Appendix A: Summary of evidence from surveillance

2023 surveillance breast cancer: early and locally advanced breast cancer (NICE guideline NG101) and advanced breast cancer (NICE guideline CG81)

Overall surveillance decision

We will update the guidelines at this time in the areas of:

- Genetic testing
- Psychological support for all people with breast cancer
- Further surgery after breast conserving-surgery based on tissue margins
- Chemotherapy for advanced breast cancer
- Neoadjuvant chemotherapy for people with HER2-positive invasive breast cancer and triple-negative invasive breast cancer
- Platinum-based neoadjuvant chemotherapy regimens for people with triple-negative invasive breast cancer
- Ovarian function suppression for premenopausal and perimenopausal women with oestrogen receptor-positive early, locally advanced and advanced breast cancer
- Biological therapy for advanced breast cancer
- Lymphoedema for all people with breast cancer
- Menopausal symptoms for all people with breast cancer

We will amend the guidelines at this time in the areas of:

- Providing information and support (amalgamate and align recommendations for early, locally advanced and advanced breast cancer)
- Decision aids (amend recommendation wording to highlight importance of shared decision making and use of decision aids for all people with breast cancer, with links added to NICE guideline NG197)
- Endocrine therapy for advanced breast cancer (content alignment with NICE technology appraisals on CDK4/6 inhibitors and NICE technology appraisal TA496)
- Brain metastasis (content alignment with NICE guideline NG99 recommendations on management of confirmed brain metastases)

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Background information

Studies were considered for inclusion using criteria defined by the guideline review protocols and are summarised from the information presented in their abstracts.

More detailed summaries, including numerical data, are provided for studies assessed as having an impact on guideline recommendations or indicate that the evidence base should be monitored. Where evidence indicated an update, but there was insufficient information within an abstract(s) to make a decision, full texts were checked for further details where necessary. Details are provided within impact sections.

Only guideline sections for which new evidence has been identified are discussed.

Recommendations from NICE guidelines are referred to in the format *guideline number- recommendation number* e.g., NG101-1.1.1. Recommendations from both guidelines have been grouped into sections where they conceptually overlap.

Diagnosis and assessment

This section includes recommendations on:

- imaging assessment in advanced cancer (CG81-1.1.1 to 1.1.5)
- preoperative assessment of the breast and axilla (NG101-1.1.1 to 1.1.2)
- preoperative staging of the axilla (NG101-1.1.3)
- predictive factors (CG81-1.1.6 and NG101-1.6.1 to 1.6.5)
- adjuvant therapy planning (NG101-1.6.6 to 1.6.9): no evidence or intelligence was identified in the 2022 surveillance review that was relevant to the review question on which predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy.
- genetic testing (NG101-1.1.4)

Imaging assessment in advanced cancer

NICE guideline CG81 recommendations:

- 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]

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

The 2018 surveillance review for NICE guideline CG81 found no new evidence for this area. Topic experts highlighted the use of PET-CT and bone scintigraphy however agreed that recommendations were permissive of these methods and no update was needed at this time.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review evaluated bone single-photon emission CT/CT in cancer care. The outcomes were sensitivity and specificity (Rohani et al. 2021). In total 4 prospective cohort studies, 8 retrospective cohort studies (n=1,511) were included (search dates: All to 30 August 2020). A meta-analysis showed that the sensitivity and specificity of single-photon emission computed tomography/computed tomography (SPECT/CT) for diagnosing indeterminate bone lesions are 93.0% (95%CI=0.91 to 0.95) and 96.0% (95%CI=0.94 to 0.97), respectively. There was heterogeneity of the articles due to different imaging protocols, duration of follow-up and scoring methods for interpreting the SPECT/CT results. The heterogeneity poses a challenge for accurate interpretation of the true diagnostic capability of SPECT/CT.

A systematic review evaluated F-18 fluroestradiol (F-18 FES) positron emission tomography/computed tomography (PET/CT) for people with recurrent or metastatic breast cancer. The reference standard was immunohistochemistry, and the outcomes were sensitivity and specificity (Mo et al. 2021). In total 8 diagnostic test accuracy studies (n=284) were included (search dates: January 1980 to 15 May 2020). Meta-analyses showed that F-18 FES PET/CT has a sensitivity of 86% and a specificity of 85%.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

A systematic review evaluated how ^{18}F-FDG PET changed the management of patients with breast cancer with respect to the detection of recurrence/metastasis after curative surgery, such as mastectomy or lumpectomy. (Pak et al. 2021). In total 13 studies (study types were not provided) (n=982) were included (search dates: All to March 2020). In patients with elevated tumour markers (*n* = 350) and in those who underwent PET for routine surveillance, the pooled rates of management change were 52.3% and 12.4%, respectively. The authors concluded that ^{18}F-FDG PET should be performed in patients with breast cancer and equivocal or suspicious recurrence/metastasis on conventional imaging or with elevated tumour markers during follow-up.

Intelligence gathering

The breast cancer health inequalities briefing notes that 'deprived groups are less likely to participate in breast cancer screening, less likely to have an urgent referral, and more likely to present via outpatient route leading to delay in diagnosis and more advanced stage of breast cancers at diagnosis, needing intensive combination treatment that includes tumour resection, radiotherapy, and chemotherapy. Delay of breast cancer diagnosis is a major contributing factor to many inequalities in care and outcomes in deprived groups. Also, people from minority ethnic family backgrounds are over-represented in deprived communities, further exacerbating inequalities.' It also found that fewer people with a disability participate in screening due to various barriers, and that they generally have delayed diagnosis and present with advanced stage breast cancers.

System intelligence indicates that in clinical practice there is an increasing use of PET scans. It was also reported that an update of recommendations might reduce inequality and variability in practice as well as having a cost effectiveness impact.

Impact statement

New evidence is unlikely to change guideline recommendations.

There is evidence from 1 systematic review which indicates that ^{18}F-FDG PET may have an impact on the management of patients with breast cancer after surgery who have equivocal or suspicious recurrence/metastasis on conventional imaging or in cases involving elevated tumour markers during follow-up. However, as the systematic review involved a mixed patient group (i.e. not specific to advanced breast cancer) further research is required to determine whether and/or under which circumstances ^{18}F-FDG PET may be more appropriate than CT scan and/or MRI in assessing metastases.

As system intelligence indicates that there is an increasing use of PET scans in clinical practice, the committee may want to consider whether recommendations on imaging should be updated even though there is only limited evidence in this area.

There is also evidence that deprived groups, people from minority ethnic family backgrounds and people with a disability may have delays in diagnosis of breast cancer due to various

factors, in particular, less participation in national screening. There are currently no recommendations on measures that may improve access to/attendance at national breast cancer screening programmes for these populations. Whether this gap could be addressed through new recommendations within the breast cancer guideline or via other NICE products or teams, such as engagement with field teams and/or NICE implementation should be considered during the update process for the guideline.

Preoperative assessment of the breast and axilla

NICE guideline NG101 recommendations:

- 1.1.1 Do not routinely use MRI of the breast in the preoperative assessment of people with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS). **[2009]**
- 1.1.2 Offer MRI of the breast to people with invasive breast cancer:
  - if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
  - if breast density precludes accurate mammographic assessment
  - to assess the tumour size if breast-conserving surgery is being considered for invasive lobular cancer. **[2009]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

Evidence was identified in the 2015 surveillance review for the review question 'what is the role of breast magnetic resonance imaging (MRI) in the preoperative staging of patients with biopsy-proven ductal carcinoma in situ (DCIS) or invasive breast cancer?'. The new evidence suggested that using MRI in staging of breast cancer had no effect on recurrence at 8 years. It was concluded that this evidence was unlikely to affect the current recommendation that routine MRI in preoperative assessment is not recommended. Additionally, there was evidence that some features of tumours seen on MRI and other imaging modalities may be associated with HER2 overexpression; however, the evidence did not provide any information about using these features as part of diagnosis.

