. Approximately 15% of patients showed a change in endocrine receptor status, from positive to negative, comparing primary with locoregional or metastatic tumour samples. 93% of patients tested for HER2 status showed no change between paired samples.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

2.2 Monitoring disease progress

Imaging is useful in assessing how patients respond to treatment. The choice of imaging technique will depend on the site of the patient's metastatic disease.

The progress of bone metastases is difficult to assess. Those due to breast cancer may be either osteolytic, osteoblastic (sclerotic) or mixed osteolytic and osteoblastic. Plain radiographs are relatively insensitive in assessing lytic bony metastases because 50% of the bone matrix may be destroyed before a lucency is visualised. When osteolytic metastases heal, new bone is laid down and the lesion then appears sclerotic; however new areas of sclerosis could also be due to the development of new osteoblastic metastases. It is therefore not always possible to say whether new sclerotic lesions in bone indicate healing and a response to treatment, or disease progression. Osteoblastic bony metastases are regarded as unassessable on plain radiographs.

There can also be problems with bone scintigraphy which detects bony metastases by the osteoblastic response excited by the presence of the tumour. This means that bone scintigraphy is more sensitive for detecting osteoblastic than lytic metastases but, like plain radiographs, cannot distinguish between healing of previously lytic disease and progression of osteoblastic disease. If a bone scintigram is done early in treatment, a so-called 'flare reaction' may be seen in which there is an increase in the degree of abnormal activity on the bone scintigram due to the healing osteoblastic response.

Ultrasound can be used to monitor the progress of liver metastases but is affected by factors such as patient body habitus and inter-operator variability, and is much less reproducible than other cross-sectional techniques such as CT.

CT and MRI are reproducible cross-sectional techniques which can be used to assess disease progress. PET-CT has the potential to provide additional functional information. Estradiol labelled with positron emitting fluorine (FES) has been used as an alternative to 18F-deoxyglucose (FDG) in breast cancer patients who are oestrogen receptor positive and may be helpful in indicating whether the metastatic disease is likely to respond to endocrine therapy.

Recommendations

- Do not use bone scintigraphy to monitor the response of bone metastases to treatment.

Qualifying statement There is a poor evidence base with a single prospective study. There is no evidence that bone scintigraphy can be used to assess the response to treatment.

- Do not use PET-CT for monitoring patients with advanced breast cancer

Qualifying statement: There is no evidence that monitoring with PET-CT improves management compared to standard imaging modalities in patients with advanced breast cancer.

Clinical Evidence

The evidence for this topic was limited comprising six small case series, five of which were retrospective (Ciray et al., 2001, Couturier et al., 2006, Huber et al., 2002, Stafford et al., 2002, Mortimer et al., 1996 and Linden et al., 2006) and describing four different imaging methods. All patients had locally advanced or metastatic breast cancer which in most papers was stated to have been bone dominant disease.

MRI fat-suppressed-long-echo-time-inversion images were superior to T1-weighted-sequence images in accurately assessing the response to the treatment of bone metastases.

Radiography detected treatment responses to any form of cancer therapy within three months in 80% of cases and differentiated between regression and progression of disease.

Fluorodeoxyglucose-PET (FDG-PET) scans correlated positively with the levels of tumour markers and clinical category suggesting efficacy in the assessment of tumour response. Semi-quantitative analysis of scan data predicted overall survival and, after three cycles of treatment, correlated with the short term response to chemotherapy. Coupled to fluoroestradiol, PET scans accurately reflected the response to endocrine therapy.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

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3 Providing Information and Support for Decision Making

The treatment of advanced breast cancer has changed considerably recently. An increase in the treatment options available has led to more complex decisions for both healthcare professionals and patients. The Department of Health has developed policies that encourage greater participation of patients in decision-making about their own healthcare and provide individuals with more choice about how, when and where they receive treatment.

In order to make decisions, patients with advanced breast cancer need to understand their diagnosis and the reasoning behind treatment options. High quality information in a language understood by the patient is fundamental to decision making and ultimately the patients' satisfaction with treatment choices. However, individual patients will have different preferences for quantity, completeness and format of information which may change over time and over the course of their illness. Some may wish to receive a lot of information from the point of diagnosis, while others will prefer to be given information gradually as treatment progresses. Information can be provided face-to-face or as written or audio-visual material, use of which can be tailored for different levels of educational attainment or mental capacity[5]. Patients need to feel confident that they have understood the information they are given and have the opportunity to ask questions.

Recommendations

- Assess the patient's individual preference for the level and type of information, and reassess this as circumstances change
- On the basis of this assessment, offer consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions.

Qualifying statement: These recommendations are based on moderate-quality evidence from randomised trials.

The level of involvement that individuals want in making decisions about their treatment and care will vary and this needs to be considered by the healthcare professionals involved in their care. Treatment choices often involve complex issues such as balancing the possible adverse effect of treatment with quality of life, and incorporating the views of family, cultural and religious beliefs and social circumstances. Decision making can increase anxiety in patients who want to be certain they are making the right choice. Individuals will need sufficient time to make their decision as well as support from the health professionals involved in their care, family, friends and people who have experienced similar situations.

Decision aids, interventions which help people make specific and deliberate choices, are available. These include tape recordings of consultations, question prompt sheets, face to face counselling and interactive computer

[5] Mental capacity act, 2005

programmes. Such aids should at least provide information on the options and potential outcomes relevant to that person's health status.

Recommendations

- Assess the patient's individual preference for how much they wish to be involved in decision making, and reassess this as circumstances change.
- Help patients make difficult decisions about their treatment. Be aware of the range and value of decision aids available and make the most appropriate aid available to the patient.

Qualifying statement: These recommendations are based on moderate-quality evidence from randomised trials

Clinical Evidence

Information Provision

The evidence on patient information comprised one systematic review (Gaston and Mitchell, 2005) and five RCTs (Winzelberg et al., 2003, Jones et al., 2006, Williams and Schreier, 2005, Aranda et al., 2006 and Walker and Podbilewicz-Schuller, 2005). RCT evidence focused broadly on person to person interventions, written information or audiovisual aids.

The review found that patients with advanced disease often required as much information from their clinician as patients with early breast cancer but the desire for involvement with treatment decisions sometimes declined as disease progressed. The review found consultation tapes to be effective but general information tapes, although well received, occasionally caused confusion. Written information was only effective if pitched at the appropriate educational level for the patient. Question prompt sheets were useful and resulted in better consultations whilst giving the patient written information to take home improved communication with the family.

A web-based support group significantly reduced levels of depression, stress and anxiety in users when compared with controls. However, a nurse-led intervention of active listening, empathy and support together with provision of information cards tailored to the patient's need and coaching in self-care, stress reduction and communication was only effective for women with high initial psychological needs.

Information booklets supplemented by a patient's own clinical information were thought more likely to tell the patient something new and were considered less limited in scope when compared to a generic booklet. Patients found an automatically selected range of breast cancer literature more informative and less overwhelming than a number of self-selected booklets chosen from a computer generated list.

An audio tape of education about exercise and relaxation as a means to combat anxiety, fatigue and sleep problems associated with chemotherapy, together with a self-care diary, reduced the increase in patient-reported anxiety as treatment progressed when compared with standard care. A videotape plus a list of basic questions to be asked at a multi-disciplinary team consultation, when added to standard written information, made no

significant impact on depression, patient anxiety, quality of life or feelings of helplessness/hopelessness.

Decision Making

Two systematic reviews (O'Brien et al., 2002 and O'Connor et al., 2002) and two RCTs (Siminoff et al., 2006 & Davison and Degner, 2002) provided evidence for the use of decision aids. All were recent papers and of high quality. The majority of study participants had breast cancer.

The reviews showed that decision aids were effective for patients in their decision making, better than standard care for patients to gain knowledge and realistic expectations and better than standard care in reducing indecision, conflict and passivity. However, decisions aids made no significant difference to patients' satisfaction with their decisions or treatment choice and had no effect on health related outcomes such as anxiety or quality of life

Good evidence showed that giving patients the choice of assuming a passive, active or co-operative role in making treatment decisions with their clinician had a greater influence on treatment outcomes than the actual choices themselves.

A personally tailored software tool (Adjuvant!) giving breast cancer patients their 10-year prognosis, depending on case history and choice of adjuvant therapy, was significantly more influential on decision making than a generic pamphlet without data.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

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4 Systemic Disease-Modifying Therapy

The management of patients with advanced breast cancer is complex. When making treatment choices there is a trade off between quality of life, the risks of toxicity and the probabilities of benefit in terms of improving symptoms, quality of life or survival. Decisions need to be based on an understanding by the patient of the effectiveness and side effects of the treatments offered. Many factors will influence treatment choices. Ultimately, the choice about what treatment to have will be made by the patient, and their decision will be influenced by their beliefs, values, goals, social/family circumstances and their quality of life. Clinical advice will take into account the presence or absence of comorbidities, treatment effectiveness, performance status, the site and extent of disease, the presence or absence of symptoms, and the rate at which the disease appears to be progressing.

There are three categories of systemic disease-modifying therapy – endocrine therapy, chemotherapy and biological response modifiers. There is also the option of having no disease-modifying treatment. Supportive and palliative care will be needed by all patients along with the active treatments. Complementary therapies are also chosen by some patients instead of or together with active treatment. Their use is not discussed in this guideline.

Endocrine therapy has been used to treat patients with advanced breast cancer for over 100 years and chemotherapy for several decades. Endocrine therapy is only effective in hormone receptor positive disease whereas chemotherapy can be effective in both hormone receptor negative and positive disease. Only patients with a HER2 positive cancer will be offered treatment with trastuzumab. The decision about which treatment to use is based on an assessment of the likelihood of tumour response, relief of cancer related symptoms, improvement in quality of life and survival. This needs to be balanced against the risks of side effects of treatment. Although endocrine therapy is usually less toxic than chemotherapy, response to treatment tends to be slower in onset. In addition a number of new chemotherapeutic drugs with different side effect profiles have become available in the last few years so that uncertainties remain about the best treatment for certain individuals.

Recommendations

- For patients with hormone receptor-positive advanced breast cancer, offer endocrine therapy as first-line treatment unless there is a clinical need to achieve a rapid tumour response.
- For patients with hormone receptor-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, offer chemotherapy as first-line treatment if they are fit enough and are prepared to accept the toxicity.
- For patients with hormone receptor-positive advanced breast cancer, offer endocrine therapy following chemotherapy.

Qualifying statement: These recommendations are based on one systematic review and GDG consensus.

Clinical Evidence

Only one paper was appraised for this topic. A high quality systematic review (Wilcken *et al*., 2006) examined ten RCTs of chemotherapy vs endocrine therapy, the most recent of which was published in 1995 (even though Cochrane databases were searched as recently as October 2006).

Neither chemotherapy nor endocrine therapy demonstrated an advantage in overall survival and tumour response was variable between studies. No data were presented for quality of life (QOL) or adverse events but, in narrative form, the reviewers stated that in the majority of studies chemotherapy had resulted in higher levels of toxicity (predominantly nausea, vomiting and alopecia) but that it was not clear in which direction QOL had been affected as the results were conflicting.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

4.1 Endocrine Therapy

Hormonal therapies are widely used in the management of advanced breast cancer. A range of different treatment options is available and many patients will be treated with several of these during the course of their illness. Endocrine therapy is appropriate for the approximately 70% of patients who have hormone receptor positive advanced breast cancer. It has no role in the management of patients with hormone receptor negative breast cancer. Although not used in combination with chemotherapy, endocrine therapy is combined in certain circumstances with biological response modifiers, although high-quality evidence to justify this is lacking.

Tamoxifen was the first line endocrine treatment for advanced breast cancer for many years. More recently aromatase inhibitors (AIs) have been used as first line endocrine treatment in postmenopausal women with advanced breast cancer.

Many patients will have received adjuvant endocrine therapy with either tamoxifen or an AI (NICE, 2006) for primary breast cancer prior to developing advanced breast cancer and some may relapse while still taking them. There is currently no evidence on the most appropriate endocrine treatment for patients who have received prior treatment with an AI.

Other endocrine therapies include ovarian ablation for pre-menopausal women and fulvestrant for postmenopausal women. Older, less often used therapies include progestogens, androgens, stilboestrol and trilostane, the latter two are licensed for postmenopausal women only.

The factors that need to be taken into account when considering what endocrine therapy is appropriate for a particular patient include:

- Whether or not they have had previous endocrine therapy (including as an adjuvant)
- If so, which agent
- The extent and duration of any previous response to endocrine therapy
- Menopausal status.

Definition of the menopause is a particularly difficult topic when considering the endocrine therapy of breast cancer. Aromatase inhibitor therapy is only effective in suppressing oestrogen levels in postmenopausal women; in pre-menopausal women it can actually result in elevation of estradiol levels. In the UK a woman is usually regarded by gynaecologists as postmenopausal if one year has elapsed since the last menstrual period, in the absence of any other cause (e.g. pregnancy). A number of the therapies used in the primary and adjuvant treatment of breast cancer, including chemotherapy and endocrine therapy with tamoxifen, can result in a temporary lack of menstruation. There are reports of women who had been amenorrhoeic for more than one year following adjuvant chemotherapy being treated with aromatase inhibitors and then subsequently becoming pregnant.

In the light of these uncertainties our recommendations are based on the following definitions:

- A woman who has been amenorrhoeic for more than one year should be regarded as being postmenopausal unless she has previously had chemotherapy, endocrine therapy with tamoxifen, hormone replacement therapy or a hysterectomy (without bilateral oophorectomy), and provided there is no other obvious cause such as pregnancy.

- A woman who does not meet the definition of postmenopausal given above before starting chemotherapy, should not be considered postmenopausal until two years without menstruation have elapsed since completing that treatment.

- If a woman does not meet the definition of postmenopausal given above before starting tamoxifen, caution should be exercised before introducing aromatase inhibitors

- Women who have had a hysterectomy (without bilateral oophorectomy), or women who have been treated with HRT that includes a monthly withdrawal bleed, should be over 55 before being considered postmenopausal

Measurement of serum FSH, LH and estradiol levels may be a useful adjunct to clinical evaluation in some situations.

Recommendations

- Offer a third-generation aromatase inhibitor (either non-steroidal or steroidal) to:
  - postmenopausal women with hormone receptor-positive breast cancer and no prior history of endocrine therapy

- postmenopausal women with hormone receptor-positive breast cancer who have previously been treated with tamoxifen.

Qualifying statement: these recommendations are based on high quality evidence of clinical and cost effectiveness. There is not enough evidence to recommend any particular aromatase inhibitor.

- Offer tamoxifen as first-line treatment to pre-menopausal and peri-menopausal women with hormone receptor-positive advanced breast cancer not previously treated with tamoxifen.
- Offer ovarian suppression to pre-menopausal and peri-menopausal women who have responded to tamoxifen and then develop progressive disease.

Qualifying statement: these recommendations are based on evidence of clinical effectiveness from one high-quality systematic review of randomised trials in pre-menopausal women. There was GDG consensus that peri-menopausal women should be treated in the same manner.

- Offer tamoxifen as first-line treatment to men with oestrogen receptor-positive advanced breast cancer.

Qualifying statement: This recommendation is based on evidence from two small retrospective case series and GDG consensus that this was an appropriate and effective treatment.

Clinical Evidence

Women

The evidence base for this question comprises one guideline (Eisen et al., 2004), four systematic reviews (Mauri et al., 2006; Gibson et al., 2007; Ferretti et al., 2006 and Crump et al., 1997), three RCTs (Chia et al. 2008, Mouridsen et al. 2007 and Goss et al. 2007) and a small, low quality comparative study (Catania et al. 2007a). The number of study participants exceeded 30,500 women, the majority of whom were post-menopausal with metastatic breast cancer. Most of the papers were of high quality, although the guideline did review non-published abstracts.

Pre-menopausal women with metastatic breast cancer experienced no significant difference in tumour response or survival between ovarian ablation and tamoxifen as first line therapy. Atamestane and toremifine as first line combination therapy resulted in similar tumour response and survival compared with letrozole alone.

Fulvestrant and exemestane showed equal clinical benefit for women that had previously received non-steroidal AIs for the treatment of advanced breast cancer. Limited evidence also suggested that fulvestrant conferred short term benefit to heavily pre-treated women with metastatic disease by postponing the requirement for chemotherapy.

Good evidence showed that there was significant clinical benefit, increased progression-free survival and ~13% reduction in the risk of death with third generation AIs compared with standard endocrine therapy (the analyses included all treatment lines). No individual AI was better than another in this

regard. Very limited evidence suggested that there was no significant difference between the AIs and standard therapy in patient reported quality of life. However, more gastro-intestinal symptoms and hot flushes were associated with AI therapy compared to standard endocrine therapy but were fewer reports of blood clots and vaginal bleeding.

Men

Three papers (Kantarjian et al. 1983, Patel et al. 1984 and Lopez et al. 1985a) presented case series of men who had received a great variety of endocrine therapies, including surgery. None of the treatments were highlighted for specific analysis and the numbers of each patient sub-group are too low to make a summary of any value.

Otherwise, there were eight retrospective case series (El Omari-Alaoui 2002, Giordano 2002, Harris et al. 1986, Lopez 1985b & 1993, Patterson et al. 1980 and Ribeiro 1976 & 1983) which reviewed data from case files of male patients treated for breast cancer. The papers spanned nearly three decades and involved 321 males - four papers were from the United Kingdom. None of the studies were comparative and, although of low quality, represent probably the best available evidence on this topic.

Very limited evidence (n=5) suggested that aminoglutethimide may be suitable therapy for men with advanced breast cancer who have been previously orchidectomised. Diethylstilboestrol therapy was effective for men with soft tissue disease but failed to elicit a significant tumour response in those with more widespread metastatic breast cancer.

Limited evidence suggests that cyproterone was an effective therapy in some men but there were no factors by which response could be predicted and the treatment resulted in impotence and loss of libido for many patients. Androgen blockade with buserelin did not appear to enhance the response but may have prevented response flare. A very limited case series (n=5) showed that anastrazole therapy did not result in a positive response in ER +ve males with metastatic breast cancer.

Two poor quality studies reviewed data on treatment with tamoxifen. Some patients were included in both studies. The authors reported objective response rates from 37.5% to 48% and response duration from 1 month to 5 years. Where endocrine status was known, only the ER +ve sub-group was associated with favourable tumour response. Few adverse events were reported.

Health Economic Evaluation

This question yielded a relatively large evidence base so the review criteria were tightened to include those studies that were most relevant to the decision problem; thus only studies taken from the perspective of the UK NHS were reviewed. A total of five studies met the stricter inclusion criteria from an initial search which identified 358 papers. No additional papers were identified in an update search. None of the economic evaluations compared hormone therapy with a ‘do-nothing’ alternative, probably due to the fact that hormone

therapy in postmenopausal women with advanced breast cancer is standard clinical practice. Neither did any of the evaluations compare all the relevant interventions against each other.

The three older studies evaluate various third-generation aromatase inhibitors (AIs) against Megestol as second-line treatment which was the standard hormone therapy at the time. The more recent studies evaluate Letrozole against Tamoxifen as first-line treatment, in line with current clinical practice.

Study	Line of therapy	Intervention	Comparison
Karnon and Jones, 2003	first	Letrozole	Tamoxifen
Karnon and Johnston et al, 2003	first	Letrozole (then tamoxifen)	Tamoxifen (then letrozole)
Lindgren et al 2002	second	Exemestane	Megestrol
Drummond et al, 1999	second	Anastrozole	Megestrol
Nuijten et al, 1999	second	Letrozole	Megestrol

All studies presented cost-effectiveness analyses (results in terms of cost per life years gained) and the two Karnon papers also presented cost-utility analyses (results in terms of cost per QALYs gained). Since we are investigating the use of AIs in the treatment of patients with advanced breast cancer, a consideration of quality of life is particularly important.

All studies used modelling techniques to model the decision problem over a lifelong time horizon. This meant including the costs and health benefits associated with subsequent treatment. All papers used RCTs to inform the clinical data and costs from nationally published sources. The Karnon and Jones and the Nuijten analysis used a similar model structure that was more comprehensive than the other models, using a Markov process and allowing for various clinical pathways subsequent to hormone treatment. Expert opinion was ascertained using formal methods of elicitation in these studies. None of the studies used the current discounting recommendation of 3.5% for both health benefits and costs; many of the studies used differential discount rates. By using a lower discount rate for health benefits these studies will have overestimated future health benefits of the interventions which would result in higher incremental cost effectiveness ratios than have been reported. However since the time horizon is not long (lifetime perspective yet never more than 6 years) this effect is not likely to change the conclusions from the studies.

