Advanced breast cancer: diagnosis and treatment

NICE guideline: short version

Draft for consultation, May 2017

This guideline covers care and support for people with advanced (stage 4) breast cancer. It aims to help them and their healthcare professionals make shared decisions about tests and treatments to improve outcomes and quality of life.

Who is it for?

- Healthcare professionals
- Palliative care services
- People with advanced breast cancer, their families and carers

This guideline will update NICE guideline CG81 (published February 2009).

We have added a new recommendation on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.

You are invited to comment on the new recommendation in this guideline. This is marked as:

- **[2017]** because the evidence has been reviewed and the recommendation has been updated.

You are also invited to comment on recommendations that NICE proposes to delete from the 2009 guideline.

We have not updated recommendations shaded in grey, and cannot accept comments on them.

See Update information for a full explanation of what is being updated.

This version of the guideline contains the draft recommendations, context and recommendations for research. The supporting information and evidence for the 2017 recommendation is contained in the 2017 addendum.

Evidence for the 2014 and 2009 recommendations is contained in the 2014 addendum and the 2009 full version of the guideline.

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Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Diagnosis and assessment

Imaging assessment

1.1.1 Assess the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI). **[2009]**

1.1.2 Assess the presence and extent of metastases in the bones of the axial skeleton using bone windows on a CT scan or MRI or bone scintigraphy. **[2009]**

1.1.3 Assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone scintigraphy and/or plain radiography. **[2009]**

1.1.4 Use MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases encroaching on the spinal canal). **[2009]**

1.1.5 Positron emission tomography fused with computed tomography (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. **[2009]**

Pathological assessment

1.1.6 On recurrence, consider reassessing oestrogen receptor (ER) and human epidermal growth factor 2 receptor (HER2) status if a change in receptor status will lead to a change in management. **[2017]**

Monitoring disease status

1.1.7 Do not use bone scintigraphy to monitor the response of bone metastases to treatment. **[2009]**

1.1.8 Do not use PET-CT to monitor advanced breast cancer. **[2009]**

1.2 Providing information and support for decision making

1.2.1 Assess the patient's individual preference for the level and type of information. Reassess this as circumstances change. **[2009]**

1.2.2 On the basis of this assessment, offer patients consistent, relevant information and clear explanations, and provide opportunities for patients to discuss issues and ask questions. **[2009]**

1.2.3 Assess the patient's individual preference for how much they wish to be involved in decision making. Reassess this as circumstances change. **[2009]**

1.2.4 Be aware of the value of decision aids and the range available. Make the most appropriate decision aid available to the patient. **[2009]**

1.3 Systemic disease-modifying therapy

1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer. **[2009]**

1.3.2 Offer chemotherapy as first-line treatment for patients with ER positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. **[2009]**

1.3.3 For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy. **[2009]**

Endocrine therapy

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. **[2009]**

1.3.5 Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. **[2009]**

1.3.6 Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. **[2009]**

1.3.7 Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. **[2009]**

Chemotherapy

1.3.8 On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. **[2009]**

1.3.9 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. **[2009]**

1.3.10 For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), 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). **[2009]**

1.3.11 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[1]. **[2009]**

Biological therapy

1.3.12 For patients who are receiving treatment with trastuzumab[2] for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone. **[2009]**

1.4 Supportive care

1.4.1 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 Improving outcomes in breast cancer: manual update (NICE cancer service guidance [2002]) and Improving supportive and palliative care for adults with cancer (NICE cancer service guidance [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,

[1] This recommendation is from Gemcitabine for the treatment of metastatic breast cancer (NICE technology appraisal guidance 116; 2007). It was formulated as part of that technology appraisal and not by the guideline developers. It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation is available.

[2] Recommendations on the use of trastuzumab are covered by Guidance on the use of trastuzumab for the treatment of advanced breast cancer (NICE technology appraisal guidance 34; 2002). .