2023 surveillance

Studies that impact recommendations

None identified

Studies that do not impact recommendations

A systematic review evaluated the impact of preoperative MRI on the management of DCIS (Canelo-Aybar et al. 2021). Three RCTs and 23 observational studies (n=20,415) were included (search dates: note reported in abstract (NR)). RCT data indicated that MRI results in no significant difference on the relative risk of having initial breast-conserving surgery (evidence assessed as low certainty), nor for total mastectomy rate (very low-certainty evidence). Observational study data showed no difference in the odds of re-operation after breast-conserving surgery (low-certainty evidence). It was also reported that 'MRI may change the initial treatment plans in 17%' of cases, but there was no significant effect on locoregional recurrence (very low-certainty evidence).

A systematic review assessed the accuracy of MRI in predicting the size of pure DCIS (Roque et al. 2022). Twenty-two cross-sectional studies were included, with 15 (n=NR) included in a meta-analysis (search dates: up to January 2021). It is reported that 'MRI accurately predicted 55% of the tumours' sizes and concordance between MRI and pathology was greater for smaller tumours'. The meta-analysis found that the difference between assessment of tumour size between MRI and histopathology was 3.85 mm, with a 95% CI: −0.92 to 8.60, indicating no statistical difference between the size of DCIS evaluated with MRI and pathology, but the I^2 of 97% indicates there was considerable heterogeneity in the data from different studies. A subgroup analysis found no statistically significant differences in overall effect size between different MRI fields, temporal resolution, slice thickness or acquisition times. The authors report that 'results were concordant with low risk of bias studies .. without heterogeneity ($I^2 = 0\%$)'.

A systematic review compared the diagnostic performance of contrast-enhanced MRI with contrast-enhanced mammography in the preoperative assessment of breast cancer (Shahraki et al. 2022). Number of studies/study design was not reported, but a total 1,225 patients were included (search dates: NR). There was no difference in pooled sensitivity between contrast-enhanced MRI and mammography (0.935; 95% CI=0.920 to 0.949 and 0.946; 95% CI=0.931 to 0.958 respectively), but contrast-enhanced mammography had slightly higher pooled specificity compared with contrast-enhanced MRI (0.783; 95% CI=0.758–0.807 and 0.715; 95% CI=0.688 to 0.741 respectively). The authors also reported that contrast-enhanced mammography had a higher positive predictive value and diagnostic conformance rate than MRI.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

A systematic review assessed the use of machine learning-based MRI in diagnosing axillary lymph node metastasis in breast cancer patients (Chen et al. 2021). Fourteen studies (study design=NR; n=2,247) were included (search dates: until 27 December 2020). The area under the curve (AUC) was reported, which provides a summary of diagnostic accuracy from 0 to 1, with 0.5 indicating random chance, 0.7 to 0.8 considered acceptable, 0.8 to 0.9 excellent, >0.9 outstanding. The overall AUC for machine learning-based MRI in diagnosing axillary lymph node metastasis in breast cancer patients was 0.80 (95% CI=0.76 to 0.83). Negative

predictive value was 0.83, pooled sensitivity was 0.79 (95% CI=0.74 to 0.84) and specificity was 0.77 (95% CI=0.73 to 0.81). A subgroup analysis was also reported assessing different MRI sequences and algorithms which indicated that T1-weighted contrast-enhanced machine learning-based MRI has a higher sensitivity thanT2-weighted fat-suppressed imaging and diffusion-weighted imaging; and that support vector machines (SVMs) had a higher specificity than linear regression (LR) and linear discriminant analysis (LDA), but LDA showed a higher sensitivity than LR and SVM; i.e. MRI sequences and algorithms affect the diagnostic performance of machine learning-based MRI.

Intelligence gathering

Comments were received during stakeholder consultation in March 2018 on draft NICE guideline NG101 querying the use of MRI for breast cancer patients. The stakeholder said that the 'use of MRI has not been shown to improve outcomes for breast cancer patients', but instead can result in delays to surgery and 'an unnecessary increase in mastectomy rates'. They provided references to support their comment. All references were checked, with the majority pre-dating the 2015 surveillance review search period or not directly relevant to the use of MRI in the preoperative staging of breast cancer. The evidence is not considered to impact the current recommendations, which are very specific about under which circumstance MRI can be offered.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence on the use of MRI in the preoperative assessment of people with biopsy-proven DCIS is not considered as having an impact on recommendation 1.1.1 to not routinely use MRI of the breast in this group. While the findings of Roque et al. 2022 indicate that MRI may accurately assess the size of pure DCIS, this is based on cross-sectional study data only; and Canelo-Aybar et al. 2021 found no evidence (from RCT and observational study data) that MRI preoperative assessment improves surgical outcomes. This indicates that the benefits of MRI in the preoperative assessment of people with biopsy-proven DCIS remain uncertain.

The one systematic review comparing contrast-enhanced MRI with contrast-enhanced mammography indicated that mammography is slightly superior to MRI in preoperative assessment of breast cancer, which is consistent with the current recommendations to offer MRI only under circumstances where there is a discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment or if breast density precludes accurate mammographic assessment.

No new evidence was identified in relation to the use of MRI in the preoperative assessment of invasive lobular cancer to assess the tumour size if breast-conserving surgery is being considered.

The new evidence on the use of machine learning-based MRI in diagnosing axillary lymph node metastasis in breast cancer patients indicates that machine learning-based MRI has

acceptable diagnostic accuracy, indicating, as concluded by the authors, that machine learning-based MRI may not yet be usable in clinical routine, but is an area that should be monitored for further results.

Preoperative staging of the axilla

NICE guideline NG101 recommendations:

- 1.1.3 Perform pre-treatment ultrasound evaluation of the axilla for people having investigations for early invasive breast cancer and, if abnormal lymph nodes are identified, perform ultrasound-guided needle sampling. [2009]

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

While no evidence was identified in the 2015 or 2012 surveillance reviews that was relevant to the evidence review question 'what is the role of pre-treatment ultrasound assessment in staging the axilla?' the surveillance decision in 2015 was: 'When considering the need to update the guidance on axillary lymph node dissection and axillary radiotherapy, topic experts felt that the role of ultrasound assessment should be considered as part of the update. This review question should be updated'. During draft scope development of NICE guideline NG101 stakeholders were consulted on this as an area for update and it was decided this would not be a focus of the 2018 update.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review compared the performance of ultrasonography, MRI, and fluorodeoxyglucose positron emission tomography (PET) for axillary staging, with a focus on micrometastases or macrometastases (Boulc'h et al. 2021). Sixty-two diagnostic accuracy studies (n=10,374) were included (search dates: between January 2002 and March 2018). Meta-analysis reported that: for ultrasonography, sensitivity and specificity for detecting metastatic axillary lymph nodes was 51% (95% CI=43 to 59%) and 100% (95% CI=99 to 100%) respectively, for MRI sensitivity was 83% (95% CI=72 to 91%) and specificity 85% (95% CI=72 to 92%), for PET sensitivity was 49% (95% CI=39-59%) and specificity 94% (95% CI=91-96%). The false negative rate with ultrasonography for more than 2 metastatic axillary lymph node macrometastases was 0.28 (95% CI=0.22 to 0.34) and 0.96 (95% CI=0.86 to 0.99) for micrometastases. The false positive rate with PET for detecting micrometastases was 0.41 (95% CI=0.29 to 0.54). No data were available for MRI.