All baseline ICERs for the comparison between Letrozole or Anastrozole and Tamoxifen were below £5,075 per life year gained and £9,200 per QALY. Similar results were obtained for Letrozole, Anastrozole or Exemestane versus Megestrol with a maximum ICER of £9,667 per life year. All of these results were tested to varying degrees of sophistication with sensitivity analysis and were robust to all scenarios presented. However a major limitation of the studies was that all were supported by the pharmaceutical

industry. Since not all assumptions were tested, bias from this source cannot be ruled out. In addition none of the studies compared third-generation aromatase inhibitors against each other, so there is no evidence as to which AI is most cost-effective, in either the first- or second- line setting.

An independent analysis would be useful, especially if it incorporated indirect comparison methods to compare all the interventions of interest against each other. This was not undertaken as part of the economic work for this guideline since it was felt that the evidence showed all the baseline ICERs for new AIs in first- or second-line fall within an acceptable level of cost-effectiveness; thus independent modelling on this topic was not considered a high priority.

Research recommendations

- Clinical trials are needed to investigate the most effective endocrine therapy for postmenopausal women with oestrogen receptor-positive tumours who progress on treatment with a third-generation aromatase inhibitor.
- Clinical trials are need to investigate the effectiveness of ovarian suppression in combination with an aromatase inhibitor compared with that of tamoxifen in pre-menopausal women with oestrogen receptor-positive tumours.
- All randomised controlled trials of treatment after failure of all available treatments for which good quality evidence exists should either contain a placebo arm, or provide a valid justification for not doing so.

4.2 Chemotherapy

Chemotherapy is used in the treatment of both hormone receptor positive and negative patients with advanced breast cancer. Despite the risks of toxicity the benefits in terms of symptom control, quality of life and survival mean that it is an appropriate option for many patients. A number of different chemotherapy drugs, or classes of drug, are active, including anthracyclines (doxorubicin, epirubicin), taxanes (docetaxel and paclitaxel), capecitabine, vinorelbine, gemcitabine, alkylating agents such as cyclophosphamide, and platinum-based drugs such as carboplatin.

First generation cytotoxic drugs were relatively ineffective as single agents and so were often used in combinations. As more effective agents have been developed, they have more often been used sequentially as single agents rather than in combination. However there are uncertainties (and practice variation) about whether this is an appropriate policy for all patients and whether some should be treated with combination chemotherapy.

Recommendations

- Use sequential single agents on disease progression to treat the majority of patients with advanced breast cancer who require chemotherapy.
  Qualifying statement: These recommendations are based on limited randomised trial evidence and GDG consensus.

- Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity

Qualifying statement: this recommendation is based on randomized trial evidence confirming increased response rate and toxicity from combination chemotherapy and uncertainty over overall survival benefit compared with sequential single agent chemotherapy.

Clinical Evidence

Combination versus sequential chemotherapy

Evidence for comparing single chemotherapy with sequential chemotherapy comprised five RCTs (Creech et al., 1979, Chlebowski et al., 1979, Sledge et al., 2003, Smalley et al., 1976 and Baker et al., 1974) and one observational study (Chlebowski et al., 1989). The older studies were not always very stringently reported.

Two small, poor quality trials found no significant difference in tumour response, response duration, time to progression or overall survival when chemotherapy agents were given together or sequentially (on disease progression). Two other studies and a retrospective analysis of their data showed that whilst combined therapy resulted in superior tumour response and apparently significantly longer median overall survival, follow-up revealed that long term survival was no different between study arms.

One large RCT demonstrated that combining anthracycline and taxane, rather than giving the drugs sequentially in either order, resulted in a better tumour response and superior time to progression but did not improve median overall survival.

Consistently, adverse events due to combined therapy were reported as being more numerous or of greater severity than those experienced with single agents.

Combined versus single chemotherapy regimes

Evidence for comparing single chemotherapy with combined chemotherapy comprised one very high quality systematic review (n > 7,000 study participants) (Carrick et al., 2005) a more modest systematic review (Takeda et al., 2007) three RCTs (Eijertsen et al. 2004, Pacilio et al., 2006 and Martin et al., 2007) and two post-study papers published from the pivotal trial by O'Shaughnessy et al., 2002) (Leonard et al., 2006 and Miles et al., 2004).

Good evidence suggests that the relative risk of death was significantly reduced for patients given combined chemotherapy agents compared with single drugs as first or second line treatment. The advantage was greatest for combinations which did not include their comparator. Combined therapies containing anthracyclines or alkylating agents were significantly better at reducing the relative risk of death whereas taxanes did not improve survival as part of a combined therapy.

RCT evidence from three trials showed that first line treatment with combined therapies including an anthracycline and/or taxane compared with the same anthracycline or taxane, provided no survival advantages but were associated with higher levels of adverse events. Quality of life outcomes were equivocal. Similarly, a small RCT compared second line (or higher) combined therapy of vinorelbine and gemcitabine with vinorelbine alone and reported no significant difference in overall survival between arms but more adverse events with combined therapy. In contrast, a post-study analyses of long term patient outcomes from a trial of capecitabine (CAP) and docetaxel (DOC) vs DOC alone showed that either combined or sequential therapy with the two agents was significantly better in terms of survival than receiving DOC alone.

Although considerable data were published within systematic reviews about comparison of adverse events and quality of life between combined and single agent regimes the findings were equivocal across studies.

Recommendation

- For patients with advanced breast cancer who are not suitable for anthracyclines (adjuvant anthracyclines or first-line metastatic anthracyclines, or contraindicated), systemic chemotherapy should be offered in the following sequence:
  - first line: single-agent docetaxel,
  - second line: single-agent vinorelbine or capecitabine,
  - third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

Qualifying statement: This recommendation was based on the findings of a health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated.

While it was acknowledged that there is no direct evidence comparing alternative chemotherapy sequences, the GDG considered it important to explore the cost effectiveness of plausible sequences using the best available data. An indirect treatment comparison methodology was an important component of this, but it was restricted to an assessment of the relative effectiveness of alternative first-line treatments based on the available RCT data.

The base case analysis showed that the most cost-effective treatment sequence based on a threshold of £30,000 per QALY was docetaxel monotherapy followed by vinorelbine monotherapy followed by capecitabine monotherapy. The ICER for this sequence was estimated to be £23,660 per QALY. When applying a threshold of £20,000 per QALY, the most cost-effective sequence was docetaxel monotherapy followed by capecitabine monotherapy, followed by no further chemotherapy.

The GDG however acknowledged that the economic analysis was subject to a level of uncertainty that would make distinguishing between certain strategies difficult. In addition, it was the GDG's view that the benefit from three lines of

therapy was potentially underestimated in the analysis leading to ICERs that were too high. The GDG noted that the there was no strong evidence underpinning the effectiveness estimates of third-line interventions (including 'no chemotherapy') in any of the alternative strategies considered. The difference in expected benefits and costs between the optimal strategy beneath a threshold of £30,000 and the sequence docetaxel-capecitabine-vinorelbine (dominated in the base-case analysis) was very small. It was the GDG's view that essentially these two alternatives were equivalent and that the sequence docetaxel-capecitabine-vinorelbine would also be a cost effective option.

The GDG acknowledged that the existence of nationally agreed price discounts for paclitaxel can significantly alter the cost effectiveness of the sequences examined in the analysis. While it was the strong belief of the GDG that the sequence docetaxel-vinorelbine-capecitabine is cost-effective in most instances, the choice of taxane should also take into account the existence of any nationally agreed discounts.

While there is evidence to suggest that combination therapy (for example when capecitabine is used concurrently with docetaxel) may lead to improved survival, this can be associated with an unacceptable side-effect profile. However, the GDG considered that there will be circumstances when combination therapy would be appropriate and cost-effective. For example, patients may consider that a greater probability of response is important to them. Under these circumstances, patients should be made fully aware of the expected side effect profile and be likely to tolerate the additional toxicity.

The recommendations contained in the recent NICE technology appraisal guidance 116 are being incorporated into this guideline. The combination of gemcitabine and paclitaxel is only recommended as an option if docetaxel monotherapy or the combination of docetaxel and capecitabine would also be appropriate. However, the GDG considered that in the majority of circumstances, patients should start treatment with taxane monotherapy (preferably docetaxel) followed by vinorelbine or capecitabine monotherapy second line then capecitabine or vinorelbine monotherapy third line.

Clinical Evidence

Vinorelbine

The level of evidence on the use of vinorelbine (VIN) as a monotherapy or in combination with other agents is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs. As such, the findings from these studies should be interpreted with caution. The majority of patients were believed to have had prior anthracycline therapy.

<u>Vinorelbine monotherapy</u>

One small, statistically underpowered RCT (Pajk et al. 2008) compared VIN with capecitabine (CAP) in a small number of heavily pre-treated women and reported no significant difference in response or survival outcomes but more

adverse events (particularly neutropenia) in the VIN group. Two poor quality phase II studies evaluated VIN for women with metastatic disease (Udom et al., 2000 and Zelek et al., 2001) finding that as second or third line treatment response rates of up to 41%, response duration of 4 months and time to progression of ~2.75 months were reported.

Vinorelbine combined therapy

Two poor to moderate quality RCTs tested VIN in combination with 5'-fluorouracil (5´-FU) vs docetaxel (DOC) - Bonneterre et al., 2002) or gemcitabine (GEM) vs VIN - Martin et al., 2007). VIN + 5´-FU combined resulted in similar treatment outcomes as DOC monotherapy but with a higher incidence of neutropenia. VIN + GEM resulted in superior progression-free survival, but not significantly different overall survival or response duration, compared with VIN alone.

Thirteen poor to moderate quality phase II, non-comparative, studies described VIN combined with: trastuzumab (TRZ) (Burstein et al., 2003, Chan et al., 2006, Jahanzeb et al., 2002, Bartsch et al., 2007, De Maio et al., 2007 and Catania et al., 2007), CAP (Ghosn et al., 2006 and Davis, 2007), DOC (Mayordomo et al., 2004), GEM (Ardavanis et al., 2007 and Colomer et al. 2006), 5'-FU (Stuart, 2008), mitozantrone (MTZ) (Onyenadum et al. 2007), cisplatin (CIS) followed by DOC (Shamseddine et al. 2006) and CAP followed by DOC (Ghosn et al. 2008).

For all phase II combination studies, the overall tumour response rates ranged from 33-75%, median overall survival from 13-35.8 months, median response duration from 2.6-17.5 months, median time to progression (reported in two studies) from 6.6-8.6 months and median progression-free survival (reported in two studies) from 9.6-9.9 months. The most commonly reported adverse events attributed to VIN were neutropenia, nausea and vomiting and alopecia.

Capecitabine

The level of evidence on the use of capecitabine (CAP) as a monotherapy or in combination with docetaxel (DOC) is generally of poor quality consisting mainly of low patient number, non-comparative phase II studies with one good phase III RCT. As such, the findings from these studies should be interpreted with caution.

Capecitabine monotherapy

Nine phase II studies (El Helw and Coleman, 2005, Fumoleau et al., 2004, Lee et al., 2004, Pierga et al., 2004, Reichardt et al., 2003, Wist et al., 2004, Sezgin et al. 2007, Venturini et al. 2007 and Yap et al. 2007) and one retrospective case series (Leonard et al., 2002) were identified. The majority of patients are believed to have been treated with anthracycline and taxane.

Across all studies, the overall tumour response rates ranged from 10-42%, median overall survival from 9.4-18.1 months, median response duration from 3.8-15.4 months and median time to progression from 3.5-6.6 months. The most commonly reported adverse event was hand-foot syndrome which at grade 3/4 occurred in up to 21% of patients.

Capecitabine combined therapy

The evidence for combined therapy with CAP and DOC comprised one phase III RCT (Chan, 2005) three phase II studies (Mackey et al., 2004, Silva et al. 2008 and Mrozek et al. 2006) and a retrospective analysis of post-study data (Miles et al., 2004).

The RCT compared CAP + DOC with gemcitabine and reported no significant difference between study arms in overall response rate, median time to treatment failure or response duration. There were higher levels of hand-foot syndrome and diarrhoea in the CAP and DOC arm. Phase II studies offered poor quality and conflicting evidence on reduced doses of CAP and DOC reporting overall tumour response rates ranged from 44-50%, median overall survival of ~19 months (1 study), median response duration of ~ 9.1 months (1 study) months and median time to progression of ~5.5 months (1 study). A post study analysis of a pivotal RCT (O'Shaughnessy et al., 2002) confirmed a survival advantage with CAP and DOC, either combined or sequentially, when compared with either agent as monotherapy.

Taxanes

There was good quality evidence on the use of taxanes as first or second line monotherapy or in combination, comprising a high quality Cancer Care Ontario guideline (Verma et al., 2003), two good systematic reviews (Ghersi et al., 2005 and Bria et al., 2005) and three RCTs (Lin et al. 2003, Cassier et al. 2008 and Jones et al., 2005). The total patient number exceeded 14,800.

Anthracycline naïve women did not derive any benefit from paclitaxel (PAC) as first line monotherapy compared with controls. A large systematic review found that for anthracycline naïve patients, when taxanes were added to anthracycline based regimes, there were no significant differences in time to progression (TTP) or overall survival (OS) but tumour response was significantly improved. However, PAC and doxorubicin (DOX) combined therapy resulted in superior median OS and TTP compared with cyclophosphamide, 5´-FU and DOX. There was no evidence to suggest a significant difference in quality of life between DOC and PAC when either was combined with anthracycline as first line therapy.

Meta-analysis demonstrated significant improvements in TTP, tumour response and time to treatment failure in favour of taxane containing regimes compared with non-taxane containing regimes and a borderline advantage in OS. However, statistical significance for OS and TTP was lost when only first line therapy with taxanes was considered. Taxanes and taxane-containing regimes were reported to have a higher incidence of neurotoxicity and leukopenia but fewer cases of nausea and vomiting than controls.

PAC monotherapy was preferable to mitomycin in terms of TTP but not other outcomes. DOC monotherapy correlated with improved OS (compared with combined mitomycin and vinblastine) and improved TTP and tumour response compared with several other multi-agent therapies. Good RCT data demonstrated a significant advantage in OS, TTP and response duration for

patients on DOC versus PAC monotherapy although the tumour responses were similar. Another RCT found no significant differences in efficacy or survival outcomes between PAC and DOC as first-line therapy combined with DOX then given as monotherapy.

Health Economic Evaluation (see also Appendix 1)

Introduction

The choice of chemotherapy regimens with which to treat patients with advanced breast cancer has been the subject of many economic evaluations. Despite this, none of the economic studies identified by a systematic review of these topics provided a comprehensive analysis with which to answer the review question. The guideline development group identified that sequential use of chemotherapy agents was an important comparator that to date has not been evaluated against combination therapies. In addition none of the economic evaluations compared more than three different interventions. An independent modelling exercise was conducted to address these concerns. In the absence of direct evidence, an indirect treatment comparison was also conducted on first-line treatment options to make use of all the data from available randomised controlled trials.

Methods

Four first-line therapies, two second-line therapies and two third-line therapies were considered in the analysis. In addition the guideline development group thought a 'no chemotherapy' option consisting of supportive and palliative care was an important and relevant comparator to the active chemotherapy options, although it was acknowledged no data were available on this 'intervention' so expert opinion was used to inform the parameters. It was assumed a chemotherapy agent cannot be reused later in a sequence of therapy so in total seventeen strategies were evaluated against each other in a decision analytic framework.

The perspective adopted was that of the UK National Health Service in line with the NICE Reference Case for economic evaluations. Given the nature of metastatic disease, quality of life was considered a particularly important outcome. As such a cost-utility analysis was undertaken with quality adjusted life years (QALYs) as the primary health outcome. QALYs were estimated using published utility values derived from oncology nurses (Cooper et al. 2003). The secondary health outcomes assessed were life years and progression-free life years.

A decision tree was constructed to represent the seventeen sequences of chemotherapy agents, and the potential for encountering toxicities or not responding to treatment.

The clinical evidence required to populate the model was obtained from a number of different sources. An indirect treatment comparison was conducted to synthesise data from eight RCTs investigating first line (post-anthracycline) chemotherapy for advanced breast cancer. This provided consistent data on the probabilities of toxic death, discontinuing treatment due to toxicity, response or disease stabilisation and progression-free survival estimates

associated with each intervention. Second-line data for vinorelbine were estimated from an RCT (Martin et al, 2007) with a mixed patient population (in terms of line of treatment received) and second-line data for capecitabine from a non-randomised retrospective study (Pierga et al, 2004). Third-line treatment was assumed to be as effective as second-line treatment. No evidence was available for the 'no chemotherapy' option, so expert opinion was sought from the guideline development group. No evidence was available on overall survival resulting from any of the strategies, so this was assumed to be equal to the sum of time to progression from each line of treatment, plus the time lag between ending one treatment and starting another (1 month), plus the time from progression to death (estimated to be 5 months).

The costs considered in the analysis were those relevant to the NHS, and included drug acquisition costs, administration costs, cost of assessment and follow-up, cost of treating adverse events, cost of supportive and palliative care. Costs were based on NHS Reference Costs or taken from the literature, and were estimated using 2006-7 prices. When necessary, costs were uplifted using the Hospitals and Community Health Services Pay and Prices Index (PSSRU, 2007). Discounting was not carried out; neither on costs nor benefits. However, since the time horizon of the decision model (lifetime) was short, this limitation is unlikely to affect the results or conclusions that can be drawn from the analysis. A series of one-way deterministic sensitivity analyses were conducted to assess the robustness of the study results by varying the values of relevant parameters in order to identify those variables that had the biggest impact on the results.

Summary of results

The results of the base-case analysis showed that the total QALYs ranged from 0.36 to 1.19 per patient, whilst total costs per patient were estimated to range from £14,000 up to £31,500. An incremental analysis was undertaken on the results, comparing each strategy (or sequence of therapies) against the next best alternative after first removing any dominated strategies (highlighted in grey in table 1). Using a threshold value of £20,000 per QALY, strategy 14 (docetaxel followed by capecitabine followed by no chemotherapy) was shown to be most cost-effective since it maximises health benefits given the budget constraint. However the guideline development group considered a higher threshold value of £30,000 per QALY, at which strategy 15 (docetaxel followed by vinorelbine and then capecitabine) would be considered most cost-effective since it maximises QALYs. Due to the multitude of strategies in the analysis, the results need careful interpretation. Since there is very little difference between strategies 13 (docetaxel followed by capecitabine followed by vinorelbine) and 15, in terms of QALYs, and given the uncertainty surrounding these point estimates, it is not clear which strategy is dominated and thus which should be excluded from the incremental analysis.

Table 1: Results of the base-case analysis

Strategy	T1	T2	T3	Total Expected QALYs	Total Expected Costs	ICER
3	GEM+DOC	CAP	VIN	1.1896	£31,479	**£160,748**
5	GEM+DOC	VIN	CAP	1.1857	£30,859	**£40,959**
6	GEM+DOC	VIN	No Chemo	0.8230	£27,124	
13	DOC	CAP	VIN	1.0738	£26,442	
4	GEM+DOC	CAP	No Chemo	0.9734	£25,882	
15	DOC	VIN	CAP	1.0592	£25,675	**£23,660**
8	PAC	CAP	VIN	0.9739	£24,521	
10	PAC	VIN	CAP	0.9642	£23,872	
16	DOC	VIN	No Chemo	0.6997	£21,962	
1	DOC+CAP	VIN	No Chemo	0.7694	£21,406	
7	GEM+DOC	No Chemo		0.5827	£21,056	
14	DOC	CAP	No Chemo	0.8500	£20,727	**£19,072**
11	PAC	VIN	No Chemo	0.6009	£20,119	
9	PAC	CAP	No Chemo	0.7527	£18,871	**£16,119**
17	DOC	No Chemo		0.4718	£15,928	
2	DOC+CAP	No Chemo		0.5452	£15,526	**£8,325**
12	PAC	No Chemo		0.3645	£14,022	

GEM = gemcitabine; DOC = docetaxel; CAP = capecitabine; VIN = vinorelbine; PAC = paclitaxel

A number of scenarios were considered using one-way deterministic sensitivity analysis. These showed the results to be sensitive to price discounts available on paclitaxel and the effectiveness of third-line therapy. However this approach to sensitivity analysis is limited and was taken into account by the guideline development group when deliberating over the evidence.

For the full report of the economic analysis see Appendix 1.

Recommendations (from NICE technology appraisal guidance 116)

- Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

  Qualifying statement: This recommendation is from 'Gemcitabine for the treatment of metastatic breast cancer', NICE technology appraisal guidance 116 (2007). It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Research recommendation

- Randomised clinical trials should evaluate the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.