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.' **[2009]**

1.5 Managing complications

Lymphoedema

1.5.1 Discuss with people who have or who are at risk of breast-cancer related lymphoedema that there is no indication that exercise prevents, causes or worsens lymphoedema. **[2014]**

1.5.2 Discuss with people who have or who are at risk of breast cancer related lymphoedema that exercise may improve their quality of life. **[2014]**

1.5.3 Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme. **[2009]**

1.5.4 Offer all patients with lymphoedema complex decongestive therapy (CDT) as the first stage of lymphoedema management. **[2009]**

1.5.5 Consider using multilayer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery. **[2009]**

1.5.6 Provide patients with 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. **[2009]**

1.5.7 Provide patients with lymphoedema with clear, written information and the contact details of local and national lymphoedema support groups. **[2009]**

Cancer-related fatigue

1.5.8 Offer all patients with advanced breast cancer for whom cancer related fatigue is a significant problem an assessment to identify any treatable causative factors, and offer appropriate management as necessary. **[2009]**

1.5.9 Provide clear, written information about cancer-related fatigue, organisations that offer psychosocial support and patient led groups. **[2009]**

1.5.10 Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue. **[2009]**

Uncontrolled local disease

1.5.11 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. **[2009]**

1.5.12 A wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. **[2009]**

1.5.13 A palliative care team should assess all patients with uncontrolled local disease in order to plan a symptom management strategy and provide psychological support. **[2009]**

Bone metastases

1.5.14 Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. **[2009]**

1.5.15 The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication. **[2009]**

1.5.16 Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain. **[2009]**

1.5.17 An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery. **[2009]**

Brain metastases

1.5.18 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. **[2009]**

1.5.19 Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis. **[2009]**

1.5.20 Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy. **[2009]**

1.5.21 Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate. **[2009]**

Putting this guideline into practice

[This section will be completed after consultation]

NICE has produced tools and resources to help you put this guideline into practice.

[Optional paragraph if issues raised] Some issues were highlighted that might need specific thought when implementing the recommendations. These were raised during the development of this guideline. They are:

- [add any issues specific to guideline here]
- [Use 'Bullet left 1 last' style for the final item in this list.]

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. **Raise awareness** through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.

2. **Identify a lead** with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.

3. **Carry out a baseline assessment** against the recommendations to find out whether there are gaps in current service provision.

4. **Think about what data you need to measure improvement** and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.

5. **Develop an action plan**, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.

6. **For very big changes** include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.

7. **Implement the action plan** with oversight from the lead and the project group. Big projects may also need project management support.

8. **Review and monitor** how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See our into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Context

Breast cancer is the most common cancer affecting women in England and Wales, with about 40,500 new cases diagnosed and 10,900 deaths recorded in England and Wales each year. In men breast cancer is rare, with about 260 cases diagnosed and 68 deaths in England and Wales each year.[3,4] Of these new cases in women and men, a small proportion is diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body. In addition, there are 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 patients with advanced breast cancer, 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. This clinical guideline helps to address these issues and offers guidance on best practice.

[3] Office for National Statistics (2008) Cancer statistics registrations: registrations of cancer diagnosed in 2005, England. Series MB1 number 36. London: Office for National Statistics.
[4] Welsh Cancer Intelligence and Surveillance Unit (2008) Cancer incidence in Wales 1992−2002. Cardiff: Welsh Cancer Intelligence and Surveillance Unit.

In 2014, we reviewed the evidence on exercise for people with or at risk of lymphoedema and added 2 new recommendations.

In the current update, we have reviewed the evidence on assessing oestrogen receptor (ER), human epidermal growth factor receptor 2 (HER2) and progesterone receptor (PR) status on disease recurrence.

More information

To find out what NICE has said on topics related to this guideline, see our web page on breast cancer.

Recommendations for research

The 2014 and 2009 guideline committees made the following recommendations for research.

1 Assessment of the role of exercise

What is the role of arm and shoulder specific exercises compared with and/or used as an adjunct to established lymphoedema treatments (such as compression garments and complex decongestive therapy)?