A systematic review evaluated the diagnostic value of contrast-enhanced ultrasound for sentinel lymph node status in breast cancer patients (Niu et al. 2022). Five diagnostic studies (n=771) were included (search dates: database inception to 31 March 2020). In contrast-enhanced ultrasound a uniform enhancement pattern is considered indicative of a benign lymph node, and a heterogeneous, no pattern, or weak enhancement pattern indicates a node is malignant. A meta-analysis reported sensitivity of 0.960 (95% CI=0.856 to 0.989), specificity of 0.807 (95% CI=0.581 to 0.926), positive likelihood ratio of 4.987 (95% CI=2.104 to 11.822), negative likelihood ratio of 0.049 (95% CI=0.014 to 0.168), and diagnostic odds ratio of 101.294 (95% CI=31.202 to 328.837).

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

None identified.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence supports the use of ultrasound preoperative staging of the axilla.

Predictive factors

NICE guideline NG101 recommendations:

- 1.6.1 Request the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth receptor 2 (HER2) status of all invasive breast cancers simultaneously at the time of initial histopathological diagnosis. **[2018]**
- 1.6.2 Assess the ER status of all invasive breast cancers using standardised and quality-assured immunohistochemical techniques, and report the results quantitatively. **[2009]**
- 1.6.3 Assess the PR status of all invasive breast cancers using standardised and quality-assured immunohistochemical techniques, and report the results quantitatively. **[2018]**
- 1.6.4 Assess the HER2 status of all invasive breast cancers using standardised and quality-assured techniques, and report the results quantitatively. **[2009]**
- 1.6.5 Ensure that the ER, PR and HER2 statuses are available and recorded at the preoperative and postoperative multidisciplinary team meetings when systemic treatment is discussed. **[2018]**

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

Recommendations in this section should not be updated, but amendments may be required to avoid duplication with NICE diagnostics guidance DG34 recommendations, while ensuring relevant content from NICE diagnostics guidance DG34 is presented as part of the breast cancer guideline.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

This area was reviewed with recommendation 1.1.6 being added to NICE guideline CG81 in August 2017. No new evidence was identified at the 2018 surveillance review for this area, topic experts commented that this area had been fully addressed by the 2017 amendments.

2023 surveillance

Studies that impact recommendations

None identified

Studies that do not impact recommendations

None identified

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified

Intelligence gathering

The NHS long term plan reports how advances in precision medicine 'mean treatment itself will become increasingly tailored to individuals, and patients will be offered more personalised therapeutic options' and they provide the example, that 'new research showed that, based on their tumour genetics, thousands of women with breast cancer could now avoid chemotherapy'.

A patient group said that rather than cross-referencing to tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (NICE diagnostics guidance DG34), NICE guideline NG101 should have its own recommendations on Oncotype DX, Endopredict and Prosigna tests for guiding adjuvant chemotherapy decisions. They also said that there should be recommendations on providing information on receptor status to patients at the point of diagnosis, and that clinicians should explain how receptor status can inform available treatment options and decisions.

Impact statement

New evidence is unlikely to change guideline recommendations.

NICE diagnostics guidance DG34 provides recommendations on tumour profiling tests to guide adjuvant chemotherapy decisions in people with early breast cancer. In order to avoid duplication, recommendations are not repeated across NICE guidelines. The guideline should ensure that NICE diagnostics guidance DG34 is clearly cross-referenced and any duplication within NICE guideline NG101 recommendations removed. We understand that there is also new evidence on Oncotype DX from 2 large RCTs (TAILORx, reported in Sparano et al. 2018 and RxPONDER, see Kalinsky et al. 2021). NICE diagnostics guidance DG34 should consider the impact of these 2 studies. We will liaise with NICE centre for health technology evaluation, diagnostics assessment team to confirm their decision on whether to update DG34 or not.

With regards to providing information on receptor status to patients, this should be part of standard care and communication, especially as it guides treatment decisions, and should therefore not require a separate recommendation given recommendation 1.2.1 says that 'all members of the breast cancer clinical team should follow the recommendations on communication in NICE's guideline on patient experience in adult NHS services'.

For NICE guideline CG81, no new evidence was found at this surveillance review or the 2018 surveillance review. No additional information was highlighted by topic experts or patient groups. As such there is unlikely to be an impact on recommendation 1.1.6 at this time.

Genetic testing

NICE guideline NG101 recommendations:

- 1.1.4 Offer genetic testing for BRCA1 and BRCA2 mutations to women under 50 years with triple-negative breast cancer, including those with no family history of breast or ovarian cancer. (Also see the recommendations on genetic testing in the NICE guideline on familial breast cancer.) **[2017, amended 2018]**

Surveillance decision

Recommendation 1.1.4 in NICE guideline NG101 on genetic testing (and recommendations on genetic testing in NICE clinical guideline CG164) should be updated.

Previous surveillance

No evidence identified.

2023 surveillance

Evidence on genetic testing was not associated with an evidence review question, instead recommendation 1.1.4 was made based on recommendations on genetic testing within

familial breast cancer (NICE clinical guideline CG164), as such evidence on genetic testing was not searched for as part of this surveillance review.

Intelligence gathering

A patient group and topic expert highlighted that recommendations supported by NHS England on genetic testing have changed (see National genomic test directory NHS England 2022). It is now advised that there is routine testing of BRCA1, BRCA2, PALB2, ATM, CHEK2 for women diagnosed with invasive cancer (grade 2 or 3) aged 39 years old or less and for men diagnosed at any age (both regardless of family history); and BRCA1, BRCA2, PALB2, ATM, CHEK2 testing is routinely offered for women diagnosed with triple-negative breast cancer aged 59 years old and younger.

The patient group also said that they have received clinical feedback that there is a lack of awareness about the expanded eligibility criteria and limited available support from clinical genetic specialists in some services, which is hindering the implementation of up-to-date recommendations on genetic testing.

We also identified an NIHR evidence alert: genetic risk scores for breast cancer are not accurate in some ethnic groups (March 2022). This reports that while genetic tests accurately predict the risk of breast cancer in White Europeans, these risk scores are inaccurate and exaggerate risk in Black, Asian, mixed-race and Ashkenazi Jewish women, so need adapting for use in women from these groups.

Impact statement

New evidence is likely to change guideline recommendations.

Recommendation 1.1.4 on genetic testing is out-of-date with the latest guidance from NHS England and should therefore be updated. An update of NICE guideline NG101 should also consider how this impacts on recommendations on genetic testing in NICE clinical guideline CG164 to ensure consistency across guidelines. In addition, the finding that established genetic risk scores may be overestimating the breast cancer risk of women from Black, Asian, mixed-race and Ashkenazi Jewish backgrounds should be considered in an update.