4.3 Biological Response Modifiers

Over the last 10 to 15 years the identification of some of the molecular processes occurring in breast cancer has led to the development of new treatment possibilities using agents which can be directed specifically at these

molecular processes. The term "biological response modifiers" is used to describe such treatments. They may be used alone or in combination with chemotherapy or endocrine therapy.

There are currently three main biological response modifiers used in patients with advanced breast cancer – trastuzumab, bevacizumab and lapatinib. Many more biological response modifiers are expected to gain a licence for the treatment of breast cancer over the next few years.

Trastuzumab is a recombinant humanised monoclonal antibody, given intravenously, that attaches to the HER2 receptor protein on the surface of the cancer cell and affects its growth. Trastuzumab is only used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated test. Approximately 25% of patients with advanced breast cancer have tumours that overexpress HER2. Because it does not cross the blood-brain barrier it is not effective in treating metastatic disease of the central nervous system.

Bevacizumab is a similar monoclonal antibody that affects the growth of tumour blood vessels. Lapatinib is an oral agent which affects tumour growth by switching off the metabolic pathways of the HER2 receptor and the epidermal growth factor receptor (EGFR). Lapatinib is the subject of a NICE technology appraisal (www.nice.org.uk/guidance/index.jsp?action=byID&o=11731).

Currently, trastuzumab is the only one of these agents approved for use in the NHS in England and Wales, for patients with advanced breast cancer, in combination with chemotherapy. There is controversy and practice variation about continuing its use when chemotherapy is stopped or changed at the time of disease progression.

Trastuzumab was approved by NICE in 2002 for treating women with advanced breast cancer solely in combination with paclitaxel, the only combination licensed at that time (NICE 2002). The GDG was aware of widespread adoption in the UK of the combination of trastuzumab and docetaxel, which has been licensed since the original appraisal and which was considered to be more clinically effective. Because of the limited data available from the one published trial on this new combination, it was not possible to develop a robust health economic model and so the GDG could make no recommendation about the use of the combination of trastuzumab with docetaxel. As a result the recommendations from TA 34 still stand and the GDG have recommended that a technology appraisal is conducted to investigate the clinical and cost-effectiveness of this new combination.

Recommendations

- Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel) is recommended as an option for people with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received

chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate.

- Trastuzumab monotherapy is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients.
- HER2 levels should be scored using validated immunohistochemical techniques and in accordance with published guidelines. Laboratories offering tissue sample immunocytochemical or other predictive tests for therapy response should use validated standardised assay methods and participate in and demonstrate satisfactory performance in a recognised external quality assurance scheme.'

Qualifying statement: These recommendations are from 'The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer', NICE technology appraisal guidance 34 (2005).They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

- Patients who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system.

Qualifying statement: This recommendation is based on the absence of evidence that continuing trastuzumab leads to a better outcome.

Clinical Evidence

For patients undergoing therapy with a biological response modifier who experience disease progression there was only limited evidence on trastuzumab (TRZ) which comprised a RCT (von Minckwitz et al. 2008) a prospective post RCT study (Tripathy et al., 2004) five retrospective case series (Fountzilas et al., 2003, Gelmon et al., 2004, Garcia-Saenz et al., 2005, Montemurro et al., 2006 and Stemmler et al., 2005) and a phase II study (Bartsch et al., 2006).

Limited data from a post-RCT analysis showed no significant improvements in safety or efficacy for women with disease progression who continued TRZ combined with different chemotherapies when compared with women in whom TRZ was given for the first time after their disease progressed on chemotherapy alone. Most case series also offered little evidence in support of continuing TRZ therapy beyond progression since, where relevant comparisons were made, no significant improvements were found for survival, efficacy or safety.

One retrospective case series demonstrated a significant survival advantage for women who had received both first and second line therapy with TRZ but, taken from a non-randomised study, the data was open to strong selection bias. Weak phase II evidence showed no significant difference in the length of time to progression between first, second or further lines of TRZ therapy which was interpreted as support for TRZ continuation.

A very recent, unpublished RCT showed that TRZ improved the efficacy of second line capecitabine in Her2 +ve patients with metastatic disease who had previously received TRZ in the adjuvant or first line setting. The response rate, clinical benefit rate, time to progression and overall survival were all statistically significantly superior for the combined therapy and with no additional significant toxicity.

Research Recommendation

- The use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial.
- Randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should receive further biological response modifiers.

4.4 No systemic disease-modifying treatment

The decision not to have a systemic disease-modifying treatment is an active one. Ultimately there will come a point when there is no realistic possibility of benefit from further systemic disease-modifying treatment.

Where active intervention may be appropriate the decision to accept treatment or not is made by the patient after discussion with their healthcare professional. It is a decision that needs to be supported, and does not prevent a later decision to receive an active treatment. For example, patients with hormone receptor negative, HER2 negative cancers may receive several different courses of chemotherapy, with intervals in between such treatments during which they receive no active disease-modifying treatment. A patient may, when fully informed, opt not to receive systemic disease-modifying treatment at any point, and although it is important to explore the reasons for such a choice, it is one that needs to be respected. For the majority of patients with advanced breast cancer, there will come a point when the most appropriate choice is to receive no further systemic disease-modifying treatments.

The provision of supportive and palliative care must be an essential consideration in the management of individuals with advanced breast cancer. Supportive and palliative care needs should be assessed and met throughout the patient journey, whatever treatment choices are made.

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5 Community-based Treatment and Supportive Care

5.1 Community-based treatment

Primary care and community services are a first point of contact for patients and families. Patients place high value on the relationships, often long-established, with the professionals in their Primary Care Team. Many patients with advanced breast cancer will have had a long illness pathway and, with the greater part of their cancer journey being spent at home, often have been accompanied on their journey by their GP and/or community nurse. For many, breast cancer becomes a chronic condition. Although the number of patients with advanced breast cancer is probably decreasing the level of intervention and care required is likely to increase.

Cancer treatments have traditionally been delivered in hospital. However, with the increasing volume of treatment activity at cancer centres and units, some services are beginning to develop treatment provision in the community. This includes some chemotherapy provided at home by the independent sector. Some community nursing services are developing teams with enhanced clinical skills to extend the range of treatments and care available in the community and decrease the need for hospital admission. In relation to advanced breast cancer care, this may include the monitoring of interval bloods and care of central lines with support from hospital colleagues.

Consideration of community-based treatments raises considerable challenges including the development of quality assured clinical protocols and care pathways, enhanced clinical skills in the community, a clear understanding of clinical governance responsibilities and active communication with all concerned including out of hours providers. Logistical challenges such as the timing of pharmacy preparation of regimens, safe physical delivery to where the treatment is to be administered (transport) and safe disposal of empty containers are additional considerations. Clear arrangements for the management of chemotherapy complications would also be needed. Irrespective of where treatment is administered, the patient who becomes ill needs to know what to do**,** whom to contact first, as does the primary care professional. Clinical guidance for primary care professionals (and A&E staff) on recognising an ill patient after chemotherapy together with agreed care pathways devised by oncology and primary care would minimise the risk of adverse events. Economic and workforce implications require careful consideration to avoid depletion of skilled chemotherapy nurses from centres and units.

While some treatments may be deliverable in the community, the issue of patient choice and satisfaction needs to be considered. Some patients may feel more secure in a hospital setting; others may wish to remain at home wherever possible.

Choice and Supportive and Palliative Care

Patients with advanced breast cancer have complex physical and psychosocial needs. Holistic care that aims to maximise quality of life also requires disease management and this is best achieved where oncology, supportive and palliative care services are integrated. Achieving a seamless transition from active treatment to supportive and palliative care may be difficult. When the options for active treatment become limited and the patients' insight into their poor prognosis develops, they will need support in planning for end of life care, including deciding their preferred place of care.

Clinical Evidence

One moderate quality but dated RCT (Mor et al., 1988), three small RCTs (Hall and Lloyd, 2008, Smith et al., 1994 and Majid et al., 1989) and one high quality Canadian systematic review (Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante, 2004) looked at several forms of home therapy vs in-patient treatment for patients with cancer. Only one paper specifically looked at breast cancer patients (Hall and Lloyd, 2008).

None of the studies identified a significant clinical advantage with regard to treatment in the community compared with the hospital nor was there a difference in patient quality of life, as measured by standard scales. However, there was broad agreement across studies that patient satisfaction was considerably higher with treatment in the home or community compared with the hospital in-patient experience.

Health Economic Evaluation

Although this topic was originally considered a priority for economic evaluation, the lack of clinical evidence meant it was not possible to make a recommendation. Therefore the economics were not investigated further.

Research Recommendation

Research is needed to explore whether patients with advanced breast cancer would prefer intravenous therapies to be delivered at home, near home or in the hospital setting.

5.2 Supportive Care

A diagnosis of advanced breast cancer can be devastating for the patient and their family and carers leading to anxiety, depression and uncertainty. People with advanced breast cancer and their families and carers often have complex and changing psychosocial, physical, spiritual and financial support needs.

Psychosocial needs are often influenced by family and social circumstances for example individuals caring for young children or elderly parents may need support to care for their dependents during treatment. Regular assessment of such needs may help to ensure they are met and that people are signposted to appropriate support. Access to supportive and palliative care can improve the patient's experience, but patients often report that they were unaware of the psychosocial support services available.

Patients with advanced breast cancer frequently report differences in the support available compared to when they were diagnosed with primary breast cancer. In particular there appears to be less good access to a key worker, as in many centres the breast care nurses' role ends with the diagnosis of advanced disease. Access to a key worker has been shown to be beneficial to patients and their families.

A diagnosis of advanced breast cancer may leave patients feeling isolated. They may want to contact others with a similar diagnosis or to have the opportunity to talk about their emotions and fears. There are a range of local and national support services available including counselling services, psychologists, support groups, peer support, help lines and internet forums. Families may also need access to psychosocial support services to help them cope with the impact of a diagnosis of advanced breast cancer on the family.

At a later stage in the treatment, patients and their families and carers will have to make choices about end of life preferences and will have questions about the type of palliative care services available.

All these issues have been addressed in previous NICE guidance documents on Cancer Services, '*Improving Outcomes in Breast Cancer: Manual Update* (NICE 2002) and *Improving Supportive and Palliative Care for Adults with Cancer* (NICE 2004). The former emphasises the role of the breast care nurse in ensuring patient-centred care, effective communication and access to psychosocial and practical support. The latter (which of course has a wider focus) also makes specific recommendations about the co-ordination of care and the 'nomination of a person to take on the role of 'key worker' for individual patients'.

A particular concern is the provision of care and support for younger patients with families. Unfortunately there is insufficient evidence to make a specific recommendation for this group.

Recommendations

- Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in previous NICE guidance documents ('Improving outcomes in breast cancer: Manual update' [2002] and 'Improving supportive and palliative care for adults with cancer' [2004]), in particular the following two recommendations:
  - 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points such as diagnosis at commencement, during, and at the end of treatment; at relapse; and when death is approaching.'
  - 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of 'key worker' for individual patients.'

Qualifying statement: These recommendations are based on anecdotal evidence and experience of GDG members that previous NICE guidance has not been fully implemented and GDG consensus that implementation would improve patients' experience.

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6 Management of Specific Problems

6.1 Lymphoedema

Lymphoedema is a swelling of body tissue caused by failure of the lymphatic system. In patients with breast cancer it is usually the arm on the side of the original breast cancer that is affected. It is a chronic condition resulting in discomfort, pain, functional limitation, increased risk of recurrent infections and psychological distress. In combination with disease in the axilla it can increase pressure over the brachial plexus compromising neurological function. Patients may need access to a wide multi-professional team including allied health professionals, clinical psychologists and tissue viability services as well as dedicated lymphoedema therapists.

Patients with advanced breast cancer may develop lymphoedema because of damage to the lymph nodes and vessels following surgery or radiotherapy, or by the pathological changes associated with progressive localised disease. Lymphoedema can be present at the time of diagnosis of advanced disease or develop at any point during the illness, when it may be a sign of loco-regional disease progression. It is important that potential underlying causes such as axillary thrombosis, extensive axillary or supraclavicular disease, are investigated and treated.

Early identification and management of the swelling is important, but there are no agreed diagnostic tests and assessment methods.

Complex Decongestive Therapy (CDT[6]) is the recognised conservative management of lymphoedema (Rockson et al. 1998). In the palliative setting treatment modifications may be required and outcomes may be reduced or difficult to maintain.

CDT consists of two main phases. The initial phase is an intensive period of daily treatment (five days per week) for up to six weeks delivered by a healthcare professional trained in its use. It includes:

- manual lymphatic drainage (MLD)
- multi-layer lymphoedema bandaging (MLLB)
- skin care
- remedial exercise.

The second, a maintenance phase, encourages the transfer of care from professional to patient/carers and includes:

- provision and use of compression/containment garments
- simple lymph drainage (self/carer administered)
- self skin care and exercise programme
- nocturnal bandaging in some circumstances.

[6] Complex decongestive therapy (CDT) is also known as Decongestive Lymphatic Therapy (DLT) and Complex Physical Therapy (CPT)

Lymphoedema is a chronic condition and the patient will need regular check-ups (and further intensive treatment if needed) for the rest of their life.

It may however not be clinically appropriate or acceptable to the patient with advanced breast cancer to participate in such an extensive programme.

Concerns have been raised that the massage component of CDT, manual lymphatic drainage (MLD) may cause spread of the tumour but there is no evidence to support this belief.

Although CDT is widely used, there are currently no national guidelines abouts its use, and very little reliable evidence about its effectiveness in patients with advanced breast cancer. Equally there is little evidence about the use of other interventions such as radiotherapy to obstructing tumour masses or bulk reduction surgery. It is also very uncertain how cellulitis should be managed in these patients.

The recommendations below apply to the management of lymphoedema in patients with advanced breast cancer. These treatments can be modified to fit the needs of specific patients but this will require input from a lymphoedema specialist. These recommendations are equally appropriate for the management of lymphoedema in patients with early breast cancer.

Recommendations

- Assess patients with advanced breast cancer and lymphoedema for treatable underlying factors before starting any lymphoedema management programme.
- Offer all patients with lymphoedema related to advanced breast cancer complex decongestive therapy (CDT) as the first form of lymphoedema management.
- Consider using multi-layer lymphoedema bandaging (MLLB) for volume reduction, as a first treatment option before compression hosiery.
- Provide patients with advanced breast cancer and lymphoedema with at least two suitable compression garments. These should be of the appropriate class and size, and a choice of fabrics and colours should be available.
- Provide patients with advanced breast cancer and lymphoedema with the contact details of local and national lymphoedema support groups.

Qualifying statement: these recommendations are based on GDG consensus and extrapolation of evidence of the management of patients with early breast cancer.

Clinical Evidence

Fourteen papers addressed the topic of lymphoedema management comprising a guideline (Harris et al., 2001) one very high quality systematic review (Moseley et al., 2007) two systematic reviews of less quality (Kligman et al., 2004 and Rinehart-Ayres et al., 2007) four randomised trials (Didem et al., 2005, Irdesel et al., 2007, Badger et al., 2004 and Johansson et al., 2005) and five case series or phase II studies (Vignes et al., 2007; Hamner and

Fleming, 2007; Sitzia et al., 2002, Kim et al., 2007, Koul et al., 2007 and Fiaschi et al. 1998). These papers all addressed lymphoedema management in women who had been treated for breast cancer but did not have active disease and, as such, the evidence only related to early breast cancer. The treatments evaluated included complex decongestive therapy (CDT), manual lymph drainage (MLD), pneumatic compression bandaging/garments, massage and exercise.

Intensive treatments, such as CDT and MLD, given by trained therapists and other health professionals, yielded better results than simpler maintenance treatments performed by the patient, carer or family member in the home. Patients given CDT experienced significant lymphoedema reduction and improvement in quality of life outcomes but an association between variables could not be proved definitively by a non-randomised study.

Pneumatic compression therapy was not significantly better at reducing limb volume when compared with no treatment, education or MLD but, when added to MLD, significantly improved oedema reduction and limb girth.

Multi-layer bandaging with hosiery was significantly better at reducing limb volume when compared with hosiery alone, an improvement still significant after six months.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research recommendation

- Research is needed to compare the effectiveness of complex decongestive therapy with less intensive interventions in patients with advanced breast cancer. The research should incorporate both objective and quality of life measures.

6.2 Cancer-related Fatigue

Cancer-related fatigue (CRF) is a symptom of advanced cancer. Patient advocates report that it frequently goes unrecognised. CRF is defined by the National Comprehensive Cancer Network as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning”. If unrelieved the symptoms of CRF can impair quality of life over a long period of time.

There are a variety of factors thought to contribute to CRF including the cancer treatment itself, anaemia, nutritional factors, psychological factors, cognitive factors, sleep disorders, inactivity and medications. Many advanced breast cancer patients may have co-existing chronic illness which may increase the severity of fatigue and complicate its management. As the disease progresses the experience of fatigue tends to intensify. The relationship between internal factors, both physiological and psychological,

and external environmental factors, as causal, modifying, or associated factors in CRF has not been fully investigated.

Once treatable factors such as anaemia and depression have been identified and treated, the current management of CRF is unsatisfactory. Drugs that have been used include glucocorticoids, psychostimulants, antidepressants and erythropoietin. Non-pharmacological interventions include communication, cognitive behavioural therapies, exercise and complementary therapies.

Recommendations

- Offer all patients with advanced breast cancer for whom fatigue is a significant problem an assessment to identify any treatable causative factors and offer appropriate management as necessary.
- Provide clear, written information about fatigue, organisations that offer psychosocial support and patient-led groups.

Qualifying Statement: These recommendations are based on GDG consensus and very poor quality evidence.

- Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue.

Qualifying statement: This recommendation is based on a high-quality systematic review and meta-analysis.

Clinical Evidence

Evidence on the management of cancer-related fatigue (CRF) comprised two systematic reviews (Minton et al., 2007 and Cramp & Daniel, 2008) one on drug therapies and one on exercise regimes, together with two RCTs (Headley et al., 2004 and Bordeleau et al., 2003) and a poor quality case series (Carson et al., 2007).

Good evidence showed no significant effect of progestational steroids, including megesterol acetate, compared with placebo in the treatment of CRF.

Meta-analysis of data from 28 RCTs showed a highly significant effect of exercise compared with controls on fatigue reduction both in cancer patients as a whole and in a large sub-group with breast cancer. Since the review included all forms of exercise, a specific regime, intensity or duration could not be recommended.

There were no positive outcomes from a yoga program, seated exercise activity or weekly support group meetings with respect to improving levels of fatigue as assessed by standard measurement tools. No papers were identified to determine the effectiveness of cognitive behavioural therapy or psychotherapy in patients with advanced breast cancer.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research recommendation

- Randomised controlled trials are needed to assess the value of psychological interventions in the management of fatigue in patients with advanced breast cancer. Both short- and long-term outcomes should be evaluated. An appropriate validated tool to measure fatigue should be used.
- Further research is required into which excercise programmes are most effective for patients with advanced breast cancer and to identify the most efficient way to deliver these in an NHS service.

6.3 Uncontrolled local disease

Patients with advanced breast cancer may develop local disease with skin ulceration involving the chest wall and axilla which is initially ameanable to systemic treatments, radiotherapy or surgery. Ultimately, in some patients these options may be exhausted, resulting in uncontrolled local disease. A fungating tumour may bleed, exude a discharge and become infected causing pain and an unpleasant smell. For the patient the symptoms and signs are a visible reminder of their illness and may lead to social isolation from both friends and close relatives, and further psychological distress. Carers may find it repulsive and difficult to deal with, both physically and emotionally, and this may exacerbate physical and social isolation. Sometimes patients may not even disclose the existence of a fungating tumour to their family or healthcare professionals until it has become well established.

Uncontrolled local disease is a difficult clinical condition either to eradicate or to palliate. There are a number of important issues to consider including:

- Control of infection and its associated consequences such as unpleasant smell
- Management of the wound
- Management of social and psychological consequences
- Management of pain
- Control of bleeding

The management of uncontrolled local disease needs to be individualised and will usually involve a combination of treatments. A team approach is therefore very important and will include nurses, surgeons, oncologists and psychological support.

Recommendations

- A breast cancer multidisciplinary team should assess all patients presenting with uncontrolled local disease and discuss the therapeutic options for controlling the disease and relieving symptoms.
- A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team.

- A palliative care team should assess all patients with uncontrolled local disease and their families in order to plan a symptom management strategy and to provide psychological support.

Qualifying statement: These recommendations are based on poor quality evidence, expert position papers and GDG consensus.