Why this is important

Well-designed randomised controlled trials should consider differing arm and shoulder-specific aerobic and/or resistive exercises that focus on strength and flexibility to improve local lymph flow, for example, swimming, weight lifting, tai chi and yoga. The studies should have a follow-up period that is sufficient to capture long-term outcomes including changes to current lymphoedema or any new-onset lymphoedema in other parts of the limb. Outcomes for this research should include quality-of-life measures. **[2014]**

2 Endocrine therapy

Clinical trials are needed to investigate the most effective endocrine therapy for postmenopausal women with ER-positive tumours who progress on treatment with an aromatase inhibitor.

Why this is important

Although there is good evidence to support the use of aromatase inhibitors for postmenopausal women with ER-positive tumours, there is little evidence to determine what is the best sequence of alternative hormone treatments when they progress. **[2009]**

3 Chemotherapy

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

Why this is important

Most patients with advanced breast cancer who receive chemotherapy will be given at least two different regimens and many will receive three. The available evidence to support decisions about the most clinically and cost effective sequence in which to use these drugs is extremely limited. There is also very little good-quality evidence about the relative clinical and cost effectiveness of currently recommended treatments, either in combination or in sequence. Following on from the recommendations in this guideline, it would be important to establish clinical trials to investigate this problem in a more systematic fashion than hitherto. **[2009]**

4 Biological response modifiers (progressive metastatic disease)

The use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial. Trial design should incorporate collection of data required for prospective cost-effectiveness analysis.

Why this is important

There is currently no high-quality published evidence about whether continuing trastuzumab is effective in prolonging survival in patients with HER2-positive advanced breast cancer who develop progressive disease (outside the central nervous system) during or after first-line treatment with trastuzumab and cytotoxic chemotherapy. Any studies should be carefully planned to permit a high quality cost-effectiveness analysis. **[2009]**

5 Biological response modifiers (adjuvant trastuzumab)

Randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should be offered further biological response modifiers. Trial design should incorporate collection of data required for prospective cost-effectiveness analysis.

Why this is important

As more patients with HER2-positive advanced breast cancer have trastuzumab as part of their initial adjuvant treatment following a diagnosis of early breast cancer, an increasing number of patients with advanced breast cancer will have had previous exposure to this agent. There is no evidence currently about whether trastuzumab or other biological therapies are effective in this situation. **[2009]**

6 Uncontrolled local disease

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.

Why this is important

The problem of how best to manage uncontrolled local disease is very poorly addressed by the current evidence. Although it is probably quite an uncommon condition, it is likely that across the country there are enough patients to generate evidence from well-coordinated national studies. A national register should be considered as part of this because of the current uncertainties about the frequency of the problem. **[2009]**

Update information

May 2017

A new recommendations has been added on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.

This is marked as:

- **[2017]** because the evidence has been reviewed and the recommendation has been updated.

NICE proposes to delete some recommendations from the 2009 guideline, because the evidence has been reviewed and the recommendations have been updated. Recommendations that have been deleted or changed sets out these recommendations and includes details of replacement recommendations. Where there is no replacement recommendation, an explanation for the proposed deletion is given.

Recommendations that are shaded in grey are marked as follows:

- **[2014]** if the evidence was reviewed and the recommendation was added in 2014
- **[2009]** if the evidence has not been updated and reviewed since 2009.

See also the original NICE guideline and supporting documents.

Recommendations that have been deleted or changed

Recommendations to be deleted

Recommendation in 2009 guideline	Comment
Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status. (1.1.6)	Replaced by: On recurrence, consider reassessing oestrogen receptor (ER) and human epidermal growth factor 2 receptor (HER2) status if a change in receptor status will lead to a change in management.
Patients with tumours of known human epidermal growth factor receptor 2 (HER2) status whose disease recurs should not have a further biopsy just to reassess HER2 status. (1.1.7)	Replaced by: On recurrence, consider reassessing oestrogen receptor (ER) and human epidermal growth factor 2 receptor (HER2) status if a change in receptor status will lead to a change in management.
Assess ER and HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status. (1.1.8)	Recommendation deleted because most people now have assessment of ER and HER2 status at diagnosis; in people who have not had this, it is standard practice to assess on recurrence.

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