Information and non-pharmacological support

This section includes recommendations on:

- providing information and support (CG81-1.2.1 to 1.2.2, CG81-1.4.1 and NG101-1.2.1, 1.2.2 and 1.2.4 to 1.2.5)
- decision aids (CG81-1.2.3 to 1.2.4)
- psychological support (NG101-1.2.3)
- lifestyle information (NG101-1.14.1 to 1.14.2)

Providing information and support

NICE guideline NG101 recommendations:

1.2.1 All members of the breast cancer clinical team should follow the recommendations on communication in NICE's guideline on patient experience in adult NHS services. **[2009, amended 2018]**

NICE guideline CG81 recommendations:

- 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]**
- 1.4.1 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 NICE's cancer service guidance on improving outcomes in breast cancer and improving supportive and palliative care for adults with cancer, in particular the following 2 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.' [2009]

Surveillance decision

While new evidence does not impact the content of recommendations, recommendations on providing information and support across the 2 breast cancer guidelines should be amalgamated and amended to ensure consistency.

Previous surveillance

No relevant evidence was identified in the 2015 or 2012 surveillance reviews of NG101.

No new evidence was found for CG81 recommendations 1.2.1 and 1.2.2 at the 2018 surveillance review and no topic expert information was given on this area. Evidence from the 2015 surveillance review found that telehealth technology did not compromise patient satisfaction or safety. For CG81 recommendation 1.4.1 no new evidence was found. Topic experts said that a designated key worker or designated breast cancer nurse was needed, as were procedures for psychological intervention, however it was felt that recommendation 1.4.1 already covered these issues.

2023 surveillance

Studies that impact recommendations

None identified

Studies that do not impact recommendations

A Cochrane review assessed the effects of individual interventions carried out by specialist breast cancer nurses on quality of life (QoL), anxiety, depression, and participant satisfaction (Brown, Cruickshank and Noblet 2021). Fourteen RCTs (n=2,905) were included (search dates: up to June 2020). Results were described narratively: psychosocial interventions delivered by specialist breast cancer nurses for women with primary breast cancer were at least as effective as standard care and other supportive interventions, and might be associated with improvements during diagnosis, treatment, and survivorship. Specialist breast cancer nurse-led telephone follow-up interventions were found to be equally as effective as standard care, for women with primary breast cancer.

A systematic review that pre-dates the Cochrane review assessed the effects of nurse-led interventions on health-related quality of life (HRQoL) symptom burden, self-management and behavioural outcomes in women with breast cancer (Chan et al. 2020). Thirty-one RCTs (n=4,651) were included (search dates: January 1999 to May 2019). It was reported that all studies were at risk of bias; that 22 RCTs reported 'at least one superior intervention effect'; that compared with control interventions, 63% of nurse-led 'teaching, guidance and counselling' intervention and 100% case management interventions were associated with 'superior' effects on symptom burden during treatment and survivorship; but that effects of nurse-led interventions on HRQoL, symptom self-management and behavioural outcomes in women with breast cancer were inconsistent (see clinical follow-up for additional results).

A systematic review evaluated different types of support received by metastatic breast cancer patients as well as the need for support expressed by them. Outcomes were synthesised narratively because it was not possible to quantitatively synthesise the data (Bochenek-Cibor et al. 2022). In total 11 cross-sectional surveys (n=4,614 from 32 countries) were included (search dates: January 2008 to January 2019). The country in which people were living in was the most important factor influencing the appropriate level of support. Most people with MBC were satisfied with their psychosocial, emotional, informational, and medical support. Most people with metastatic breast cancer reported receiving sufficient support from their family, friends, and healthcare providers. Ten studies showed a high need for informational support. People with metastatic breast cancer also declared a need for psychosocial, medical, and sexual support. People with metastatic breast cancer generally receive support from their community, but they express high need for information and treatment choice.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified

Intelligence gathering

In relation to NICE guideline NG101 recommendations on providing information and support, a patient group highlighted findings in the Paterson Inquiry report (Department of Health and Social Care 2020) that it should be standard practice that consultants in both the NHS and the independent sector write to patients, outlining their condition and treatment, in simple language, and copy this letter to the patient's GP, rather than writing to the GP and sending a copy to the patient. This is however consistent with the wording of recommendation 1.13.4 and the recommendations within shared decision making (NICE guideline NG197).

For NICE guideline CG81, a patient group suggested that this is an area in which advanced breast cancer patients could be offered information about clinical trials to prompt conversations between patients and health care providers. They also suggested that people presenting with advanced breast cancer should be discussed by the multidisciplinary team, which could be relevant to recommendations 1.2.1 or 1.2.2. The patient group suggested a mirroring of NICE guideline NG101 recommendation 1.2.4 (Discuss opportunities for people with breast cancer to be involved in research and encourage entry into clinical trials and other studies') in NICE guideline CG81 for advanced cancer. The patient group also suggested a recommendation regarding signposting patients to other areas of support and information such as charities may be useful, however this could be considered to be included in the information and support given in NICE guideline CG81 recommendations 1.2.1-1.2.2.

A patient group highlighted that NICE guideline CG81 recommendation 1.4.1 may require changes due to the change in trajectory of advanced breast cancer since 2009, particularly in the areas of continuing work while undergoing treatment and fertility. However the topic of fertility in people with cancer is covered by NICE guideline CG156, section 1.16 'people with cancer who wish to preserve fertility'. The patient group also highlighted that recommendations could be made for access to a clinical nurse specialist for those living with advanced cancer who may have very complex emotional and supportive care needs during lifelong treatment. The patient group suggested a mirroring of recommendation from the previous CG80 guideline which stated: All patients with advanced breast cancer should be assigned a named breast care nurse specialist, with the right skills, knowledge and experience, as well as allocated time and resource, to support them throughout diagnosis, treatment and follow-up. A patient group also mentioned the use of telephone consultations since COVID, and that consideration should be given to whether patients prefer telephone or face-to-face appointments.

The breast cancer health inequalities briefing highlighted the impact of education and health literacy on information-seeking behaviour: it found that 'fewer older women with cancer seek additional information to that provided by their healthcare professionals and most prefer face-to-face information'. It reported that 'population groups identified as experiencing disproportionately low or inadequate health literacy include more deprived groups, migrants and people from minority ethnic family backgrounds, older people, people with long-term health conditions, disabled people (including those who have long-term physical, mental, intellectual, or sensory impairment). Low health literacy in these groups may explain … difficulty making treatment choices and reduced quality of life after a cancer diagnosis.'

Impact statement

New evidence is unlikely to change guideline recommendations.

In relation to NICE guideline NG101, the new evidence on the effect of nurse-led interventions on participant satisfaction and psychological outcomes of people with breast cancer is consistent with recommendation 1.2.2 that all people with breast cancer should have a named clinical nurse specialist or other specialist key worker with equivalent skills, who will support them throughout diagnosis, treatment and follow-up. No evidence was identified that was relevant to recommendation 1.2.4 on discussing and encouraging entry into clinical trials and other studies. Recommendations 1.2.1 and 1.2.5 cross-references existing NICE guidance (patient experience in adult NHS services NICE guideline CG138 and fertility problems NICE guideline CG156 respectively), and are therefore not within the scope of this surveillance review. Information needs for people with low health literacy and the format in which information is provided are considered in the recommendations within NICE guideline CG138.

For NICE guideline CG81, the new evidence found at this review regarding types of support received is consistent with recommendations 1.2.1, 1.2.2 and 1.4.1. The question of specialist nurse care was raised by topic experts at the 2018 review, and again by a patient group at this surveillance review however no new evidence was found in this area. The issue of specialist nurse care is covered by NICE guideline NG101 recommendation 1.2.4 and as such NICE guideline CG81 should be updated for consistency.