Clinical Evidence

The standard of publications on the topic of uncontrolled local disease was very poor comprising seven low patient number case series (Bower et al., 1992; Kuge et al., 1996; Lund-Nielsen et al., 2005; Kumar et al., 1987; Kolodziejski et al., 2005, Faneyte et al.. 1997 and Pameijer et al., 2005), the majority of which were retrospective. Whilst the studies concerned women with breast cancer, some with wounds clearly classified as fungating, others with local recurrence in the chest wall, the evidence was considered inadequate and a position paper was commissioned.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research Recommendation

- The relevant research organisations should be encouraged to address the topic of uncontrolled local disease and devise appropriate research studies. This might include development of a national register.

6.4 Bone metastases

Modern systemic anti-cancer treatment means that patients with breast cancer may live with bone metastases for a long time. Management involves:

- trying to prevent skeletal events
- controlling pain
- treating complications such as fractures, immobility, and spinal cord compression.

A variety of different treatments including bisphosphonates, external beam radiotherapy (given in a single or with multiple fractions), radionuclide therapy and surgical fixation are available. Although bisphosphonates are frequently used, it is not clear whether oral or intravenous therapy is better or which bisphosphonate is the most effective.

Rehabilitation may also be important for these patients.

Recommendations

- Offer bisphosphonates to patients newly diagnosed with bone metastases, to prevent skeletal-related events and to reduce pain.

Qualifying statement: This recommendation is based on strong evidence of clinical effectiveness in reducing skeletal related events and pain, and reasonable evidence of cost effectiveness for the NHS in preventing skeletal related events.

- The choice of which bisphosphonate to use for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication.

Qualifying statement: This recommendation was based on GDG consensus that there was no strong evidence of comparative clinical effectiveness and conflicting evidence of comparative cost effectiveness.

- Use external beam radiotherapy in a single fraction of 8 Gy to treat patients with bone metastases and pain

Qualifying statement: This recommendation was based on evidence from randomised trials.

- An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery.

Qualifying statement: This recommendation was based on GDG consensus.

Clinical Evidence

The evidence base on the management of bone metastases included a systematic review (Sze et al., 2002), a guideline (Warr et al., 2002), five RCTs (Tripathy et al., 2004, Hartsell et al., 2005, Salazar et al., 2001, Wardley et al., 2005 and Rasmussen et al., 1995), two comparative or cohort studies (Weinfurt et al., 2004 and Pecherstorfer et al., 2006) and six case series (Broos et al.,1993, Gerszten et al., 2005, Gristina et al., 1983, Scarantino et al., 1996, Borojevic et al., 1999 and Durr et al., 2002). There were no papers dealing specifically with solitary bone metastases, bone metastases as part of wider metastatic disease or rehabilitation.

Good evidence, including a treatment guideline, suggested that whilst bisphosphonates made little impact on overall survival, they could reduce pain and the occurrence of skeletal events. There was no comparative evidence to suggest that one bisphosphonate was better than others in any respect. A meta-analysis found no significant difference between oral clodronate and placebo or no treatment in terms of bone metastasis-free survival, disease-free survival or non-skeletal metastasis-free survival.

High quality evidence, including a systematic review with meta-analysis, demonstrated that single and multiple fractions of radiotherapy were equally effective at relieving pain. There was no strong evidence that single fractions resulted in a higher rate of subsequent fracture or spinal cord compression. An equivalence in outcomes between stereotactic radiosurgery as salvage therapy after disease progression with conventional radiotherapy and upfront external beam radiotherapy suggested a possible treatment for previously irradiated patients with few treatment options left.

The evidence on the use of radiotherapy to prevent skeletally related events was equivocal.

Four observational studies provided limited evidence suggesting a potential role for surgery in giving pain relief.

Health Economic Evaluation

Six papers were selected from the original list of 959 papers identified from the search of economic evidence. Despite the numerous interventions identified for this topic, all six papers referred to the use of bisphosphonates in the prevention of skeletal related events. There was no economic evidence on the use of bisphosphonates for pain relief. None of the studies compared all the bisphosphonates against each other; instead they were either individually compared against no treatment or compared against a limited number of alternatives. All presented cost-utility analyses, four of which were undertaken in a UK setting, the other two in America and Canada.

One of the six papers in the review is a Health Technology Assessment report (Ross et al, 2004). This report presents an economic review of the (then) published literature, and also a model which estimates the cost-effectiveness of pamidronate in the treatment of hypercalcaemia and prevention of skeletal morbidity. Although the report is not limited to breast cancer specifically, it does report findings in patients with breast cancer separately, and on that basis is included in this review. The HTA report has the advantage that it is an independent analysis, unlike the other three UK economic papers.

The model built for the HTA report (Ross et al, 2004) considers costs from both a hospital and social care perspective. The report indicates that the community care costs associated with fracture care might be considerable and if omitted might substantially underestimate the cost-effectiveness of bisphosphonates. The authors conclude that the use of pamidronate is highly cost-effective (£1,300 per QALY compared to no treatment) in the prevention of skeletal morbidity in patients with breast cancer and skeletal metastases, and that it may be cost-saving when fracture care, and/or other variables are taken into account. Despite the basecase analysis yielding a favourably low incremental cost-effectiveness ratio, the results are subject to a high degree of uncertainty. In their analysis the base case cost-effectiveness result is sensitive to bisphosphonate cost, event rate and events costs but no sensitivity analysis on the cost-utility analysis is made explicit. They do present a one-way sensitivity analysis on the cost-effectiveness analysis showing the worst case scenario ranges from cost-saving to a incremental cost per skeletal related event per patient averted is 53 times higher than the baseline result. If we apply this to the baseline cost-utility estimate of £1,380 per QALY, bisphosphonates could range from being cost-saving to £73,140 per QALY.

The most recent study, Botteman et al 2006, uses many of the assumptions employed by Ross et al 2004, but updates the costs used and incorporates results of a recent zoledronic acid vs. placebo trial. The authors conclude that zoledronic acid dominates other bisphosphonates (it is both less costly and more effective), although it should be noted that this study includes authors employed by the manufacturers of zoledronic acid. De Cock et al on the other hand, in their two papers (chemotherapy treated patients 2005a, and hormone therapy patients 2005b) both of which include authors from the manufacturer

of ibandronate, infer that oral ibandronate dominates i.v. zoledronic acid and i.v. pamidronate.

The North American studies reported very different levels of cost-effectiveness (range CAN$18,000 to US$305,000 per QALY). These ratios imply that bisphosphonates may not be cost effective compared to no treatment in a North American context.

The economic modelling from a UK NHS and social services perspective conducted in the studies included in this review indicates that use of bisphosphonates in the management of bone metastases from breast cancer appears to be cost-effective. However the papers reviewed show conflicting evidence over which of the bisphosphonates is most cost-effective. Since bisphosphonates as a class of drugs seem to be highly cost-effective, further independent analysis was not considered a high priority.

6.5 Brain Metastases

Some patients with advanced breast cancer will develop symptomatic brain metastases, usually at multiple sites. The highest incidence of brain metastases is in women with HER2-overexpressing tumours. Because the blood–brain barrier prevents access of most chemotherapy or targeted drugs prescribed for treatment of primary or metastatic disease, improvements in systemic treatment may lead to an increasing incidence of central nervous system metastases.

The diagnosis of brain metastases can have profound physical and psychological effects on the patient (and their family and carers) because of:

- Loss of independence,
- Physical deterioration
- Communication difficulties
- Issues with body image (such as hair loss from radiotherapy and weight gain from corticosteroids).

Further distress can result from the patient realising that they have progressive disease and a particularly poor prognosis.

The three main treatment options are surgery, corticosteroids and radiotherapy. Surgery is usually only considered for patients who have a solitary metastasis or occasionally a limited number of brain metastases; this applies to the minority of patients. Corticosteroids are usually given for immediate symptom relief but only reduce the inflammatory oedema with no direct effect on the tumour. High doses cannot be given long term because of significant side effects and eventual disease progression. Most patients will then also have whole brain radiotherapy (WBRT) which may improve their symptoms and function and allow the dose of corticosteroids to gradually be reduced. Systemic therapies may also be effective treatment.

Any treatment decision needs to take into account that the chances of a clinical benefit are reduced by poor performance status, increased age,

multiple lobes of the brain being affected and having uncontrolled metastases elsewhere.

Whether or not active intervention is offered, full supportive care tailored to the individual will be required for all patients. This may include palliative care; rehabilitation with physiotherapy, occupational therapy assessment and input from speech and language therapists; social care; psychological support and the opportunity to choose place of care.

Recommendations

- Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.
- Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis.
- Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy
- Patients for whom active treatment for brain metastases would be inappropriate should be referred for specialist palliative care.

Qualifying statement: These recommendations are based on evidence from retrospective case series.

Clinical Evidence

The papers addressing the management of brain metastases were mainly retrospective case series none of which were of particularly good quality. Most studies did not differentiate between single, multiple or solitary metastases. Two papers specifically addressed the treatment of leptomeningeal metastases (Rudnicka et al., 2007 and Fizazi et al., 1996).

Papers were reviewed on surgery (Pieper et al., 1997 and Wroski et al., 1997) stereotactic radiosurgery (Comb et al., 2004, Lederman et al., 2001, Amendola et al., 2000, Firlik et al., 2000, Levin et al., 2002, Akyurek et al., 2007 and Muacevic et al., 2004) chemotherapy (Rivera et al., 2006, Rosner et al., 1986, Boogerd et al., 1992, Franciosi et al., 1999, Oberhoff et al., 2001, Lassman, 2006 and Trudeau, 2006) and whole brain radiotherapy (WBRT) (Bartsch et al., 2006, Fokstuen et al., 2000, Korzeniowski and Szpytma 1987, Lenztsch et al., 1999, Liu et al., 2006, Ogura et al., 2003 and Mahmoud-Ahmed et al., 2002, Viani et al., 2007 and Johansen et al., 2008).

WBRT of cerebral metastases resulted in median overall survival of between approximately 4 and 7 months. Patients who received whole brain radiotherapy after surgery had improved survival with a median overall survival of approximately 15 to 16 months. However, where measured, performance status did not improve as a result of surgery. Recursive partition analyses of retrospective WBRT data by one group identified prior surgery, absence of extracranial metastases and RPA class I as significant prognostic factors for survival. A much smaller study found only single vs multiple brain metastases of significance.

Treatment with stereotactic radiosurgery (SRS) resulted in median overall survival ranging from 7.5 to 15 months. Of those receiving SRS, patients with smaller tumours seemed to fare better. Most studies predicted better survival for younger patients and those with good performance status. First-line therapy with SRS was comparable in terms of response and survival to salvage therapy after WBRT in one poor quality study.

The studies analysing data on a variety of chemotherapeutic agents reported extremely variable response and survival data and, as patient numbers were low in each study, no one agent or combination of agents appeared to be better than any other in the treatment of brain metastases. Response rates of up to 64% were reported with median overall survival to a maximum of 61 months in one study. The standard of evidence was weak.

Chemotherapy, including high dose intravenous methotrexate in one study, appeared to be crucial in the treatment of leptomeningeal metastases and both intrathecal and intravenous chemotherapy improved patient survival. WBRT may have been shown in other studies to have improved quality of life but had a questionable effect on survival for these patients.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost-effectiveness literature on this topic has not been reviewed.

Research Recommendation

- A randomised controlled trial is needed to compare stereotactic radiotherapy with whole brain radiotherapy in patients with advanced breast cancer and solitary or a limited number of brain metastases.

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Appendix 1

A cost-utility analysis of chemotherapy sequences for the treatment of patients with advanced breast cancer

INTRODUCTION

Since metastatic breast cancer is incurable, the quality of patients' lives during the final stages of life with various forms of active chemotherapy and supportive and palliative care is of great importance. However the economic cost of this treatment and care to the NHS must be considered and balanced.

NICE has previously issued guidance on the use of the taxanes, capecitabine and vinorelbine for use in the treatment of patients with advanced breast cancer in the form of three technology appraisals (TA30 (2001); TA54 (2002); TA62 (2003)). These appraisals are now being updated within the guideline for the treatment of advanced breast cancer. In light of new clinical evidence it is important that the economics of these chemotherapy agents are re-examined. In addition, the sequencing of these agents has not been considered in the economic literature to date and the neglect of sequential therapy as a comparator to combination therapies in previous technology appraisals was a concern to both the Appraisal Committee of the recent Gemcitabine STA (TA 116) and to the Advanced Breast Cancer Guideline Development Group.

EXISTING ECONOMIC EVIDENCE

There are a number of good quality economic evaluations investigating the cost-effectiveness of first and second-line chemotherapy regimes in patients with metastatic breast cancer, most of which were appraised for the original technology appraisals (summarised below). Four new full economic evaluations have been published since the review undertaken for the appraisals (Verma et al, 2005; Cooper et al, 2003; Verma & Ilersich, 2003; Li et al 2001). One partial economic evaluation considering the costs of third-line chemotherapy was published in 1999 but was not included in the previous reviews since third-line therapy was not part of the inclusion criteria. The main limitations of these studies are that none compare more than three types of therapy, nor do they consider more than one line of therapy. This highlights the need for de novo economic modelling to directly answer the review question.

TA30 – Taxanes

In the original appraisal no economic evaluations for the first line treatment[7] of breast cancer with a taxane were identified. For second-line treatment[8], seven economic evaluations were identified and reviewed. One compared paclitaxel with mitomycin but was submitted in confidence to NICE and therefore was not published in the subsequent HTA report. The other six compared paclitaxel and docetaxel in cost-utility analyses where the range of incremental QALYs gained was £1990-£2431[9]. In addition three analyses compared docetaxel and vinorelbine - one of which was carried out in the UK and yielded a cost-utility ratio for incremental QALYs gained was £14,050. The original guidance did not give any indication as to which taxane was preferred for second-line treatment of breast cancer, despite the evidence showing that docetaxel has a highly favourable cost-effectiveness ratio compared with paclitaxel.

TA54 – Vinorelbine

Evidence at the time of TA54 was scarce. The evidence reviewed for the appraisal showed no clinical benefit of vinorelbine monotherapy over other therapies as first-line treatment. Vinorelbine monotherapy as second-line treatment was slightly less effective than taxane therapy but was much less toxic. For a sub-group of patients (e.g. elderly) this was considered a useful treatment option and was backed up by economic evidence. None of the RCT data favoured vinorelbine combinations and the case-series data did not provide a robust alternative interpretation. The economics involved in the original appraisal comprised of two literature reviews (one investigated the use of vinorelbine as a single agent and the other investigated vinorelbine in combination with other agents), with no independent modelling. The reviews found no economic evaluations investigating vinorelbine as combination therapy, and identified four economic analyses for vinorelbine monotherapy (Brown et al, 2001; Silberman et al, 1999; Launois et al, 1996; Leung et al, 1999), though one of these was in abstract form and therefore provided little detail. Three of these were fairly well conducted cost-effectiveness or cost-utility analyses, one of which was carried out in a UK setting from an NHS perspective (the remaining three were undertaken in Canada, the US and France). However they gave conflicting results, "when comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel, one economic evaluation reported that vinorelbine was more effective and less costly than taxane therapy, one found vinorelbine to be less effective and less expensive than either of the taxanes and a third evaluation found vinorelbine to be less effective and more expensive than taxane therapy" (Lewis et al, 2002). In

[7] It is important to note that the term ‘first-line treatment’ is used here to describe treatment given to patients who are not anthracycline-resistant or failing. Since the number of patients in this category is now very small, the term ‘first-line treatment’ in the rest of this report refers to the first therapy received by a patient with advanced disease for which anthracycline therapy is not suitable.

[8] Similarly, ‘second-line treatment’ as referred to here is later referred to as ‘first-line treatment’ in the rest of this appendix.

[9] The accepted threshold for evaluating the cost-effectiveness of any given treatment in the context of the UK is around £20,000-£30,000 per QALY. As such the range of £1,990-£2,431 per QALY shows docetaxel therapy to be very cost-effective compared to paclitaxel therapy.

addition none of the studies adequately addressed the uncertainty surrounding their results.

TA 62 - Capecitabine

The only economic evidence available at the time of the appraisal was one abstract (not reviewed) and the economic model submitted by the manufacturer for both capecitabine monotherapy and in combination with docetaxel. Neither of these models has since been published in a peer-reviewed journal.

OBJECTIVES

This economic evaluation will assess the cost-effectiveness of several sequences of the main chemotherapy regimes (listed below), as well as supportive and palliative care, that are used to treat metastatic breast cancer patients who have received prior anthracycline therapy.

A secondary objective is to rule out certain strategies (i.e. sequences of therapy) that are likely not to be cost-effective from an NHS perspective.

To facilitate the economic analysis, an indirect treatment comparison will be carried out on RCTs for first-line treatment.

METHODS

Study Population

In contrast to the populations considered in the technology appraisals, the population of interest in this study is patients with metastatic breast cancer who have previously received anthracycline treatment which may have been given as adjuvant treatment. Aggressive treatment of early stage breast cancer has led to the presentation of such patients becoming the 'norm', and increasingly patients are even presenting with advanced disease that is resistant to or has failed taxane and anthracycline therapy (Jones et al, 2001).

Whilst no explicit distinction is made, it is assumed patients in whom the disease is hormone responsive will receive alternative/additional treatment. The clinical and economic evidence for the management of these patients is explored elsewhere in the guideline.

Interventions

First-line therapy options (T1):

Capecitabine + docetaxel combination therapy (*'T1: CAP + DOC'*)
Gemcitabine + docetaxel combination therapy (*'T1: DOC + GEM'*)
Paclitaxel monotherapy (*'T1: PAC'*)
Docetaxel monotherapy (*'T1: DOC'*)

Second-line therapy options (T2):

Capecitabine monotherapy (*'T2: CAP'*)
Vinorelbine monotherapy (*'T2: VIN'*)
Supportive and Palliative Care only (*'T2: No Chemo'*)

Third-line therapy options (T3):
Capecitabine monotherapy (*'T3:CAP'*)
Vinorelbine monotherapy (*'T3: VIN'*)
Supportive and Palliative Care only (*'T3: No Chemo')*

Table 1: Standard dosages assumed by the model

	Dosage 1	*Dosage 2*
Capecitabine + docetaxel	1250mg/m^2 twice daily on days 1 - 14	75 mg/m^2 on day 1
Gemcitabine + docetaxel	1250mg/m^2 on days 1 and 8	75 mg/m^2 on day 1
Paclitaxel monotherapy	175 mg/m^2 on day 1	-
Docetaxel monotherapy	100 mg/m^2 on day 1	-
Capecitabine monotherapy	1250mg/m^2 twice daily on days 1 - 14	-
Vinorelbine monotherapy	30 mg/m^2, days 1 and 8	-

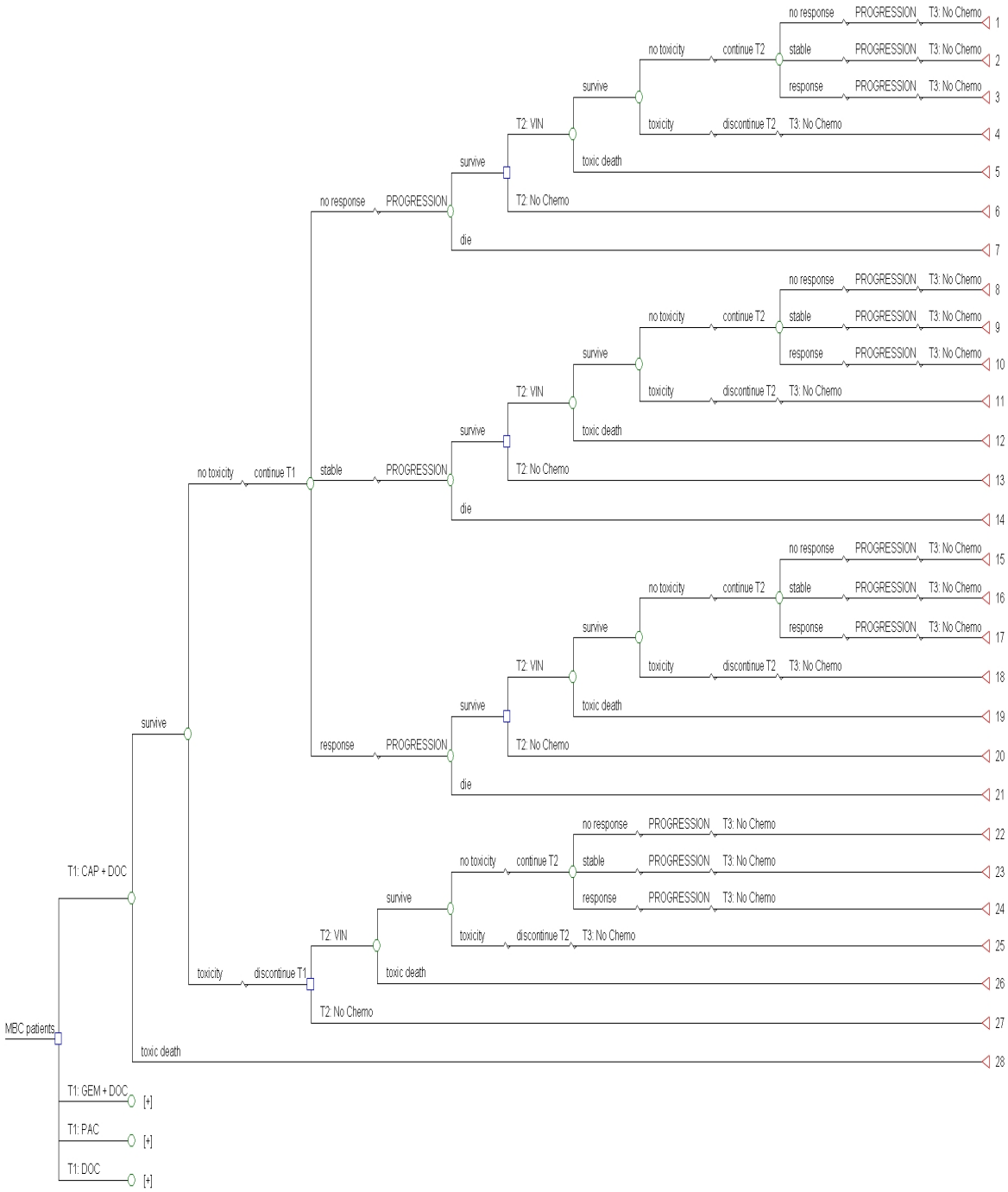
Structure of the Model

A decision tree was constructed to represent all the possible consequences resulting from a sequence of treatment. A total of 724 branches were estimated for seventeen different sequences of chemotherapy, listed below in table 2. It was assumed that a chemotherapy agent could not be used twice in the same sequence.