Decision aids

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

This section should be amended, with recommendation 1.2.3 withdrawn and replaced with a cross-reference to NICE guideline NG197 on shared decision making; which should also clarify that this is relevant to all people with breast cancer.

Previous surveillance

No evidence was identified on decision aids for people with advanced breast cancer in the 2015 or 2018 surveillance reviews.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review assessed the effectiveness of decision aids for treatment, prevention and screening of breast cancer patients (stage not described) (Gao et al. 2020). Twenty-two RCTs (n=NR) were included (search dates: to January 2020). With regard to treatment decisions, a meta-analysis found that compared with 'conventional' methods, decision aids significantly reduced treatment decision conflicts. No differences were found in anxiety, decision regret, knowledge, informed choice or decision making satisfaction between the conventional and decision aid groups.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

We identified an NIHR evidence alert on older women with breast cancer chose less aggressive treatment when they used a decision aid. This reported on the findings of a multicentre cluster RCT (46 breast units, n=1,339) which compared the use of 2 decision aids with usual care in treatment decision making in women with breast cancer aged 70 years and older. Decision aids were found to have an impact on treatment choice: women in the decision aids group were significantly less likely to choose to have surgery or chemotherapy, and women with oestrogen receptor-positive breast cancer were significantly more likely to choose primary endocrine therapy in the decision aids group compared with usual care group. There were no differences in QoL at 6 months follow-up, or mortality from cancer during 3 years of follow-up. The study also reported that women who used decision aids were better informed about their treatment options. The NIHR evidence alert does however report that 'fewer women than expected used a decision aid when it was offered. In addition, staff changes, their preferences, a lack of IT in consulting rooms and security firewalls in some Trusts' IT systems contributed to low use. The researchers say that introducing decision aids will be challenging.' It does however report that online tools, approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) are freely available to download and print. And there is ongoing work to use the results from other research on older women with breast cancer to add information to the decision aids on how treatments affect women's long-term survival and quality of life.

There is a NICE guideline on shared decision making (NICE guideline NG197) which includes recommendations on using decision aids for healthcare professionals and organisations. Recommendations highlight that using patient decision aids is one part of an overall toolkit to support shared decision making alongside other skills and interventions, that decision aids should be quality assured and relevant to the situation; and that systems should support staff

to provide patient decision aids in multiple ways to suit people's needs (printed or online and available in different languages and formats). There are also recommendations on putting shared decision making into practice which highlight, for example, supporting shared decision making by offering interventions at different stages, including before, during and after discussions, so that people are fully involved throughout their care.

Impact statement

New evidence is likely to change guideline recommendations.

The new evidence and intelligence are consistent with recommendation 1.2.4 to be aware of decision aids and use the most appropriate one with patients. However NICE guideline NG197 provides more detailed recommendations on the use and quality of decision aids, within the context of shared decision making. It is therefore proposed that the guideline ensures that the recommendation section in NICE guideline NG197 on using decision aids is appropriately placed within the information and non-pharmacological support section for all people with breast cancer (there are no current recommendations on decision aids within NICE guideline NG101, but recommendation 1.2.1 does cross-reference to the recommendations on communication in patient experience in adult NHS services (NICE guideline CG138) which had a section on shared decision making that has been superseded by NICE guideline NG197).

It is important, as highlighted in NICE guideline NG197, that patient-appropriate, quality assured decision aids are used, and we will share the information on the MHRA approved online tools for use with older adults with breast cancer, plus the reported difficulties in implementing it, with the NICE system engagement team.

With regards to recommendation 1.2.3 on approach to shared decision making, it is proposed that this recommendation is withdrawn and replaced with clear links to the recommendations on putting shared decision making into practice in NICE guideline NG197 which provides more detailed recommendations.

Psychological support

NICE guideline NG101 recommendations:

- 1.2.3 Offer all people with breast cancer prompt access to specialist psychological support and, where appropriate, psychiatric services. **[2009]**

Surveillance decision

New recommendations on interventions to prevent and manage psychological distress in patients with breast cancer should be developed.

Previous surveillance

Evidence was identified in the 2015 surveillance review on interventions aiming to manage psychological distress including mindfulness-based stress reduction, exercise such as yoga

and tai chi, and individualised care plans. The evidence was assessed as being consistent with guideline recommendations because although some interventions showed evidence of improvements in quality of life, these did not always translate into improvements in clinical outcomes such as depression and anxiety. Mindfulness-based stress reduction showed promise for reducing depression and anxiety, and yoga showed promise for increasing QoL. Several systematic reviews found important differences between studies in the specifications of the interventions, so it was concluded that further rigorous research is needed to define the effectiveness of interventions.

2023 surveillance

Studies that impact recommendations

Psychological interventions

Cognitive behavioural therapy (CBT)

A Cochrane review on psychological interventions for women with non-metastatic breast cancer included 24 RCTs on CBT and 4 RCTs on psychotherapy (search dates: to 16 May 2013) (Jassim et al. 2015). Meta-analyses showed that compared with controls, CBT significantly improved anxiety (8 RCTs, n=776; low-quality evidence), depression (7 RCTs, n=637; low-quality evidence) and mood disturbance (8 RCTs, n=1,536; moderate-quality evidence) in women with non-metastatic breast cancer. A significant improvement in QoL was only found for individually tailored CBT compared with control (3 RCTs, n=141; very low-quality evidence). For psychotherapy, the studies were 'assessed as high risk of bias and provided limited evidence of the efficacy of psychotherapy'.

A recent systematic review also assessed the effect of CBT on QoL of breast cancer patients (Getu et al. 2021). Eleven RCTs (n=1,690) were included (search dates: to January 2020). A meta-analysis found that there was a significant, medium overall effect size of CBT on QoL in breast cancer patients.

Mindfulness

A Cochrane review assessed the effectiveness of mindfulness-based stress reduction interventions compared with no intervention in women diagnosed with breast cancer (8 RCTs recruited participants with early breast cancer and 2 of the RCTs did not restrict inclusion to a certain cancer type; majority had completed cancer treatment) (Schell et al. 2019). Fourteen RCTs were included but only 10 (n=1,571) were eligible for meta-analysis (search dates: to April 2018). Results indicate that:

- For QoL, there was low-certainty evidence of a small improvement at the end of a mindfulness-based intervention (3 RCTs, n=339), little to no difference up to 6 months post-intervention (3 RCTs, n=428) and no difference in the long-term (1 RCT with 2 years follow-up data; n=97).

- In the short-term, mindfulness-based interventions were associated with a small significant reduction in anxiety (6 RCTs, n=749; moderate-certainty evidence), and a significant improvement in depression (6 RCTs, n=745; high-certainty evidence).
- In the medium term, mindfulness-based interventions showed a small significant reduction in anxiety (7 RCTs, n=1,094; moderate-certainty evidence) and depression (7 RCTs, n=1,097; moderate-certainty evidence).
- In the long-term, moderate-certainty evidence showed that mindfulness-based interventions resulted in 'little to no difference' in anxiety (2 RCTs, n=360) or depression (2 RCTs, n=352).

A systematic review assessed the short-term effectiveness of mindfulness-based stress reduction interventions compared with control groups for symptom reduction in women with breast cancer (Chang et al. 2021). Nineteen RCTs were included, with 11 RCTs (n=1,687) eligible for meta-analysis (search dates: to April 2020). Results indicated that depression was significantly reduced at the end of the mindfulness intervention (however the I^2 of 97% indicates there was considerable heterogeneity); and stress levels were found to have significantly decreased up to 3 months after baseline (I^2=0%).