Table 2: The seventeen strategies considered in the model

Strategy	First-line (T1)	Second-line (T2)	Third-line (T3)
1	DOC+CAP	VIN	No Chemo
2	DOC+CAP	No Chemo	
3	GEM+DOC	CAP	VIN
4	GEM+DOC	CAP	No Chemo
5	GEM+DOC	VIN	CAP
6	GEM+DOC	VIN	No Chemo
7	GEM+DOC	No Chemo	
8	PAC (3-weekly)	CAP	VIN
9	PAC (3-weekly)	CAP	No Chemo
10	PAC (3-weekly)	VIN	CAP
11	PAC (3-weekly)	VIN	No Chemo
12	PAC (3-weekly)	No Chemo	
13	DOC	CAP	VIN
14	DOC	CAP	No Chemo
15	DOC	VIN	CAP
16	DOC	VIN	No Chemo
17	DOC	No Chemo	

Figure 1: decision tree (for first 28 branches)



The model begins by considering patients with metastatic breast cancer (who have received prior anthracycline therapy). The first decision is which first-line treatment to offer the patient. The decision tree shows explicitly all the possible decisions that could be taken (given the confines of our decision problem) and all the possible consequences resulting from this first decision (again we have limited these). Four first-line treatments are considered. Time is not made explicit in a decision tree model, but we assume the patient

receives one cycle of the first line therapy. At this point, there is a possibility that the patient might die of a toxic death. If the patient dies of a toxic death, that is the end of the possible outcomes associated with the treatment. It has been assumed that a toxic death can only occur after the first cycle of therapy.

If that patient survives the risk of toxic death, (s) he will then receive two more cycles of therapy. This brings the total number of cycles of therapy the patient has received at this point to three. The patient then faces another chance event of experiencing toxicity that will lead to the discontinuation of the current first-line treatment (no chance or decision to be taken here, this necessarily follows on from experiencing major toxicity). At this point we face another decision node, the choice of which second-line treatment to take. There is a time-lag of 1 month between discontinuing first-line therapy and starting on second-line therapy. If the patient didn't experience toxicity, (s) he will continue on first-line therapy. At this point it is assumed that response can be assessed, so the patient faces a probability of responding to therapy, of having stable disease or not.

For the purposes of the model, response is defined as complete or partial tumour response to the first-line therapy. Responders and stable patients go on to receive additional cycles of treatment, receiving in total the median number of cycles as reported in the RCTs investigating that therapy (in the case of all the interventions in the mode, this was six cycles). Non-response is defined as patients who are classified as having progressive disease or their tumour was non-assessable. These patients do not receive further treatment. Regardless of whether the patient has responded to first-line treatment or not, progression is an inevitable outcome. However the time to progression will be different. Once the patient is experiencing progressive disease, (s) he faces the probability of dying from progressive disease. Indeed death only results from progressive disease or toxicity; the possibility of death from other causes was not considered to be relevant to the model due to the poor prognosis of these patients. This approach is consistent with other published economic evaluations. If the patient survives, (s) he will continue to second-line treatment.

At this decision node, there may be two or three possible second-line therapies. This is because it has been assumed that if capecitabine has been used as first-line treatment, or a part of a combination therapy given as first-line treatment (e.g. capecitabine + docetaxel), then it cannot be considered as a second-line therapy option. This is the scenario depicted in figure 1 above.

The patient then experiences the same chance events as with first-line treatment (chance of toxic death, chance of experiencing toxicity leading to discontinuation, chance of responding to second-line therapy). Once second-line therapy is discontinued or progression has been reached after completing the full course of second-line treatment, the patient continues onto third-line therapy. In Figure 1 this decision has only one possible option thus is not depicted with a decision node. Since both capecitabine and vinorelbine have been used by this point, the only treatment option left for this patient is Supportive and Palliative Care (*'No Chemotherapy'*). There is only one

possible outcome from the 'No Chemotherapy' option, so this branch terminates. If third-line treatment is a chemotherapy regime, the same chance events as with first-line and second-line treatment may occur (the chance of toxic death, chance of experiencing toxicity leading to discontinuation, chance of responding to second-line therapy).

Clinical Evidence

First-Line Treatment – An indirect treatment comparison

An RCT or a meta-analysis of RCTs comparing all the interventions of interest to this analysis is not available. Indeed using conventional techniques this would not be possible due to the different comparisons made by each trial. It is common for new therapies to be introduced into clinical practice before formal treatment comparisons with the current standard approach or other new agents have been planned or carried out.

Using just one arm of one RCT to give us information on each intervention would cause a number of methodological problems. Not only would this not make use of all the available evidence, it would also lose the effect of randomization which is what gives the RCT its gold standard.

In the absence of direct comparative evidence, an indirect treatment comparison has been performed to inform the parameters of the economic model and ultimately ensure the recommendations in the guideline are based on all available evidence. Indirect comparisons use evidence from A vs. B and A vs. C trials to draw conclusions about the effect of B relative to C. The main assumption made using this approach to evidence synthesis is that the evidence is consistent. That is, the treatment effect of B relative to C estimated by a real trial comparing B vs. C would be the same as the treatment effect estimated by the A vs. B and A vs. C trials if they had included C and B arms respectively. This assumption is also implicit in cost-effectiveness analysis, since evidence is routinely combined from a variety of sources, thus consistency has to be assumed.

The clinical evidence review for the update of each technology appraisal was performed separately, which informed the search strategy for these topics. As such a full systematic search for all treatments for metastatic breast cancer was not undertaken. The network of RCT evidence is thus made up of trials that were identified for the original appraisals, from the individual update searches for the three technology appraisals and from an unsystematic manual search aiming to identify trials that may have been excluded from the clinical review (due to stricter inclusion criteria). Randomised controlled trials that involved one or more of the interventions of interest were included in the network of evidence. Whilst the economic model assesses three lines of therapy, no RCTs were identified for second- or third-line therapy. Thus, the indirect treatment comparison was only carried out on first-line treatment options.

The indirect comparison was undertaken using two separate statistical models using the statistical computer software, WinBUGS. The first describes the

relationship between toxic deaths and discontinuation due to toxicity, whilst the second links the response rate, progression rates and mortality. The networks of RCT evidence for each statistical model are depicted below (figures 2 and 3); each line represents one RCT and the shading of certain interventions highlights those that are of interest in our decision problem. Other interventions are included to add to the information we can obtain on the interventions that are of interest, through indirect comparisons. The evidence structure is presented below the diagram in table 3. If all the trials reported all the data that was needed, all trials would have been included in both the indirect treatment comparisons. Since there were gaps in the data, three of the trials (Sjostrom 1998, Bonneterre 2002 and Monnier 1998) were excluded from the analysis of progression and survival. Whilst the analysis was undertaken from a Bayesian framework, flat priors were used in both statistical models and thus did not impact on the results.

Figure 2: RCT network for toxicity model

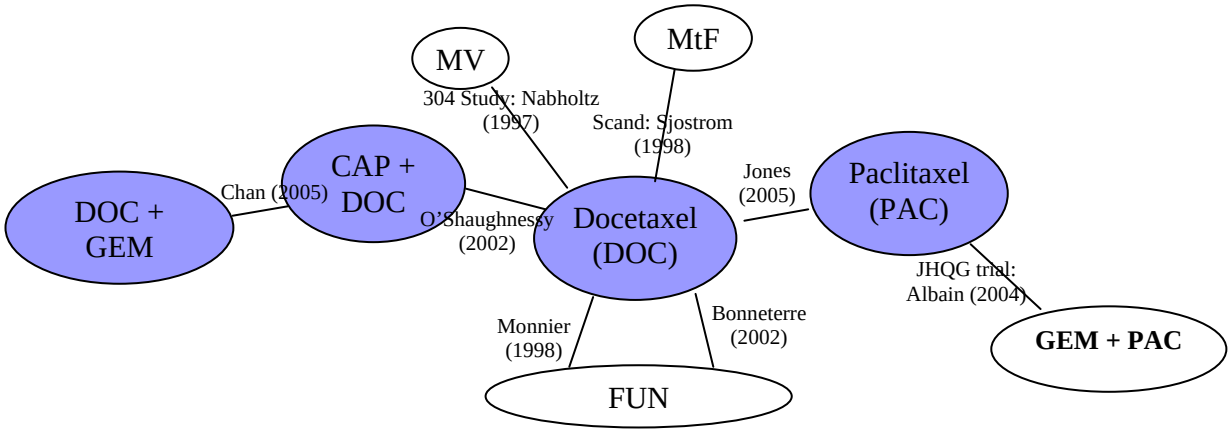


Figure 3: RCT network for survival model

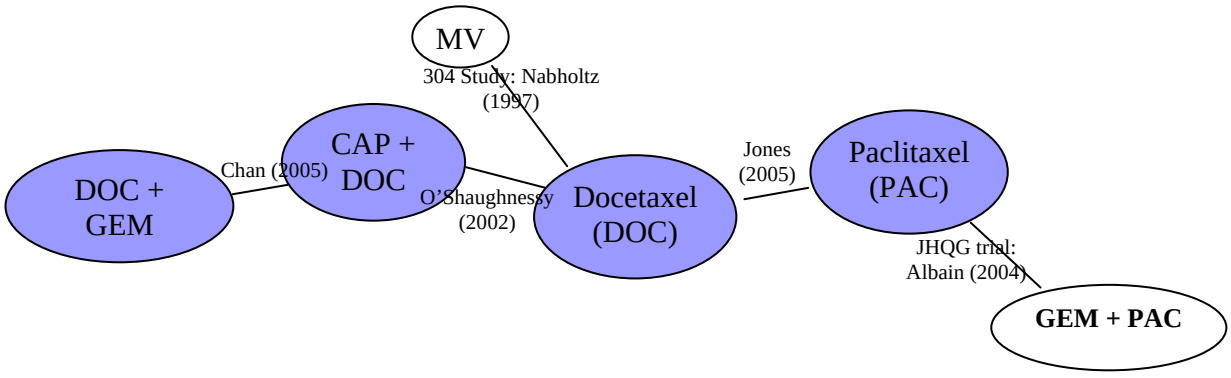


Table 3: evidence structure

Study	Number of toxic deaths	Number discontinuing due to toxicity	Number of responders	Duration of response (for responders)	Median time to progression (for all)	Median overall survival (for all)	Log hazard ratio
Jones 2005	✓	✓	✓	✓			✓
O'Shaughnessy 2002	✓	✓	✓	✓	✓	✓	
Albain 2004	✓	✓	✓	✓	✓	✓	
Chan 2005	✓	✓	✓	✓	✓		
Nabholtz 1997	✓	✓	✓		✓	✓	
Sjostrom 1998		✓					
Bonneterre 2002	✓						
Monnier 1998	✓						

The text that follows is a simple description of the methods used for the indirect treatment comparisons. The WinBUGS code is not presented here but is available from the author on request (please contact nicky.welton@bristol.ac.uk).

Toxicity model

A number of assumptions were made in order to get the most out of the data. Firstly, it was assumed that the toxic death rate did not vary by study, so a fixed effects model was used. Secondly, the two measures of toxicity (toxic death and discontinuation due to toxicity) are related by a constant, beta, which was allowed to vary by study (from a random effects model). Thirdly the baseline probability of toxic death (to which all the relative effects are compared, in this case the probability of toxic death for docetaxel) was estimated by a random effects model of the arms of the three trials involving docetaxel.

Survival model

In line with the assumptions made in structuring the economic model, it is assumed that patients are categorised at 9 weeks as responders (r), stable (s), with progressive disease (pd), or non-assessable (na). There is data on the split between these groups from most studies, although one study only reports whether a responder, stable or not, and one study only reports whether a responder or not. It was assumed that the split between categories follow a multinomial distribution:

$$(n_r, n_s, n_{pd}, n_{na}) \sim \text{Multinomial}((p_r, p_s, p_{pd}, p_{na}), N)$$

We model the effect of treatment using multinomial logistic regression. Let

$$q_{i,1} = p(responder) = p_{i,r}$$

$$q_{i,2} = p(stable \mid non-responder) = p_{i,s} / (1 - p_{i,r})$$

$$q_{i,3} = p(prog.disease \mid non-responder, non-stable) = p_{i,pd} / (1 - p_{i,r} - p_{i,s})$$

$$p_{na} = 1 - p_r - p_s - p_{pd}$$

We assume the following model for the conditional probabilities, *q*:

$$\text{logit}(q_{i,1}) = \varphi_{s(i)} + (\theta_{t(i),1} - \theta_{b(i),1})$$

$$\text{logit}(q_{i,2}) = \varphi_{s(i)} + \zeta_{s(i)} + (\theta_{t(i),2} - \theta_{b(i),2}); \qquad \zeta_j \sim N(m_\zeta, sd_\zeta^2)$$

$$\text{logit}(q_{i,3}) = \varphi_{s(i)} + \gamma_{s(i)} + (\theta_{t(i),3} - \theta_{b(i),3}); \qquad \gamma_j \sim N(m_\gamma, sd_\gamma^2)$$

Key assumptions:

- Fixed treatment effects which differ for different conditional outcomes: responders; stable|non-responder; and prog.disease|{non-responder & non-stable}.
- The proportion of responders depends on study.
- The baseline log-odds of the conditional outcomes stable|non-responder; and prog.disease|{non-responder & non-stable} differ from that for responders by study specific terms ζ_j and γ_j which come from random effects distributions.

Most studies reported median time to progression for responders and for all. We assume exponential distributions for the time to progression in responders and non-responders with rates λ_r and λ_{nr} respectively. We therefore needed a model for the progression rate for responders, λ_r, and non-responders, λ_{nr}. We put a log-linear model on the progression rate in responders and stable:

$$\log(\lambda_r) = \alpha_{s(i)} + (d_{t(i)} - d_{b(i)})$$

$$\log(\lambda_s) = \alpha_{s(i)} + \eta_{s(i)} + (d_{t(i)} - d_{b(i)}); \qquad \eta_j \sim N(m_\eta, sd_\eta^2)$$

Key assumptions:

- Study specific baselines for responders
- Random effects model for log-hazard ratio for stable vs responder
- Fixed treatment effect across studies, which is the same for responders and stable individuals.

The mean progression time in non-responders is a weighted average of mean progression time for stable, non-assessable, and progressive disease patients, giving progression rate in non-responders of:

$$\lambda_{nr} = \frac{1}{\left(\frac{(p_{na} + p_s)}{\lambda_s (1 - p_r)} + \frac{1.5 p_{pd}}{(1 - p_r)} \right)}$$

Key assumptions:

- Time to progression is 4.5 weeks (1.125 months) for those with progressive disease.
- Non-assessable patients have the same progression rate as progressive patients.

Most studies reported median time to mortality for all patients. If we assume a constant term linking progression rates with mortality rates, then we can

model mortality in exactly the same way as for progression. However, we do not know the mortality rate (1/μ) for those with progressive disease, and so this was estimated from the data.

We assume exponential distributions for the time to mortality in responders and non-responders with rates μ_r and μ_{nr} respectively. We therefore need a model for the mortality rate for responders, μ_r, and non-responders, μ_{nr}. We put a log-linear model on the mortality rate in responders and stable, which differ from log progression rates by a constant, which depends on study, but assumed to come from a random effects distribution:

$$\log(\mu_r) = log(\lambda_r) + \beta_{s(i)}; \qquad \beta_j \sim N(m_\beta, sd_\beta^2)$$
$$\log(\mu_s) = log(\lambda_s) + \beta_{s(i)}$$

The mean survival time in non-responders is a weighted average of mean survival time for stable, non-assessable, and progressive disease patients, giving mortality rate in non-responders of:

$$\mu_{nr} = \frac{1}{\left(\frac{(p_{na} + p_s)}{\mu_s(1-p_r)} + \frac{\kappa p_{pd}}{(1-p_r)}\right)}$$

Key assumptions:

- Random effects model on the log-hazard ratio's (β_j) of mortality relative to progression
- Fixed mean survival time λ for those with progressive disease.
- Non-assessable patients have the same mortality rate as progressive patients.

Second-line Treatment

There is one randomised controlled trial and seven non-randomised studies investigating second-line therapy. No evidence was found to report the effectiveness of the 'No chemotherapy' intervention.

The Martin et al (2007) RCT was used to provide data on vinorelbine monotherapy as second-line treatment by agreement with the GDG since the trial has a mixed patient population (patients received vinorelbine as first-, second- and third- line treatment). Although there were two other observational studies investigating vinorelbine monotherapy (Zelek 2001; Udom 2000) they were both small trials and the Martin RCT was considered by the GDG subgroup to provide the best estimate of vinorelbine monotherapy in the second-line setting.

Five non-randomised studies were identified for capecitabine monotherapy as second-line treatment (Fumoleau et al. 2004; Lee et al. 2004; Pierga et al. 2004; Reichardt et al. 2003; Wist et al. 2004). Whilst all were considered acceptable in terms of being able to provide reasonably robust evidence, not all trials provided data on the same parameters. Pierga et al 2004 provided

data on response duration, duration of stable disease and time to progression for all. As such this trial was used to provide information for the model on capecitabine monotherapy as second-line treatment.

No evidence was found to report the effectiveness of the 'No chemotherapy' intervention. It was assumed that 'No Chemotherapy' would result in no progression-free survival and 5 months survival with progressive disease.

Third-line treatment

No evidence for capecitabine or vinorelbine monotherapy as third-line treatment was identified. It was therefore assumed that the same data for second-line treatment would provide a suitable estimate of third-line treatment, since the patient populations included some patients receiving the study therapy as third-line. In the base-case analysis, no adjustments to the data were made although the effect of reducing the survival estimates by varying degrees will be explored in the sensitivity analysis.

Health Benefits

Probabilities

The probabilities of toxic death and of discontinuing treatment due to toxicity shown in table 4 were all estimated via the ITC statistical model. The toxicity data for second and third-line treatment are shown in table 5.

Table 4: probabilities estimated by the indirect treatment comparison

Intervention	Toxic death rate	Discontinuation due to toxicity
T1:DOC+CAP	0.020	0.337
T1:GEM+DOC	0.008	0.201
T1:PAC	0.003	0.116
T1: DOC	0.014	0.278

Table 5: probabilities for second and third-line treatment

Intervention	Source	Toxic death rate	Discontinuation due to toxicity
T2 and T3: VIN	Martin et al, 2007	0.008	0.048
T2 and T3: CAP	Pierga et al, 2004	0.000	0.162

The probabilities of response, stabilisation of disease, disease progression and non-assessability were estimated via the second ITC statistical model, shown in table 6 below:

Table 6: probabilities estimated by the indirect treatment comparison

Intervention	Response	Stable	Progression	Non-assessable
T1:DOC+CAP	0.4070	0.3427	0.1244	0.1258
T1:GEM+DOC	0.4023	0.4209	0.1148	0.0620
T1:PAC	0.2316	0.3911	0.3234	0.0539
T1: DOC	0.2899	0.3841	0.2200	0.1060

For the economic model, it was assumed that non-assessable patients were the same as patients with progressive disease.

Table 7: probabilities for second and third-line treatment

Intervention	Source	Response	Stable	Non-response
T2 and T3: VIN	Martin et al 2007	0.262	0.254	0.484
T2 and T3: CAP	Pierga et al 2004	0.152	0.335	0.513

Survival

Overall survival (OS) was assumed to be the sum of time to progression (TTP_{t1}) of first-line treatment, TTP from second-line treatment (TTP_{t2}), TTP from third-line treatment (TTP_{t3}) and the period from progression to death (assumed to be 5 months). This assumption implies that chemotherapy impacts on time to progression, and through that overall survival. However the time from (final) progression to death is fixed regardless of prior treatment.

Mean 'progression-free' survival times (in months) were estimated from the statistical model on survival and are reported below in table 8. It is assumed that time to progression for patients with progressive disease reported as their best response to treatment (or if the tumour was not assessable) is 1.125 months (4.5 weeks).

Table 8: Survival data estimated by the indirect treatment comparison (in months)

Intervention	TTP - Responders	TTP – Stable
	mean	mean
T1:DOC+CAP	12.19	7.53
T1:GEM+DOC	11.08	6.84
T1:PAC	5.63	3.47
T1: DOC	10.27	6.34

Mean values are used for the economic evaluation since they are a more appropriate measure of the average at a population level. Since only median values were reported in the Martin 2007 and Pierga 2004 trials, it was assumed that survival and time to progression followed exponential distributions. Median values were then converted to mean values by calculating the baseline hazard:

$$h = -\ln(0.5)/t_{med}$$

$$t_{mean}=1/h.$$

where, h=baseline absolute hazard; t_{med}=mediansurvival time; t_{mean}=mean survival time

Table 9: Survival data for second and third-line treatment (in months)

Intervention	Source	TTP - Responders	TTP - Stable	TTP - Progression
T2 and T3: VIN	Martin et al 2007	5.77	5.77	1.13
T2 and T3: CAP	Pierga et al 2003	12.84	9.52	3.45

Utilities

Utility weights were linked to the time spent at different points of the pathway (not strictly health states since we did not use a Markov process) to calculate QALYs. No trials reported utility losses due to toxicity or to progressive disease, so the proportion of patients in each arm of an RCT that progressed or discontinued treatment due to toxicity were relevant published utility weights to estimate the overall utility. There are a number of studies that report utility weights in the treatment of advanced breast cancer. The most recent pooling of utilities from different sources (all derived from oncology nurses using the Standard Gamble technique) was published by Cooper and co-workers (2003). A number of assumptions had to be made about the utility associated with time spent between treatment (we assume utility with progressive disease, 0.45); the time spent on treatment before response could be assessed (we assume utility associated with stable disease, 0.65, to ensure consistency with the indirect treatment comparison since at this stage by definition the disease is not yet progressive); and time before toxicities identified after 3 cycles of treatment (we assume utility associated with progressive disease, 0.45).

Table 10: utility values from Cooper et al (2003)

Health state	Pooled utilities
Response	0.81
Stable disease	0.65
Stable disease and febrile neutropenia or infection with hospitalisation	0.44
Progressive disease	0.45
Progressive disease with toxicity (assumption)	0.35
Death	0

Cost Estimation

The costs considered in this analysis are only those relevant to the UK NHS, in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated in 2006-7 prices. Where costs have been taken from sources using a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2007).

There are broadly five categories of costs considered in the model:

- Cost of treatment
- Cost of assessment/ follow-up
- Cost of treating adverse events
- Cost of supportive and palliative care
- Costs associated with death

Cost of treatment

The average dose for each regime was presented in table 1. The possibility of reducing the dose (in response to an adverse event) was not allowed for in the model. The drug acquisition cost per cycle were calculated for each

chemotherapy regime based on an average dose per patient (standard 1.75m^2), the average number of doses per cycle and the average list price per mg. Whilst it is recognised that discounts are available on some of these drugs, the list price was used in the base case as recommended in the NICE Reference Case. The effect of these drug discounts will be explored in the sensitivity analysis. Where the price is given for both the generic and proprietary drug, the cheapest is used in the base-case.

Table 11: Drug acquisition costs (1)

Drug	Vinorelbine		Paclitaxel		Docetaxel	
Brand name	(generic)	Navelbine	(generic)	Taxol	Taxotere	
Manufacturer	n/a	Fabre	n/a	Bristol-Myers Squibb	Sanofi-Aventis	
List prices, £ (BNF 54, Sept 2007):						
0 ml vial					162.75	
1 ml vial	32.95	29.75				
2 ml vial					534.75	
5 ml vial	153.98	139.98	111.41	116.05		
16.7 ml vial			333.91	347.82		
25 ml vial			500.86	521.73		
50 ml vial			1001.72	1043.46		
i.v. concentrate (mg/ml)	10	10	6	6	40	
Dose (mg/m2)	30	30	175	175	100	75
Average dose	52.5	52.5	306.25	306.25	175	131.25
Average cost per mg (£)	3.12	2.83	3.36	3.50	6.98	6.98
Average drug cost per dose (£)	163.56	148.51	1028.17	1071.01	1220.63	915.47
Premedication cost per dose (£)					2.56	2.56
Number of doses per cycle	2	2	1	1	1	1
Average drug cost per cycle (£)	**327.13**	**297.03**	**1028.17**	**1071.01**	**1223.18**	**918.02**

Table 12: Drug acquisition costs (2)

Orally administered		***Injection (powder)***	
Drug	**Capecitabine**	**Drug**	**Gemcitabine**
Brand name	Xeloda	**Brand name**	Gemzar
Manufacturer	Roche	**Manufacturer**	Eli Lilly
Dose (mg/m2)	1250	**200mg vial**	32.55
Dose per administration	2150	**1g vial**	162.76
150mg tablets required	1	**Average cost per mg**	0.16
500mg tablets required	4	**Dose (mg/m2)**	1250
Cost per 150mg pack (60 tab)	44.47	**Average dose**	2187.5
Cost per 150mg tablet	0.741166667	**Average cost per dose**	356.03
Cost per 500mg pack (120 tab)	295.06		
Cost per 500mg tablet	2.458833333	**Number of doses per cycle**	2
Cost per administration	10.5765		

No of doses per cycle	28		
Average drug cost per cycle	**296.142**	**Average drug cost per cycle**	**712.0677083**

In addition to the drug acquisition costs, the cost of administering the drug was estimated from the NHS National Reference Costs. For therapies administered by i.v. or injection (gemcitabine), the cost used was £293 for outpatient delivery of complex perenteral chemotherapy and subsequent elements. This cost includes hospital overheads, the administration costs of chemotherapy and clinical time, but does not, for example, distinguish between different i.v. infusion times of paclitaxel vs. docetaxel. For drugs administered orally (capecitabine) the administration costs were estimated using the outpatient tariff, £209 for first attendance and then £82 for subsequent attendances. It has been assumed that one outpatient appointment would be required per cycle of therapy (one every three weeks). In the case of combination therapy it has been assumed that two drugs can be administered at one time, thus requiring the cost of only one administration to be considered. In addition to the drug acquisition and drug administration costs, it has been assumed that a consultation with an oncologist (£209 for first attendance, National Reference Costs 2006-7) would be necessary at the starting cycle.

Cost of assessment/ follow-up

The cost of taking one CT scan (2 areas, with contrast) every three cycles of treatment was used as a proxy for the cost of assessing response (NHS Reference Costs, 2006-7). This is equivalent to £125 for non-responders, £250 for responders. This is an attempt to capture the continuous nature of assessing response.

Once the patient has finished chemotherapy and achieves a response there will still be a cost associated with the contact the patient receives from her consultant. (The cost of contact with other health professionals is included in supportive care package 1 below). Cost of one consultation with specialist every 2 months after treatment has finished (£105 per month, NHS Reference costs 2006-7) is used as a proxy for follow-up costs.

Response is not assessed when first-line chemotherapy ends so the cost of one CT scan is included before the patient begins the next line of chemotherapy.

Cost of treating adverse events

The cost of treating major toxicities (which necessarily lead to the discontinuation of treatment) was estimated as £804, the mean of two costs from the literature; from the cost of treating severe infection or febrile neutropenia in hospital £1,281 (Cooper et al, 2003) and the cost of treating a severe infection or febrile neutropenia at home £328 (Cooper et al, 2003), both reported here already inflated to 2006-7 prices. This cost was used

across all treatments, so was not specific to the type of toxicity that leads to discontinuation which we know does vary by therapy.

Cost of supportive and palliative care

Due to the nature of supportive and palliative, three likely 'packages' of care are described below for patients at different points along the care pathway.

- **Package 1**

The first package of care describes an average level of supportive care a patient receiving chemotherapy might be expected to receive from the time of first cycle of treatment until the onset of progressive disease at which point the next line of chemotherapy is started. Given the model structure, this package of care is given to a patient until they begin the 'no chemotherapy' option. For some strategies this package of care will be given for the whole time spent in the model.

Time-related elements:
Community nurse: home visit 20m, £24.00, 1 per fortnight (PSSRU, 2007)
GP contact: 1 surgery visit £34.00 every month (PSSRU, 2007)
Clinical nurse specialist 1hr contact time, £74.00, 1 per month (PSSRU, 2007)

Time non-related elements:
Social worker: 1hr client-related work but not direct contact time, £34.00 (PSSRU, 2007)

- **Package 2**

The second package of care describes an average level of supportive and palliative care a patient receiving the 'no chemotherapy' intervention might be expected to receive until the last two weeks of life. This package of care is also included for the patient that follows the strategies in the model with three lines of chemotherapy, from the time of progression until the two weeks before death. Unlike the care given in package 1, all elements of the care delivered in package 2 are time-related.

Time-related elements (weekly costs):
Community nurse: home visit 20m, £24.00, 1 per week (PSSRU, 2007)
Clinical nurse specialist: 1hr contact time, £74.00, 1 per week (PSSRU, 2007)
GP contact: 1 home visit, £27.50, every fortnight (PSSRU, 2007)
Therapist[10]: 1 hour, £20.00, every fortnight (PSSRU, 2007)

- **Package 3**

The third package of supportive and palliative care is a cost for the more intensive needs of patients in the final two weeks of life. If this cost was attributable to all patients dying in the model, it would be superfluous to the analysis since we are interested solely in incremental costs and incremental benefits. This package of care is not however given to patients who die in the

[10] The type of therapist was not made explicit. The unit cost of all therapists listed in the PSSRU costs was £40 per hour. This was roughly the same for an hour of home visiting time.

model from toxic death. Since the toxic death varies (albeit not greatly) between the interventions compared in the model, the cost of package 3 supportive and palliative care does need to be taken into account.

The cost used was a weighted average of the three costs reported in the Marie Curie commissioned report into the cost of dying at home (inflated as previously described to 2006/7 prices).

last 14 days - in hospital, £4,706
last 14 days - in Marie Curie hospice, £5,867
last 14 days - at home (with community support), £2,428

The weights applied to calculate this average were 40% deaths occurring in hospital, 10% occurring in a hospice and the remaining 50% of deaths occurring at home. The cost of the last two weeks of care was therefore estimated to be £3,418.

Costs associated with death

Apart from package 3 of supportive and palliative care, the other cost associated with death included in the model is the cost of toxic death. No costs related to toxic deaths were reported explicitly for any of the published economic evaluations, despite all papers considering the risk of toxic death. A proxy was used by way of the mean of two costs from the literature; from the cost of 7 days hospitalisation and treatment of severe febrile neutropenia £3,586 (Brown et al, 2001) and the cost of treating a severe infection in hospital £988 (Cooper et al 2003), both reported here already inflated to 2006-7 prices. In total the cost of toxic death used in the model is £2,287.

DISCOUNTING

Discounting was not conducted, so the results that follow are the undiscounted costs and health outcomes. However we would not expect discounting to have much impact on the results of the model since many of the possible pathways through the model are associated with survival of less than 24 months. In addition the majority of the costs for pathways that do result in a longer survival, come at the beginning rather than spread evenly across the year.

TYPE OF ANALYSIS

A cost-utility analysis was performed given that the health outcome preferred by NICE is the QALY and quality of life is of particular importance to patients with metastatic cancer. An incremental cost-effectiveness analysis was conducted after ranking the alternative strategies from the most to the least cost-effective and excluding any dominated strategies (i.e. those strategies achieving lower effectiveness and incurring higher costs when compared to any other, *highlighted in table 14 in light grey,* or those which are ruled out if they achieve lower effectiveness and higher costs than a combination of two other strategies, *highlighted in table 14 in dark grey*).

SENSITIVITY ANALYSIS

A series of one-way deterministic sensitivity analyses were conducted to assess the robustness of the study results. 'One-way sensitivity analysis' describes the process of changing one parameter in the model and analysing the results of the model analysed to see if this parameter influences any of the overall results.

Five sources were thought to contribute most to the uncertainty surrounding the analysis; the utility values used in the analysis, the data used on the effectiveness of capecitabine monotherapy, the effectiveness of third-line therapy, possible price discounts and the calculation of overall survival. A number of scenarios were investigated as outlined below:

- **Utility values**

Although the most current utility values were used in the analysis (pooled by Cooper et al, 2003), the guideline development group were concerned about the validity of values ascribed to the different health states patients may experience. An arbitrary 10% increase and decrease in all the utility values used in the model was explored. The effect of just increasing the utility ascribed to progressive disease by 10% was tested. In addition the utility ascribed to patients with toxicity was varied from the base-case value of 0.44 to 0.35 (to equal the utility associated with progressive disease with toxicity).

- **Effectiveness of capecitabine monotherapy**

It was noted that the time to progression associated with capecitabine monotherapy was high. Therefore these estimates were reduced by one third in this scenario.

- **Effectiveness of third-line treatment**

No evidence was available for the effectiveness of third-line therapy, so both capecitabine and vinorelbine monotherapies were assumed to work as well as for second-line therapy. This was justified by the fact that the data used to inform the second-line therapy parameters in the model came from trials with mixed patient populations which included patients who were receiving the study therapy as third-line. The effect of reducing the response and disease stabilisation rates by one third, and separately reducing the time to progression estimates by one third was investigated.

- **Price discounts**

Price discounts are available across England and Wales on paclitaxel and vinorelbine since generic versions are available. However there is not one single agreed price discount available for either agent that is applicable across the whole of England and Wales. Therefore a number of different price discounts for paclitaxel were investigated (50%, 60%, 70%, 80%, 90%) as well as the effect of a price reduction also available for vinorelbine, vinorelbine 45% discount, paclitaxel 90% discount (current price discounts suggested by the Purchasing and Supply Agency database, eMIT).

- **Calculation of overall survival**

Whilst it was acknowledged the calculation of overall survival was subject to uncertainty, this assumption was inherent to the structure of the model and was not tested in the sensitivity analysis. However the time from progression to death (assumed to be 5 months in the base-case analysis) was varied from 4 – 6 months.

However these scenarios are unlikely to happen independently; they are more likely to occur concurrently. A probabilistic sensitivity analysis, which allows multiple parameters to vary over specified distributions from which are then sampled at random many times, was not conducted but is planned to be undertaken during the consultation period for this guideline. This should provide a better picture of the uncertainty surrounding the analysis.

RESULTS

Base-case results

The base-case results are shown listed by strategy, in *table 13* below. There is a considerable difference between the strategies in terms of survival, quality of life and associated costs. The overall survival from each strategy ranges from just over 23 months (strategy 5: GEM+DOC, VIN, CAP) to just 8.5 months (strategy 12: PAC, No Chemo). Strategy 3 yields the highest number of QALYs (1.1896) compared to 0.3645 for strategy 12. Total costs for each strategy ranged from £14,000 (strategy 12) to over double that for strategy 3, £31,500.

Table 13: base-case results, by strategy

Strategy	First line	Second line	Third line	Total Expected Pfyears	Total Expected LYs	Total Expected QALYs	Total Expected Costs
1	DOC+CAP	VIN	No Chemo	0.7833	1.2643	0.7694	£21,406
2	DOC+CAP	No Chemo		0.5009	0.9283	0.5452	£15,526
3	GEM+DOC	CAP	VIN	1.3392	1.9352	1.1896	£31,479
4	GEM+DOC	CAP	No Chemo	1.0600	1.5768	0.9734	£25,882
5	GEM+DOC	VIN	CAP	1.3422	1.9405	1.1857	£30,859
6	GEM+DOC	VIN	No Chemo	0.8306	1.3390	0.8230	£27,124
7	GEM+DOC	No Chemo		0.5443	0.9691	0.5827	£21,056
8	PAC	CAP	VIN	1.0532	1.6240	0.9739	£24,521
9	PAC	CAP	No Chemo	0.7716	1.2763	0.7527	£18,871
10	PAC	VIN	CAP	1.0551	1.6377	0.9642	£23,872
11	PAC	VIN	No Chemo	0.5411	1.0359	0.6009	£20,119
12	PAC	No Chemo		0.2534	0.6754	0.3645	£14,022
13	DOC	CAP	VIN	1.2043	1.7680	1.0738	£26,442
14	DOC	CAP	No Chemo	0.9197	1.4150	0.8500	£20,727
15	DOC	VIN	CAP	1.2002	1.7726	1.0592	£25,675
16	DOC	VIN	No Chemo	0.6916	1.1771	0.6997	£21,962
17	DOC	No Chemo		0.4069	0.8337	0.4718	£15,928

PFyears = progression-free years, LYs = life years, QALYs = quality adjusted life years

Incremental cost-effectiveness analysis

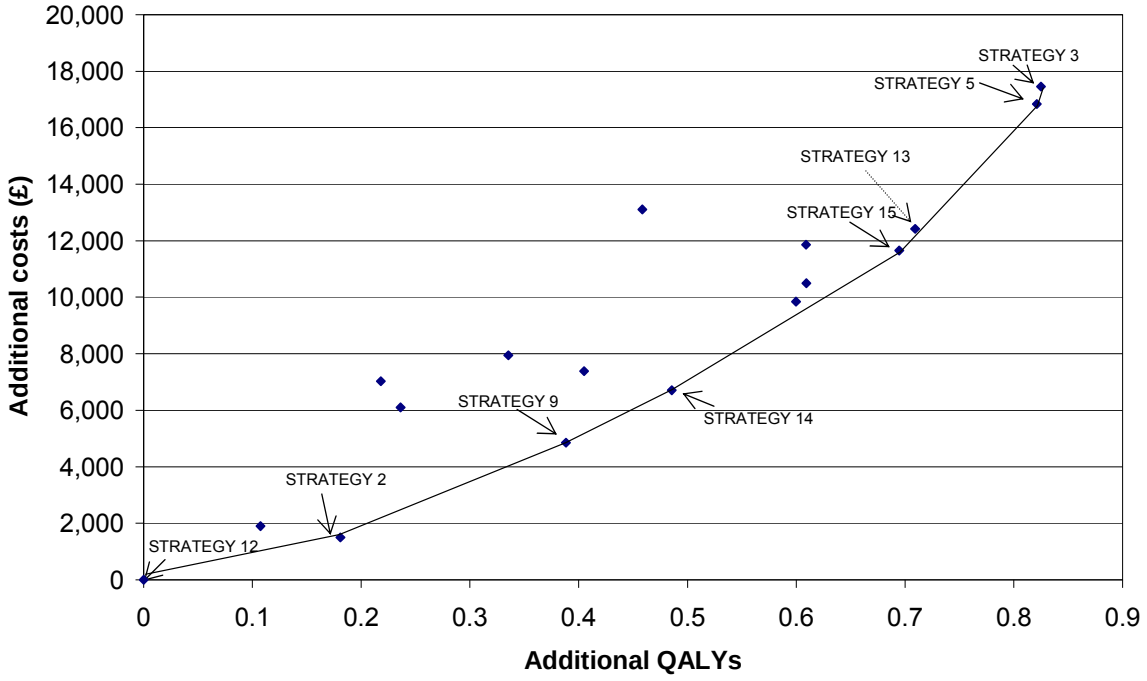
Using QALYs as the outcome measure, an incremental cost-effectiveness analysis was performed by first ranking the strategies according to the cost per patient (highest to lowest). This allowed the dominated strategies to be identified and ruled out of the incremental analysis. Any strategies achieving fewer QALYs and incurring higher costs when compared to any other are ruled out by simple dominance (highlighted in *table 14* in light grey), and any stategies that achieve fewer QALYs and higher costs than a combination of two other strategies are ruled out via extended dominance (highlighted in *table 14* in dark grey). This left seven remaining strategies (2, 3, 5, 9, 12, 14 and 15) which are labelled in figure 3 below.