Another systematic review specifically focused on assessing benefits of mindfulness-based intervention for Chinese breast cancer patients (Jing et al. 2021). Forty-five controlled trials were included (sample size and search dates not reported in abstract (NR)). Meta-analyses found significant improvements in psychosocial wellness outcomes and QoL in response to mindfulness-based interventions (unclear what the interventions were compared with).

Acceptance and commitment therapy

A systematic review (Li et al. 2021) evaluated the effects of acceptance and commitment therapy on physiological and psychological outcomes in patients with breast cancer. Thirteen RCTs (n=NR) were included (search dates: depending in databases, inception to December 2019 or to September 2020). A meta-analysis found that acceptance and commitment therapy was associated with moderate to large effects on reducing anxiety, depression, and stress, and on improving hope. Findings for fear of cancer recurrence and psychological flexibility of patients with breast cancer were inconclusive.

Supportive-expressive group therapy

A systematic review assessing the effectiveness of supportive-expressive group therapy on outcomes including QoL, anxiety, and depression in women with breast cancer, identified 10 RCTs (n=2,879; search dates: up to May 2020) (Lai et al. 2021). A meta-analysis found that supportive-expressive group therapy was associated with significant improvements in QoL (short- and long-term follow-up), anxiety and depression.

Psychological interventions (multiple)

A systematic review evaluated the effectiveness of various psychological interventions in reducing fear of cancer recurrence in breast cancer survivors (Lyu et al. 2022). Sixteen RCTs (n=NR) were included (search dates: 1 January 1976 to 28 November 2020). A meta-analysis

found that psychological interventions resulted in a significant reduction in fear of cancer recurrence (quality of evidence was evaluated as moderate). A subgroup analysis indicated that a reduction in fear of cancer recurrence was evident in mindfulness and acceptance therapy based interventions, but not in CBT combined with psychoeducation. It was also reported that interventions with 3 to 8 sessions were effective, but those with ≥9 sessions were not; and face-to-face, but not online interventions were effective.

A systematic review assessed the effects of psychosocial interventions on posttraumatic growth in patients with cancer (Li et al. 2020). Fifteen RCTs (n=NR) were included (search dates: published prior to January 8, 2020). A meta-analysis found that, overall, posttraumatic growth was significantly higher in the intervention compared with control groups, and a subgroup analysis should that these effects were highest in breast cancer patients. It was also reported that the 'most effective and commonly used method was mindfulness-based interventions'.

A systematic review evaluated the effects of multidisciplinary psychosocial rehabilitation interventions on outcomes including QoL and coping in adult cancer patients (Myrhaug et al. 2020). Thirty-one RCTs (n=NR) were included (search dates: NR). The abstract reports on a meta-analysis of RCTs including people with breast cancer which did not find any difference between intervention and control groups on HRQoL.

Another systematic review evaluated the effect of psychological interventions delivered by nurses on QoL of breast cancer patients with modified radical mastectomy (Li et al. 2022). Twelve RCTs (n=NR) were included (search dates: NR). The results of meta-analysis indicated that psychological interventions delivered by nurses are likely to improve QoL of breast cancer patients: while no difference was found for QoL between intervention and control groups when this was measured by one tool (quality of life questionnaire core 30), the I^2 of 92% indicates there was considerable heterogeneity; and a significant effect was found in favour of the intervention group when QoL was measured by the short Form 36 Questionnaire (I^2=0%).

Physical activity, mind-body interventions or exercises

Within this section we are including evidence on exercise, muscle relaxation training (controlling the process of muscle contraction and relaxation) yoga, tai chi, qigong and acupuncture.

Exercise

A systematic review assessed the effects of exercise interventions (type not specified) on mental wellbeing women with breast cancer during active treatment (Ramírez-Vélez et al. 2021). 57 publications (study design not specified; n=6,988) were included (search dates: NR). It was reported that, compared with control conditions, exercise training programmes resulted in significant reductions in anxiety and depression, and significant increases in body image, emotional function and QoL.

Another systematic review evaluated the effects of post-diagnosis exercises (type not specified) on depression, physical functioning, and mortality in breast cancer survivors (Salam

et al. 2022). A meta-analysis on data from 26 articles (study design and sample size: NR; search dates: from 1974 to 2020) found that, following an exercise intervention, there were significant improvements in depression (see lifestyle information section for findings on mortality; results for physical functioning were not reported in the abstract).

Exercise and acupuncture

A systematic review assessed the effects of acupuncture and exercise on QoL and outcomes associated with psychological distress in breast cancer patients treated with aromatase inhibitors (Zhu et al. 2021). Eleven RCTs were included (search dates: inception through May 18, 2021); with data from 10 RCTs (n=798) included in a meta-analysis. Compared with usual care, exercise was associated with a significant improvement in HRQoL and cancer-specific QoL; but there were no significant differences in measures of anxiety and depression for either acupuncture or exercise when compared with sham acupuncture or usual care respectively.

Acupuncture

A systematic review assessed the effectiveness of acupuncture on treatment-related symptoms among breast cancer survivors (Li et al. 2021). Twenty-six RCTs were included, of which 20 RCTs (n=1,709) were included in the meta-analysis (search date: through June 2021). The meta-analysis found that compared with waitlist control and usual care groups, acupuncture was associated with significant reductions in depression.

Muscle relaxation training

A systematic review assessed the effects of muscle relaxation training compared with conventional nursing on depression, anxiety and QoL in patients with breast cancer (Fang et al. 2022). Thirteen RCTs and quasi-RCTs (n=1,355) were included in a meta-analysis (search dates: to August 31st, 2021), which found significant reductions in depression and anxiety and significant improvements in QoL from muscle relaxation training compared with conventional nursing.

Yoga

A Cochrane review and 2 systematic reviews were identified that assessed the effect of yoga on outcomes related to psychological distress in people with breast cancer:

A Cochrane review assessed the effectiveness of yoga in improving health-related quality of life (HRQoL), mental health and cancer-related symptoms in women with a diagnosis of breast cancer, receiving or completed treatment (Cramer et al. 2017). Twenty-four RCTs (n=2,166) were included (search dates: up to 29 January 2016). In comparison with no therapy, yoga significantly improved HRQoL in the short-term (10 RCTs, n=675; moderate-quality evidence) but not in the medium term (2 RCTs, n=146; low-quality evidence). Yoga did not appear to reduce depression (7 RCTs, n=496; low-quality evidence) or anxiety (6 RCTs, n=346; very low-quality evidence) in the short-term. In comparison with psychosocial and/or educational interventions yoga was found to result in significant improvements in depression (4 RCTs, n=226; moderate-quality evidence) and anxiety (3 RCTs, n=195; moderate-quality

evidence) in the short-term, but not HRQoL (2 RCTs, n=153; very low-quality evidence). There were no significant differences in HRQoL when yoga was compared with exercise (3 RCTs, n=233; very low-quality evidence).

One systematic review assessed the effectiveness of yoga on QoL (and cancer-related fatigue) in women with breast cancer (O'Neill et al. 2020). Twenty-four RCTs (n=NR) were included, with 18 comparing yoga with a non-physical activity comparator and 6 with a physical activity comparator (search dates; to May 2018). In relation to QoL, there were significant improvements from yoga compared with non-physical activity, but no difference when yoga was compared with physical activity.

The other systematic review assessed the effectiveness of yoga on HRQoL, physical health and psychological health in breast cancer patients undergoing chemotherapy (Yi et al. 2021). Seven RCTs (n=693) were included (search dates: to December 2018, and updated September 2020). A meta-analysis found that there are significant, short-term improvements in depression, anxiety and HRQoL in yoga groups in comparison to 'comparators such as usual care'.

Tai chi

Two systematic reviews were identified that assessed the effect of tai chi on outcomes related to psychological distress in people with breast cancer:

A systematic review assessed the effect of tai chi on various outcomes relevant to psychological distress in patients with breast cancer (Liu et al. 2020) Sixteen RCTs (n=1,268) were included (search date: up to June 2019). Meta-analysis found that tai chi significantly improves overall QoL at 3 months follow-up, but not depression at 3 or 6 months follow-up in comparison with conventional supportive care interventions (not defined in abstract). It is also reported that tai chi in combination with conventional therapy leads to more improvements in QoL at 3- and 6-months follow-up when compared with conventional therapy alone.

Another systematic review assessed the effectiveness of Tai Chi Chuan compared with 'non-exercise therapy' on physical function and psychological wellbeing in breast cancer patients (Luo et al. 2020). Fifteen RCTs (n=885) were included (search dates: to December 31, 2018 and updated February 16, 2020). Meta-analysis found there was a significant improvement in QoL in the Tai Chi Chuan compared with non-exercise therapy group, with beneficial effects remaining at 12- and 25-weeks follow-up; and a significant improvement in anxiety at 12 weeks follow-up in the Tai Chi Chuan group compared with control group in breast cancer patients.

Qigong

Two systematic reviews provide evidence on qigong:

A systematic review assessed the effectiveness of qigong in improving outcomes including QoL and cancer-related, depression, and anxiety in women with breast cancer (Meng et al. 2021). Seventeen controlled clinical trials (n=1,236) were included (search dates: to March

2020). A meta-analysis showed that, compared with control group, qigong was associated with significant improvements in QoL (n=950), depression (n=540) and anxiety (n=439) in women with breast cancer.

Another systematic review assessed the effectiveness of Baduanjin exercise (a form of Chinese qigong) on the quality of life and psychological status of patients with breast cancer following surgery (Ye et al. 2022). Seven RCTs (n=450) were included (search date: to December 15, 2021). A meta-analysis found that, compared with the 'group without Baduanjin', Baduanjin was associated with significant improvements in QoL, anxiety and depression in postoperative breast cancer patients.

Miscellaneous

Appearance care

A systematic review evaluated the effects of appearance care interventions on psychosocial outcomes in breast cancer patients (Zhu et al. 2022). Two RCTs and 5 quasi-experimental studies were included in a meta-analysis (n=NR; search dates: from 1994 to 2022). Quality of evidence was described as moderate to high. Appearance care interventions were found to result in significant 'immediate' improvements in self-esteem, anxiety and depression; and significant short-term improvements in anxiety and depression; but the authors reported that the impact on QoL was uncertain.

Mode of delivery

Home-based, multidimensional survivorship (HBMS) programmes

A Cochrane review assessed the effectiveness of HBMS programmes on maintaining or improving the QoL in women with stages 0 to 3 breast cancer who completed primary cancer treatment (surgery or adjuvant cancer therapy, or both) up to 10 years earlier (Cheng et al. 2017). Twenty-two RCTs and 4 quasi-RCTs (n=2,272) were included (search dates: up to April 2016). An HBMS was defined as an intervention carried out at home with more than 1 of the following: educational and/or physical and/or psychological component. The results indicated that the short-term effect of HBMS programmes on QoL differed between QoL assessments tool used: there were improvements in breast cancer-specific QoL and global QoL as measured by FACT-B and EORTC-C30 up to 3 months post-intervention (moderate-quality evidence), but no improvements in QoL as measured by QoL-Breast Cancer or SF-36 (very low-quality evidence and low-quality evidence respectively). There was no evidence of a difference in QoL between groups at 4 to 6 months or 12 months post-intervention (quality of evidence not reported in abstract). There was also low-quality evidence that HBMS programmes may decrease anxiety immediately after the intervention, but this did not persist at 4 to 6 months post-intervention. There was no effect of HBMS on depression immediately after HBMS.

Online support groups

A Cochrane review aimed to assess the effectiveness of online support groups on the emotional distress, uncertainty, anxiety, depression and QoL in women with breast cancer who have completed breast cancer treatment (McCaughan et al. 2017). Six RCTs (n=492)

were included (search dates: up to 2 May 2016) which reported on anxiety (2 RCTs, n=256; mixed evidence of effectiveness), depression (5 RCTs, n=414; mixed evidence of effectiveness) and QoL (3 RCTs, n=170; no evidence of effectiveness). No evidence was found for emotional distress or uncertainty outcomes. The authors concluded that evidence was not sufficient to be able to draw conclusions on whether participation in online support groups is beneficial for women with breast cancer due to small samples within the included RCTs, which were all rated as either low or very low-quality.

Electronic and/or mobile health interventions

A systematic review on the effectiveness of electronic health interventions for patients during and after breast cancer treatment included patient-reported outcomes (Singleton et al. 2022). Thirty-two RCTs (n=4,790) were included (search dates: NR); all assessed health self-management interventions, with most involving multicomponent websites (videos, forums, and electronic reminder systems). A meta-analysis found that electronic health interventions were associated with a significant improvement in QoL, self-efficacy and distress in patients with breast cancer.

A systematic review assessed the effectiveness of telehealth interventions on cancer survivors' QoL (Li et al. 2021). Twenty-eight RCTs (n=NR) were included (search dates: from database inception to 14 April 2021). A meta-analysis showed that there were significant improvements in all cancer survivors' QoL from telehealth interventions, and a subgroup analysis found that the improvement in QoL was greatest in survivors of breast cancer. Another subgroup analysis found that application-based interventions were most effective, and a short-term duration was more effective than long-term (a sensitivity analysis indicated that pooled results were robust and reliable).

Another systematic review evaluated the effectiveness of mobile-phone-based interventions in improving psychological issues in women receiving chemotherapy for breast cancer (Akingbade, Nguyen and Chow 2022). Nine RCTs (n=1,457) were included (search dates: NR). A meta-analysis found that while there were significant improvements in QoL associated with mobile-phone-based interventions, there were no significant effects on anxiety or depression.

Virtual reality (VR)

Three systematic reviews report on the effectiveness of VR interventions in improving anxiety and depression in breast cancer patients:

One systematic review evaluated the effectiveness of VR interventions (immersive and non-immersive virtual environment) compared with traditional rehabilitation methods in the rehabilitation management of breast cancer survivors (Bu et al. 2022). Twelve articles (RCTs, case-controlled trials, and quasi-experimental studies) were included (search dates: database inception to May 25, 2021). Ten articles (n=604) were included in a meta-analysis, which found a significant improvement in measures of anxiety and depression for VR interventions.

Another systematic review and meta-analysis on the effects of VR on breast cancer-related symptom management found that VR significantly improved anxiety and depression in breast cancer patients (8 RCTs and 6 quasi-RCTs (n=797) were included; search dates: up to April 10, 2021) (Tian et al. 2022).

Another systematic on the effects of VR on rehabilitation of patients with breast cancer undergoing treatment included 8 RCTs and quasi-experimental studies (n=NR; search dates: database inception to January 2022) (Zhang et al. 2022). This also reported that a meta-analysis found a significant improvement in anxiety in VR compared with conventional care groups; and a qualitative analysis indicated that VR also improved depression.