Table 14: incremental results

Strategy	T1	T2	T3	Total Expected QALYs	Total Expected Costs	ICERs
3	GEM+DOC	CAP	VIN	1.1896	£31,479	**£160,748**
5	GEM+DOC	VIN	CAP	1.1857	£30,859	**£40,959**
6	GEM+DOC	VIN	No Chemo	0.8230	£27,124	
13	DOC	CAP	VIN	1.0738	£26,442	
4	GEM+DOC	CAP	No Chemo	0.9734	£25,882	
15	DOC	VIN	CAP	1.0592	£25,675	**£23,660**
8	PAC	CAP	VIN	0.9739	£24,521	
10	PAC	VIN	CAP	0.9642	£23,872	
16	DOC	VIN	No Chemo	0.6997	£21,962	
1	DOC+CAP	VIN	No Chemo	0.7694	£21,406	
7	GEM+DOC	No Chemo		0.5827	£21,056	
14	DOC	CAP	No Chemo	0.8500	£20,727	**£19,072**
11	PAC	VIN	No Chemo	0.6009	£20,119	
9	PAC	CAP	No Chemo	0.7527	£18,871	**£16,119**
17	DOC	No Chemo		0.4718	£15,928	
2	DOC+CAP	No Chemo		0.5452	£15,526	**£8,325**
12	PAC	No Chemo		0.3645	£14,022	

PFyears = progression-free years, LYs = life years, QALYs = quality adjusted life years, ICERs = incremental cost-effectiveness ratios (see text below for explanation).

Figure 4: incremental cost-effectiveness



The seven unshaded strategies in *table 14* above (strategies 2, 3, 5, 6, 12, 14 and 15) are non-dominated strategies which were considered in the incremental analysis. All the other strategies are considered not to be cost-effective so would never be chosen on the basis of cost-effectiveness. The incremental cost-effectiveness ratios (ICERs) shown in the last column of table 14 are the ratios of cost and health benefit for each strategy compared to the next best strategy. NICE recommends the use of a threshold of £20,000 per QALY. Using a threshold value of £20,000 per QALY, strategy 14 (docetaxel followed by capecitabine followed by no chemotherapy) was shown to be most cost-effective since it maximises health benefits given the budget constraint. However there may be compelling reasons to accept a slightly higher ICER of up to £30,000 per QALY which would make strategy 15 (docetaxel followed by vinorelbine and then capecitabine) most cost-effective since it maximises QALYs below this threshold. Due to the multitude of strategies in the analysis, the results need careful interpretation. Since there is very little difference between strategies 13 (docetaxel followed by capecitabine followed by vinorelbine) and 15, in terms of QALYs, and given the uncertainty surrounding these point estimates, it is not clear which strategy is dominated and thus which should be excluded from the incremental analysis.

Strategies 2, 9, 12 and 14 would be ruled out since more QALYs can be achieved given the maximum willingness to pay. Similarly strategies 3 and 5 would be ruled out since their ICERs of £160,748 and £40,959 respectively, are far above the maximum threshold NICE recommends; the additional 0.1265 is judged to not be worth the extra £5,184, nor is the 0.1302 QALYs for the extra £5,804.

Sensitivity Analysis

Five sources were thought to contribute most to the uncertainty surrounding the analysis; the utility values used in the analysis, the data used on the effectiveness of capecitabine monotherapy, the effectiveness of third-line therapy, possible price discounts and the calculation of overall survival. A number of scenarios were investigated and the results are outlined below:

- **Utility values**

An arbitrary 10% increase and decrease in all the utility values used in the model were tested and made no difference to the strategies that were dominated or to the ranking of the strategies in terms of cost-effectiveness. At a willingness to pay of £30,000 per QALY, strategy 15 (docetaxel, vinorelbine, capecitabine) was still the most cost-effective strategy, with the ICERs ranging from roughly £21,500 when all the utility values were increased (due to higher QALYs) to £26,250 when the utility values were decreased. At a willingness to pay of £20,000 strategy 14 remained most cost effective when utilities increased (with an ICER of £21,000) but when the utilities were reduced, strategy 9 (paclitaxel, capecitabine, no chemo) had the most favourable ICER at £17,923. When the utility ascribed to patients with toxicity was varied from the base-case value of 0.44 to 0.35 (to equal the utility

associated with progressive disease with toxicity), this made little difference to the base-case results. Total QALYs (per patient) were slighted reduced with strategy 15 but it still had a favourable ICER of £23,687.

- **Effectiveness of capecitabine monotherapy**

The time spent without progressive disease having received capecitabine monotherapy was reduced by one third in the sensitivity analysis. This resulted in strategy 13 being included in the incremental analysis, when it had been dominated in the base case. Using a threshold value of £30,000 strategy 15 was still most cost-effective, maximising QALYs given the threshold and with an ICER of £25,359. Strategy 13 (docetaxel, capecitabine, vinorelbine) was associated with an ICER of £32,445. If a stricter threshold value was applied, say £20,000, strategy 2 (Docetaxel + capecitabine, then no chemo) was most cost-effective with an ICER of £8,325.

- **Effectiveness of third-line treatment**

Two 'effectiveness' parameters for third-line treatment were varied in the sensitivity analysis; the response and disease stabilisation, and the time spent free of progressive disease for responders, stable patients and non-responders. Both parameters were separately tested, reducing them by one third. When the response and stabilisation rates were reduced there was no change to the strategies that were dominated, or to the ranking of strategies. The conclusions from the base-case held, but the two most cost-effective strategies (when examining two different thresholds, £20,000 and £30,000 per QALY) were associated with slightly higher ICERs. The survival estimates proved to have more impact, since strategy 15 (docetaxel, vinorelbine, capecitabine) was dominated. Strategy 13 was associated with an ICER of £34,878 but the best strategy was strategy 14 (docetaxel, capecitabine, no chemo) with an ICER of slightly over £19,000 per QALY.

- **Price discounts**

A number of different price discounts for paclitaxel were investigated (50%, 60%, 70%, 80%, and 90%) and, as expected, changed the base-case results. Paclitaxel replaced docetaxel as the most cost-effective starting therapy, but after this the preferred sequences in terms of cost-effectiveness did not change from the base case. The ICERs associated with strategy 10 (paclitaxel, vinorelbine, capecitabine) ranged from £19,000 to just over £21,000. Paclitaxel followed by capecitabine then no chemotherapy yielded ICERs ranging from £16,300 to £14,250 and would be most cost-effective given a £20,000 per ICER threshold. A likely discount available on both paclitaxel (90%) and vinorelbine (45%) showed strategy 10 to have an even more favourable ICER (£18,666 per QALY), making it most cost-effective at a threshold of both £20,000 and £30,000 per QALY.

- **Time from progression to death**

The time from progression to death (assumed to be 5 months in the base-case analysis) was varied from 4 – 6 months. This change, in either direction, had little effect on the base-case results serving to increase (6 months) or decrease (4 months) both the health benefits and the costs. Depending on the

threshold value, either strategy 15 or strategy 14 would be considered most cost-effective.

Overall the sensitivity analyses showed that the results of the base case were reasonably robust to the parameters investigated. The main changes resulted from big potential price discounts, substituting docetaxel for paclitaxel as the preferred starting therapy. Other changes were noted when altering the effectiveness of third-line therapy and the 'progression-free' survival resulting from capecitabine, which was due to small differences in QALYs leading to different strategies being dominated and thus excluded from the incremental results.

DISCUSSION

The base-case results of this analysis provide a clear message for recommendations on this topic, in terms of cost-effectiveness. They show that docetaxel as a single agent therapy dominates the other taxane, paclitaxel, and any combination therapy involving gemcitabine, so all strategies but those starting with first-line docetaxel are ruled out in terms of cost-effectiveness. Using the threshold of £20,000, the most cost-effective strategy was docetaxel followed by capecitabine and then no further treatment (strategy 14). The GDG may consider there to be circumstances which justify the use of a higher threshold by which to judge cost-effectiveness and thereby accept strategy 15 which also starts with docetaxel but is followed first by vinorelbine and then capecitabine. This strategy is associated with higher quality-adjusted survival. Due to the multitude of strategies in the analysis, the results need careful interpretation. There is one strategy, strategy 13 (docetaxel followed by capecitabine then vinorelbine) that is narrowly excluded from the incremental analysis on the basis of extended dominance, but only by a tiny difference in total QALYs, 0.015. Given the uncertainty surrounding these point estimates, it is not clear which strategy is dominated and thus which should be excluded from the incremental analysis. If strategy 15 was dominated, leaving strategy 13 in the incremental analysis, strategy 13 would be associated with a favourable ICER of below £30,000 per QALY. On these grounds the analysis does not provide clear evidence on whether it is always preferable to give vinorelbine first followed by capecitabine.

Strategies 2, 9, 12 and 14 can be ruled out in terms of cost-effectiveness since more QALYs can be achieved given the maximum willingness to pay. Similarly strategies 3 and 5 would be ruled out since their ICERs of £160,748 and £40,959 respectively, are far above the maximum threshold NICE recommends; the additional 0.1265 is judged to not be worth the extra £5,184, nor is the 0.1302 QALYs for the extra £5,804.

The sensitivity analysis show there may however be circumstances in which the base-case results do not hold true. The presence of substantial discounts available nationally for paclitaxel show that if this discount is maintained and is available across England and Wales, the taxane of choice would be paclitaxel rather than docetaxel, since these strategies yielded more

favourable ratios of costs and health benefits. In response to doubts over the validity of the utility value for progressive disease, a 10% increase in this value was tested and it was found that the results were not sensitive to this increase.

There are a number of limitations to this analysis. No discounting was undertaken on either the costs or benefits attributed to each strategy. However this is unlikely to have a major bearing on the results since the patients live for a short time and treatment is the biggest contributor to costs which fall at the beginning rather than throughout the year. The sensitivity analyses conducted was rather limited and using an approach which does not fully capture the uncertainty surrounding the model. In addition some of the strong structural assumptions were not tested, and therefore their impact on the conclusions of the analysis is unknown. The interventions considered in the model were not exhaustive and whilst the most common sequences were included, there may be relevant comparators that have been excluded from the analysis.

Whilst a great deal of effort has been spent on obtaining consistent data on first-line treatment, by undertaking an indirect treatment comparison, many strong assumptions had to be made to combine evidence from different sources to inform the model on the relative effect of the full treatment sequences. Evidence on second-line treatment was poor, and even poorer for third-line treatment. The survival estimates from capecitabine monotherapy seem very high, higher even than first line treatment; although the results seem to be robust to a reduction in these by a third in the sensitivity analysis. No evidence existed for the 'No Chemotherapy' option, in particular this was not associated with any quality of life increase from the published utility values for progressive disease. Expert opinion from the guideline development group was used to fill in gaps in the data, but this has not been fully explored in the sensitivity analysis and some concerns remain as to the validity of the assumptions.

The costs used were often proxies for costs that were hard to capture and may not fully capture the differences between the different therapies, for instance the differences in i.v. times were not captured by costs (or utilities). It was also assumed that combination therapy was not associated with additional administration times, thus biasing the results in favour of the combination therapies. In addition it was no vial sharing was assumed, which may not reflect clinical practice.

Despite these acknowledged limitations, this analysis does provide some useful information for which the guideline development group can use in its deliberations over the recommendations to be made on this topic. Single agent taxane (either docetaxel or paclitaxel depending on the price discounts available) is the most cost-effective starting therapy. The combination therapies are much less cost-effective primarily due to the fact repetition of a chemotherapy agent later in the sequence was not allowed in this analytical model. Three lines of chemotherapy were shown to deliver more QALYs than one or two lines. The choice of which order to deliver capecitabine and

vinorelbine is not as clear cut, and although the results show vinorelbine to be a more cost-effective second line treatment than capecitabine, the difference between the two strategies (13 and 15) is so small, the guideline development group should interpret this particular result with caution.

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Appendix 2

Abbreviations

AI	aromatase inhibitor
CDT	complex decongestive therapy
CRF	cancer-related fatigue
CT	computed tomography
EGFR	epidermal growth factor receptor
ER	oestrogen receptor
FDG	18F-deoxyglucose
HER2	human epidermal growth factor receptor 2
MLD	manual lymphatic drainage
MLLB	multi-layer lymphoedema bandaging
MRI	magnetic resonance imaging
PET	positron emission tomography
PET-CT	positron emission tomography fused with computed tomography
RCT	randomised controlled trial
WBRT	whole brain radiotherapy

Appendix 3

Glossary

Adjuvant therapy
Treatment as a follow-up to surgery designed to remove any microscopic traces of tumour which may have been left behind.

Advanced breast cancer
Disease that has spread from the breast to other body systems, travelling through the bloodstream or lymphatic system (locally advanced breast cancer is disease that has spread to large parts of the breast or nearby lymph nodes).

Aromatase inhibitor
Drugs that reduce the blood levels of oestrogen in postmenopausal women by blocking aromatase, a key enzyme which helps to form oestrogen from other steroids.

Axillary thrombosis
A blood clot in the large vein under the arm.

Axillary/supraclavicular disease
Spread of (breast cancer) disease to the lymph nodes in the armpit or above the collar bone.

Biological response modifier
A substance which aids the body's natural defence system in order to inhibit the growth of a tumour.

Bisphosphonates
A group of drugs used to treat or prevent osteoporosis and to treat the bone pain caused by some types of cancer.

Body habitus
The size and shape of a person's body.

Bone matrix
The major constituent of bone tissue which surrounds the cells.

Bone scintigraphy
A diagnostic imaging technique based on the detection of radiation emitted by a radioactive tracer injected into the body that targets abnormal areas of bone.

Brachial plexus
A network of nerves in the neck and armpit that conducts signals from the spine to the shoulder, arm and hand.

Chemotherapy
A chemical that specifically binds to and kills tumour cells.

Chest radiograph
An image of the inside of the chest, taken using X-rays. Most often used to show the lungs.

Cohort studies
Observational studies in which outcomes are compared in a group of patients that received an intervention with a similar group of people that did not.

Co-morbidity
The presence of more than one disease or health condition in an individual at a given time.

Compression/containment garment
Items of clothing which provide mild compression in order to increase the flow of blood to and from specific muscle groups.

Computed tomography (CT)
A diagnostic imaging technique that uses X-rays and a computer to produce a detailed picture of a cross section of the body

Decision aids
A variety of resources which can help patients participate in decisions about their health e.g. information booklet, CD-ROM.

Dyspnoea
Breathlessness.

Endocrine therapy
Treatment that adds, blocks, or removes hormones in order to slow down or stop the growth of a tumour.

Equivocal
Open to more than one interpretation and therefore of uncertain significance.

HER2
A gene that encodes a growth-promoting protein which helps to control how cells divide and repair themselves.

Inter-operator variability
A term to describe the variation in the ways in which several people carry out the same task.

Magnetic resonance imaging
A diagnostic imaging technique that uses powerful electromagnets, radio waves and a computer to produce well-defined images of the body's internal structures.

Manual lymphatic drainage
A massage technique that uses a gentle pumping technique to stimulate the lymphatic system and improve lymph drainage.

Meta-analysis
A method of summarizing previous research by reviewing and combining the results of a number of different clinical trials.

Metastases
Spread of cancer away from the primary site to somewhere else via the bloodstream or the lymphatic system.

Multi-layer lymphoedema bandaging
Using multiple layers of bandage around a limb to apply graduated pressure and reduce swelling due to lymphoedema.

Osteoblastic bone metastases
Cancer that has spread to the bone causing disorganised new growth.

Osteolytic bone metastases
Cancer that has spread to the bone causing areas of bone destruction.

Ovarian suppression
Surgery, radiation therapy or drug treatment which stops the functioning of the ovaries and significantly reduces oestrogen levels in the blood.

Plain radiograph
A diagnostic image obtained by directing X-rays to a specific region of the body.

Positron emission tomography
A diagnostic imaging technique using a radio-active tracer which shows increased tissue metabolism.

Proximal limb bones
Bones in those parts of the arms and legs which are nearest to the main trunk.

Radiotherapy
A treatment for cancer that uses high energy ionising radiation (usually X-rays) to prevent cell growth.

Randomised controlled trials (RCTs)
A clinical trial in which subjects are randomized to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Simple lymph drainage
Gentle massage to move excess lymph fluid away from a swollen area.

Stereotactic radiosurgery
A radiation therapy that uses special equipment to position the patient and precisely deliver a large radiation dose to a tumour while avoiding normal tissue.

Systematic review
A systematic review of the literature carried out in order to address a defined question and using quantitative methods to summarize the results.

Tamoxifen
An anti-cancer drug that blocks the effects of the hormone oestrogen in the body.

Ultrasound
An imaging method in which high-frequency sound waves are used to outline a part of the body.

Appendix 4

Guideline Scope

Guideline title

Advanced breast cancer: diagnosis and treatment

Short title

Advanced breast cancer

Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Cancer to develop a clinical guideline on the diagnosis and treatment of breast cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see appendix A). Recommendations on early and advanced breast cancer will be developed in parallel. This document is the scope for the recommendations on advanced breast cancer. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

This guideline will support current national initiatives outlined in the 'NHS Cancer Plan', the 'Calman-Hine Report', the 'Cameron Report', the 'Manual of Cancer Service Standards for England' and the 'Wales Cancer Standards'. The guidelines will also refer to the

NICE service guidance 'Improving outcomes in breast cancer' and 'Improving supportive and palliative care for adults with cancer' and the clinical guideline 'Referral guidelines for suspected cancer'.

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

Clinical need for the guideline

Breast cancer is the most common cancer for women in England and Wales, with about 37,000 new cases diagnosed[11][12] and 11,000 deaths[13] recorded in England and Wales each year. In men breast cancer is rare, with about 270 cases diagnosed[1,2] and 70 deaths[3] in England and Wales each year. Of these new cases in women and men, around 10% are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body. In addition, there is a significant number of women who have been previously treated with curative intent who subsequently develop either a local recurrence or metastases. Over recent years there have been important developments in the investigation and management of these patients including new chemotherapy, and biological and hormonal agents. There is some evidence of practice variation across the country and of patchy availability of certain treatments and procedures. A clinical guideline will help to address these issues and offer guidance on best practice.

The guideline

The guideline development process is described in detail in two publications which are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'Guideline development methods: information for national collaborating centres and guideline developers' provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see appendix).

The scope forms the basis on which the work of a guideline development group (GDG) is planned and should be very clear about which patient groups are included and which areas of clinical care will be considered.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

- Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease).

[11] Office for National Statistics (2005) Cancer statistics registrations: registrations of cancer diagnosed in 2002, England. Series MB1 number 33. London: National Statistics.
[12] Welsh Cancer Intelligence and Surveillance Unit (2005) Cancer incidence in Wales 1992−2002. Cardiff: Welsh Cancer Intelligence and Surveillance Unit.
[13] Office for National Statistics (2003) Mortality statistics: cause. England and Wales 2003. London: The Stationery Office.

Groups that will not be covered

- Women and men with invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 (this will be covered by the NICE guideline on 'Early breast cancer: diagnosis and treatment').
- Women and men with metastases to the breast from other primary tumours.
- Women and men with rare breast tumours (for example, angiosarcoma, lymphoma)
- Women and men with benign breast tumours (for example, fibroadenoma, benign phyllodes tumours).

Healthcare setting

- Primary care − excluding population-based and opportunistic screening.
- Secondary care.
- Tertiary care by specialist breast cancer teams.
- Palliative care services

Clinical management

- Investigation
- Surgery
- Radiotherapy
- Hormonal therapy
- Chemotherapy
- Biological agents and other targeted therapies
- Bisphosphonates
- Management of lymphoedema
- Patient information and communication
- Supportive and palliative care

Status

Scope

This is the final version of the scope.

Guideline

The development of the guideline recommendations will begin in June 2006.

Further information

Related NICE guidance

Published guidance

The following guidance will be cross referred to in the advanced breast cancer guideline as appropriate:

- Referral guidelines for suspected cancer. NICE clinical guideline no. 27 (2005). Available from: www.nice.org.uk/CG027

- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. NICE clinical guideline no. 14 (2004). Available from: www.nice.org.uk/CG014
- Improving supportive and palliative care for adults with cancer. Cancer service guidance (2004). Available from: www.nice.org.uk/csgsp
- Improving outcomes in breast cancer – manual update. Cancer service guidance (2002). Available from: www.nice.org.uk/csgbc
- Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal no. 87 (2005). Available from: www.nice.org.uk/TA087

Guidance to be updated

The following NICE technology appraisals will be updated within this guideline and withdrawn when the guideline is published:

- Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal no. 62 (2003). Available from: www.nice.org.uk/TA062
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal no. 34 (2002). Available from: www.nice.org.uk/TA034
- Guidance on the use of vinorelbine for the treatment of advanced breast cancer. NICE technology appraisal no. 54 (2002). Available from: www.nice.org.uk/TA054
- Guidance on the use of taxanes for the treatment of breast cancer. NICE technology appraisal no. 30 (2001). Available from: www.nice.org.uk/TA030

Guidance in development

NICE is in the process of developing the following technology appraisal (details available from www.nice.org.uk). Recommendations from this technology appraisal will be incorporated in the advanced breast cancer guideline:

- Gemcitabine for the treatment of locally advanced or metastatic breast cancer. NICE single technology appraisal. (Publication expected October 2006.)

NICE is also in the process of developing the following guidance (details available from www.nice.org.uk) and these will be cross referred to in the advanced breast cancer guideline as appropriate:

- Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. NICE clinical guideline. (Publication date to be confirmed.)

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal. (Publication expected April 2006.)
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal. (Publication expected April 2006.)

Guideline development process

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'Guideline development methods: information for National Collaborating Centres and guideline developers'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesprocess). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health

The Department of Health and Welsh Assembly Government asked the Institute:

'To prepare a guideline for the NHS in England and Wales on the clinical management of breast cancer, to supplement existing service guidance. The guideline should cover:

- the key diagnostic and staging procedures
- the main treatment modalities including hormonal treatments
- the role of tumour-specific bisphosphonates.'

Appendix 5

List of Topics Covered by Each Chapter

Chapter 2 – Presentation and Diagnosis

- Investigations for (1) assessing disease extent and (2) monitoring the response to treatment, including positron emission tomography (PET)
- Reassessment of endocrine and Her2 status on disease progression

Chapter 3 – Providing Information and Support for Decision Making

- The use of (1) decision aids and (2) information tools to improve treatment outcomes and quality of life

Chapter 4 – Systemic Disease-Modifying Therapy

- What is the choice of 1st line treatment for patients with metastatic breast cancer, endocrine therapy or chemotherapy?
- What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?
- Combination vs (i) sequential or (ii) single chemotherapy regimes:
  - Which is most effective at treating patients with metastatic breast cancer – combination chemotherapy or sequential single-agent chemotherapy
  - Which is the most effective at treating patients with metastatic breast cancer – single vs combination chemotherapy
- The clinical effectiveness and cost effectiveness of vinorelbine for breast cancer (update of TA 54)
- The clinical effectiveness and cost effectiveness of capecitabine for breast cancer (update of TA 62)
- The clinical and cost effectiveness of taxanes in the treatment of advanced breast cancer (update of TA 30)
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance 116 (2007)
- For patients taking Herceptin that relapsed with prior anthracycline (or where anthracycline was inappropriate) what is the best chemotherapy regimen (update of TA 34)
- The management of patients with metastatic HER2+ breast cancer who have had (i) no previous treatment with (ii) previous treatment with or (iii) ongoing treatment with a biological response modifier.

Chapter 5 – Community-based Treatment and Supportive Care

- The ongoing management of advanced breast cancer patients in the community setting
- What are the effective interventions used to support young families in which a parent has advanced breast cancer.

Chapter 6 – Management of Specific Problems

- The management of lymphoedema in:

  - Patients who have completed their primary treatment and have no active disease
  - Patients who have advanced breast cancer (inc. disease of the axilla)
- The role of cancer-related fatigue management in advanced breast cancer patients
- The management of patients with uncontrolled local disease in the presence of metastases or following primary treatment
- The management of metastatic bone disease (inc. bisphosphonates, samarium, radiotherapy, surgery and rehabilitation)
- The management of metastatic brain and meningeal disease (surgery, stereotactic radiotherapy, external beam radiotherapy, intrathecal chemotherapy, rehabilitation)

Appendix 6

People and Organisations Involved in Production of the Guideline

Appendix 6.1

Members of the Guideline Development Group (GDG)

GDG Chairs

Mr John Winstanley	Consultant Surgeon, Royal Bolton Hospital[1]
Dr Sarah Wilson	Medical Director, InHealth[2]

GDG Lead Clinician

Dr Nick Murray	Senior Lecturer and Honorary Consultant Medical Oncologist, Cancer Research UK Clinical Centre, University of Southampton

Group Members

Dr Murray Brunt	Consultant Clinical Oncologist, University Hospital of North Staffordshire NHS Trust
Dr Helen Burrell	Consultant Radiologist, Nottingham University Hospitals NHS Trust
Dr Susan Closs	Lead Consultant in Palliative Medicine/ Network Chair in Palliative Care (South West Wales Cancer Network), Swansea NHS Trust
Mrs Debbie Collins	Macmillan Radiotherapy Specialist, Kent Oncology Centre
Dr Dermott Davison	GP, County Antrim, Northern Ireland
Dr Chris Gaffney	Consultant Clinical Oncologist, Velindre Cancer Centre, Cardiff[3]
Mrs Kathleen Jenkins	Retired Clinical Nurse Specialist
Mrs Mary Milne	Nurse Consultant, The Parapet Breast Unit[4]
Mrs Susan Raettig	Patient/carer representative, Chair, Hull and East Riding Cancer Patient Involvement Group
Miss Jane Rankin	Lead Cancer Physiotherapist, Belfast City Hospital
Mrs Claire Ryan	Lead Research Nurse Oncology Clinical Trials, Kent Oncology Research Centre[5]
Mr John Winstanley	Consultant Surgeon, Royal Bolton Hospital[6]
Mrs Netta Wooles	Patient/carer representative
Miss Anna Wood	Head of Policy and Campaigns, Breast Cancer Care[7]

[1] From February 2008 – February 2009
[2] From June 2006 to February 2008
[3] From September 2007 – February 2009
[4] From June 2006 to July 2007
[5] From November 2007 to February 2009
[6] From June 2006 to February 2008
[7] From June 2006 to May 2008

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Dr Nick Murray	Co-chief investigator of NCRN ZICE trial of ibandronic acid versus zoledronic acid in metastatic breast cancer to bone. Roche are providing drug support	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include bisphosphonates as interventions
	Chief investigator of NCRN phase II trial of biweekly gemcitabine + carboplatin in metastatic breast cancer. Lilly are providing drug support	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include chemotherapy as interventions. Chairperson's action taken that can be asked specific technical questions about chemotherapy topics.
	Received reagent and equipment support from Becamn Coulter for tumour marker study in breast cancer	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as interventions included in the trial are not being investigated by the guideline
	Chief investigator for phase II trial of sunitinib in triple negative metastatic breast cancer. Pfizer are providing set up and per patient support	Non-personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include sunitinib as an intervention.[1]
	Received travel and subsistence expenses from Roche for attending an academic meeting on bone disease	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Received travel expenses from Sanofi Aventis for attending the European Breast Cancer Conference in April 2008	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.

[1] Sunitinib was not included as an intervention in any of the topics investigated by the guideline and was therefore not discussed by the GDG

Dr Murray Brunt	Received honorarium from Pfizer plus travel expenses for attending an advisory board on adjuvant exemestane	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include exemestane as an intervention until July 2007
	Received honorarium from AstraZeneca for attending advisory board on fulvestrant in the EFECT trial	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include fulvestrant as an intervention until November 2007
	Received honorarium from AstraZeneca to give lecture to GPs on own choice of subject. Cancelled by GPs at short notice by fee still payable for preparation	Personal pecuniary, specific	Declare and must withdraw from discussion on all topics that include interventions made by AstraZeneca until January 2008
	Received travel, subsistence and registration fee expenses from AstraZeneca to attend St Gallen breast meeting in March 07	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Commissioned by HealthEd agency to produce 2 case reports on trastuzumab for advanced breast cancer	Personal pecuniary, specific	Declare and must withdraw from discussion on all topics that include trastuzumab as an intervention until September 2008
	Received an honorarium from Roche Diagnostics for attending an advisory board on tamoxifen modifiers	Personal pecuniary, specific	Declare and must withdraw from discussion on all topics that include tamoxifen modifiers as an intervention until August 2008
	Received an honorarium from Roche for chairing an advisory board on trastuzumab	Personal pecuniary, specific	Declare and must withdraw from discussion on all topics that include trastuzumab as an intervention until September 2008
	Received an honorarium from Cephalon for chairing an educational meeting where 2 palliative care physicians gave talks	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as meeting was not specific to advanced breast cancer

Dr Helen Burrell	Received travel and subsistence expenses from AstraZeneca for attending a meeting where current topics in breast cancer were discussed	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
Dr Chris Gaffney	Received honorarium from Sanofi Aventis for chairing an educational meeting on the use of docetaxel in the treatment of head and neck cancer	Personal pecuniary, non-specific	Declare and can participate indiscussions on all topics as the meeting was not specific advanced breast cancer.
Mrs Mary Milne	Asked to participate in a project on follow-up being run by Astra Zeneca	Personal non-pecuniary	Declare and can participate in discussions on all topics
	Taken a career break to work full-time on the Astra Zeneca project	Personal pecuniary, specific	Asked to resign from the GDG as salary is now being paid by Astra Zeneca
Miss Jane Rankin	Vice Chair of Association of Chartered Physiotherapists in Oncology and Palliative Care (ACPOPC)	Personal non-pecuniary	Declare and can participate in discussions on all topics
	Member of regional (DoH) lymphoedema review group/CREST.	Personal non-pecuniary	Declare and can participate in discussions on all topics
	Received minimal funding grants (£150 each) from the 5 main lymphoedema companies (Medi Uk, Sigvaris, Juzo, Haddenham and BSN Medical) used in the UK to fund cancer conferences and lymphoedema courses	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as does not have supervisory responsibility
Mrs Claire Ryan	Needs to generate an income from commercial clinical trials which is used to support clinical and non-clinical staff salaries and the ongoing development of the Clinical Trials Unit. The clinical activity used to generate the income is derived from predominantly Phase 3 trials (also includes some Phase 2). A pre-requisite is the completion and declaration of no added interest in the clinical trial (FDA 1572 form).	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
	Department received funding from Roche and Sanofi Aventis to send a member of staff to a GI conference in 2008. Money used to cover travel expenses, registration fee and accommodation	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
Miss Anna Wood	Breast Cancer Care received sponsorship from Pfizer (contribution towards venue hire and refreshment costs) for fringe event run on "ageism in breast cancer" at Labour party conference on 26 Sept 2006	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics

	Breast Cancer Care received sponsorship from Pfizer (contribution towards venue hire and refreshment costs) for fringe event run on "ageism in breast cancer" at Conservative party conference on 3 Oct 2006	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
	Received travel and subsistence expenses from Astra Zeneca and payment of registration fee to attend the San Antonio Breast Cancer Conference in 2006	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Responded on behalf of Breast Cancer Care (consultee organisation) to NICE technology appraisals of Gemcitabine and Lapatinib in ABC	Personal non-pecuniary	Declare and can participate in discussions on all topics

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Appendix 6.2

Organisations Invited to Comment on Guideline Development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

- 3 Countries Cancer Network Palliative Care Lead Clinicians Group
- Abbott Laboratories Ltd (BASF/Knoll)
- Abbott Molecular
- Abraxis Oncology
- Afiya Trust, The
- Age Concern Cymru
- Age Concern England
- Airedale NHS Trust
- All About Nocturnal Enuresis Team
- Almac Diagnostics
- Amgen UK Ltd
- Anglesey Local Health Board
- Anglia Cancer Network
- Arden Cancer Network
- Association of Breast Surgery at BASO
- Association of Chartered Physiotherapists in Oncology and Palliative Care
- Association of Surgeons of Great Britain and Ireland
- Association of the British Pharmaceuticals Industry (ABPI)
- AstraZeneca UK Ltd
- Bard Ltd
- Barnsley Acute Trust
- Barnsley PCT
- Bath and North East Somerset PCT
- Baxter Healthcare Ltd
- Bayer Healthcare PLC
- Bedfordshire & Hertfordshire NHS Strategic Health Authority
- Bedfordshire PCT
- Birmingham Cancer Network
- Birmingham Clinical Trials Unit
- Birmingham Heartlands & Solihull NHS Trust
- Blaenau Gwent Local Health Board
- Boehringer Ingelheim Ltd
- Bournemouth and Poole PCT
- Bradford & Airdale PCT
- Breakthrough Breast Cancer
- Breast Cancer Care
- Bristol-Myers Squibb Pharmaceuticals Ltd
- British Association for Behavioural & Cognitive Psychotherapies (BABCP)
- British Association for Counselling and Psychotherapy
- British Association of Art Therapists - 2nd contact
- British Association of Plastic Surgeons
- British Dietetic Association
- British Geriatrics Society
- British Homeopathic Association
- British Lymphology Society
- British Menopause Society
- British Nuclear Medicine Society
- British Oncological Association

- British Oncology Pharmacy Association
- British Psychological Society, The
- British Society for Cancer Genetics
- Bromley PCT
- BUPA
- Calderdale PCT
- Cambridge University Hospitals NHS Foundation Trust
- Cancer Network Pharmacists Forum
- Cancer Research UK
- Cancer Services Collaborative
- CancerBACUP
- Cancer Black Care
- Cancer Voices
- CASPE
- Central Liverpool PCT
- Cephalon UK Ltd
- Chartered Society of Physiotherapy
- CIS'ters
- Clatterbridge Centre for Oncology NHS Trust
- Clinical Knowledge Summaries (CKS)
- Clinovia Ltd
- College of Occupational Therapists
- Commission for Social Care Inspection
- Connecting for Health
- Conwy & Denbighshire NHS Trust
- Co-operative Pharmacy Association
- Countess of Chester Hospital NHS Foundation Trust
- Craven, Harrogate & Rural District PCT
- Cytyc UK Ltd
- DakoCytomation Ltd
- David Lewis Centre, The
- Department of Health
- Derby-Burton Cancer Network
- Doncaster PCT
- Eisai Ltd
- Eli Lilly and Company Ltd
- Essex Cancer Network
- Faculty of Public Health
- General Practice and Primary Care
- GlaxoSmithKline UK
- Gloucestershire Hospitals NHS Trust
- Good Hope NHS Trust
- Greater Manchester & Cheshire Cancer Network
- Guerbet Laboratories Ltd
- Guys & St Thomas NHS Trust
- Hampshire & Isle of Wight Strategic Health Authority
- Harrogate and District NHS Foundation Trust
- Healthcare Commission
- Help the Hospices
- Humber and Yorkshire Coast Cancer Network
- Imaging Equipment Ltd
- Independent Healthcare Advisory Service
- Intra-Tech Healthcare Ltd
- Johnson & Johnson Medical
- King's College Hospital NHS Trust
- Kirklees PCT
- L'Arche UK
- Launch Diagnostics Ltd
- Leeds PCT
- Leeds Teaching Hospitals NHS Trust
- Leicestershire Northamptonshire and Rutland Cancer Network
- Liverpool Women's Hospital NHS Trust
- Long Term Medical Conditions Alliance
- Luton and Dunstable Hospital NHS Trust
- Macclesfield District General Hospital

- Macmillan Cancer Relief
- Maidstone and Tunbridge Wells NHS Trust
- Marie Curie Cancer Care
- Medeus Pharma Ltd
- Medical Device Innovations Ltd
- Medical Solutions
- Medicines and Healthcare Products Regulatory Agency
- Merck Pharmaceuticals
- Mid Staffordshire General Hospitals NHS Trust
- Milton Keynes PCT
- National Association of Assistants in Surgical Practice
- National Audit Office
- National Cancer Network Clinical Directors Group
- National Cancer Research Institute (NCRI) Clinical Studies Group
- National Childbirth Trust
- National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
- National Council for Palliative Care
- National Osteoporosis Society
- National Patient Safety Agency
- National Public Health Service – Wales
- Newcastle PCT
- Newham PCT
- NCCHTA
- NHS Cancer Screening Programme
- NHS Clinical Knowledge Summaries Service
- NHS Direct
- NHS Health and Social Care Information Centre
- North Bradford PCT
- North East London Cancer Network
- North East London Strategic Health Authority
- North Eastern Derbyshire PCT
- North Lincolnshire PCT
- North Sheffield PCT
- North Tees PCT
- North Trent Cancer network
- North Yorkshire and York PCT
- Northwest London Hospitals NHS Trust
- Northumbria Healthcare NHS Trust
- Nottingham City Hospital
- Nottingham University Hospitals NHS Trust
- Novartis Pharmaceuticals UK Ltd
- Nucletron B.V.
- Nutrition Society
- Organon Laboratories Ltd
- Ortho Biotech
- Ovarian Cancer Action
- Oxford Nutrition Ltd
- Peach
- Peninsula Clinical Genetics Service
- PERIGON Healthcare Ltd
- Pfizer Ltd
- Pierre Fabre Ltd
- Primary Care Pharmacists' Association
- Princess Alexandra Hospital NHS Trust
- Queen Elizabeth Hospital NHS Trust
- Queen Victoria Hospital NHS Foundation Trust
- Regional Public Health Group – London
- Roche Diagnostics
- Roche Ltd
- Rotherham General Hospitals NHS Trust
- Rotherham PCT
- Royal Bolton Hospitals NHS Trust
- Royal College of General Practitioners

- Royal College of General Practitioners Wales
- Royal College of Midwives
- Royal College of Nursing (RCN)
- Royal College of Obstetricians & Gynaecologists
- Royal College of Pathologists
- Royal College of Physicians of London
- Royal College of Psychiatrists
- Royal College of Radiologists
- Royal Society of Medicine
- Royal United Hospital Bath NHS Trust
- Royal West Sussex Trust, The
- Salford PCT
- Sandwell & West Birmingham Hospitals NHS Trust
- Sandwell PCT
- sanofi-aventis
- Schering-Plough Ltd
- Scotland Cancer Network
- Scottish Executive Health Department
- Shropshire County and Telford & Wrekin PCT
- Sheffield South West PCT
- Sheffield Teaching Hospitals NHS Foundation Trust
- Siemens Medical Solutions Diagnostics
- Sigvaris Britain Ltd
- Society and College of Radiographers
- Society for Academic Primary Care
- South & Central Huddersfield PCT
- South East Sheffield PCT
- South West Kent PCT
- South West London SHA
- South East Wales Cancer Network
- Staffordshire Moorlands PCT
- Stockport PCT
- Sussex Cancer Network
- Tameside and Glossop Acute Services NHS Trust
- Tameside and Glossop PCT
- Taunton Road Medical Centre
- Thames Valley Cancer Network
- Thames Valley Strategic Health Authority
- Trafford PCT
- UCLH NHS Foundation Trust
- UK Anaemia
- UK National Screening Committee
- University College London Hospital NHS Trust
- University Hospital Birmingham NHS Foundation Trust
- University Hospitals Coventry & Warwickshire NHS Trust
- University of Birmingham, Department of Primary Care & General Practice
- Velindre NHS Trust
- Walsall Teaching PCT
- Welsh Assembly Government
- Welsh Scientific Advisory Committee (WSAC)
- Wessex Cancer Trust
- West London Cancer Network
- Western Cheshire PCT
- West Hertfordshire Hospitals Trust
- World Cancer Research Fund International
- Wyeth Laboratories
- Wyeth Pharmaceuticals
- York NHS Trust
- Yorkshire and the Humber Specialised Commissioning Group

Appendix 6.3

Individuals Carrying out Literature Reviews and Complementary Work

Overall Co-ordinators

Dr Fergus Macbeth	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Manager

Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff

Researcher

Dr Karen Francis	National Collaborating Centre for Cancer, Cardiff

Information Specialists

Elise Collins	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Anne Cleves	Cancer Research Wales Library, Velindre NHS Trust
Bernadette Coles	Cancer Research Wales Library, Velindre NHS Trust

Health Economists

Sarah Willis	Research Assistant, London School of Hygiene and Tropical Medicine, London
Nicky Welton	Senior Research Fellow, Academic Unit of Primary Health Care, University of Bristol

Needs Assessment

Dr Robyn Dewis	Specialist Registrar in Public Health, Derby City Primary Care Trust
Jonathan Gribbin	Specialist Trainee in Public Health, Derbyshire County Primary Care Trust
Prof Mark Baker[22]	Medical Director for Oncology and Surgery and Lead Cancer Clinician, Leeds Teaching Hospitals, Leeds

[22] Provided peer review data

Appendix 6.4

Expert Advisers to the Guideline Development Group

Professor Robert J. Grieve	Consultant Clinical Oncologist, Arden Cancer Centre, University Hospitals Coventry & Warwickshire
Mrs Samantha Holloway	Lecturer, Department of Wound Healing, School of Medicine, Cardiff University

Appendix 6.5

Members of the Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop - Chair
Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Ash Paul
Deputy Medical Director, Health Commission Wales

Professor Liam Smeeth
Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Mr Peter Gosling
Lay member

Mr Jonathan Hopper
Medical Director (Northern Europe), ConvaTec Ltd