Studies that do not impact recommendations

Patient education

A systematic review reported on the effects of patient education (used alone or as adjunctive therapy) on QoL and fear of recurrence (and other outcomes) in adult breast cancer survivors (Martinez-Miranda, Casuso-Holgado and Jimenez-Rejano 2021). Fourteen RCTs (n=1,749) were included (search dates: NR), with 12 included in the meta-analysis. The meta-analysis found that patient education was associated with significant short-term improvements in global QoL and emotional QoL, but no significant effect on fear of cancer recurrence. However, all results were assessed as 'not important', indicating they are not considered to be of clinical significance.

A systematic review assessed the effect of psychoeducation on various outcomes, including anxiety, depression and QoL, in patients with breast cancer symptoms, breast cancer diagnosis, or breast cancer survivors (Setyowibowo et al. 2022). Twenty-seven RCTs (n=7,742) were included (search dates: NR). A meta-analysis found that anxiety and QoL, but not depression, were significantly improved in psychoeducation, compared with control groups.

Massage

A Cochrane review assessed the effectiveness of massage with or without aromatherapy on pain and other symptoms associated with cancer (Shin et al. 2016). In relation to RCTs in patients with breast cancer, relevant findings are that there was a significant improvement in medium- and long-term anxiety for aromatherapy-massage groups compared with no-massage (2 RCTs, n=253; search dates: up to August 2015), 'but the results were considered not clinically significant'. The authors noted the lack of evidence, small sample sizes of those RCTs that were included, and a lack of reporting key outcomes.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A patient group said that the recommendations should state that patients are offered specialist psychological support and, where appropriate, psychiatric services throughout the breast cancer pathway.

The breast cancer health inequalities briefing found that 'there is variation in whether women are told about emotional and psychological support services, including peer support groups and counselling. Only 34% of women with secondary breast cancer were aware of counselling across the UK, ranging from 48% in the Northwest to 29% in the West Midlands and Yorkshire and Humber. Similarly, only 36% were aware of opportunities to speak to others with secondary breast cancer, ranging from 47% in the Southwest to 17% in the East Midlands'.

Impact statement

New evidence is likely to change guideline recommendations.

Since the 2015 surveillance review more evidence has emerged that supports the use of specific interventions to prevent and manage psychological distress in patients with breast cancer. The new evidence indicates that for psychological interventions:

- CBT may improve QoL, anxiety and depression.
- Mindfulness-based interventions may result in immediate benefits in QoL, short-term improvements in anxiety and depression, improve posttraumatic growth, and reduce fear of cancer recurrence.
- Acceptance and commitment therapy may reduce anxiety, depression, and stress, and improve hope, but it is unclear whether it reduces fear of cancer recurrence.
- Supportive-expressive group therapy may improve QoL, anxiety and depression.

For physical activity, mind-body interventions or exercises, the new evidence indicates that:

- For exercise (activity not specified), women with breast cancer during active treatment may experience significant reductions in anxiety and depression, and significant increases in body image, emotional function and QoL. In breast cancer patients treated with aromatase inhibitors, evidence indicated there were improvements in QoL from exercise, but no improvements in anxiety and depression. For breast cancer survivors, there was evidence of significant improvements in depression.
- Muscle relaxation training was associated with improved QoL, anxiety and depression in patients with breast cancer.
- For yoga, overall, the new evidence indicates that yoga reduces depression and anxiety when compared with psychosocial/educational interventions; and that yoga might be as effective as other exercise interventions in improving QoL There was mixed evidence concerning the effect of yoga on anxiety and depression when compared with usual care, but evidence suggests there were improvements in QoL, at least in the short-term.

- Tai Chi may lead to short-term improvements in QoL and anxiety in patients with breast cancer, but impact on depression is unclear.
- Qigong is associated with significant improvements in QoL, depression and anxiety in patients with breast cancer.
- For acupuncture, the evidence was mixed concerning its effect on depression in patients with breast cancer, with evidence indicating there were no improvements in patients treated with aromatase inhibitors, but significant improvements in depression in breast cancer survivors.

There is also a small body of evidence that indicates appearance care interventions may lead to improvements in anxiety and depression in breast cancer patients.

There is also evidence on mode of delivery of interventions that aim to support the psychological needs of patients with breast cancer and breast cancer survivors, which could be considered as part of the update.

While recommendation 1.2.3. to offer all people with breast cancer prompt access to specialist psychological support and, where appropriate, psychiatric services remains valid, there is a large body of evidence to support the development of recommendations on the effective strategies to prevent and manage psychological distress in patients with early-stage breast cancer (the remit of the 2009 evidence review question on which this recommendation was based). The evidence is also relevant to patients with locally advanced or advanced breast cancer. Most systematic reviews have not specified the breast cancer stage within study samples and so findings may not all be directly relevant to patients with early and locally advanced breast cancer. While there is no existing review question on strategies to prevent and manage psychological distress in patients with advanced breast cancer, nor any recommendations within NICE guideline CG81 on psychological support, consideration of psychological support needs for all people with breast cancer should be made in an update. The primary studies on which the systematic review evidence has been based should be considered to determine which interventions are appropriate regardless of breast cancer stage, and which may differ according to breast cancer stage and where on the care pathway a patient is (diagnosis, treatment, post-treatment and/or surgery).

Lifestyle information

NICE guideline NG101 recommendations:

- 1.14.1 Advise people with breast cancer that a healthy lifestyle is associated with a lower risk of recurrence, and that this should include:
  - achieving and maintaining a healthy weight (see the NICE guidelines on preventing excess weight gain and obesity)
  - limiting alcohol intake to below 5 units per week **and**
  - regular physical activity (see the NICE guideline on physical activity for adults). **[2018]**

- 1.14.2 For guidance on smoking cessation, see the NICE guideline on stop smoking interventions and services. **[2018]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

Physical activity

Four systematic reviews report on whether changes in physical activity improve breast cancer-specific outcomes in people treated for breast cancer.

One systematic review assessed the effectiveness of recreational physical activity in reducing breast cancer recurrence in female survivors (Zagalaz-Anula et al. 2022). Eleven studies (RCTs and observational studies; n=29,677) were included (search dates: up to June 2021). There was a significant reduction in relative risk of breast cancer recurrence and disease-specific mortality from post-diagnosis recreational physical activity.

A systematic review of RCTs, prospective cohorts and meta-analyses assessing the association between physical activity after breast cancer diagnosis and survival outcomes included 18 studies (search dates: January 1, 2014 to October 1, 2019; Maumy et al. 2020). The authors reported that 'Studies unanimously concluded that overall mortality was reduced by post-diagnosis physical activity practice', 5 meta-analyses reported a significant decrease in breast cancer mortality and 2 found a decrease in the risk of recurrence.

A systematic review evaluated the effects of post-diagnosis exercises on depression, physical functioning, and mortality in breast cancer survivors (Salam et al. 2022). Twenty-six articles were included (study design and sample size: NR; search dates: from 1974 to 2020). The authors reported that post-diagnosis exercise 'led to a 37% reduction in the rate of breast cancer-specific mortality' and that all-cause mortality rate decreased by 39% when moderate physical activity was included as part of the daily routine of breast cancer survivors.

Another systematic review aimed to assess the relationship between pre- and post-diagnosis physical activity and survival outcomes in people with cancer (Friedenreich et al. 2020). For all cancers, 136 studies were included (study design not reported in abstract; search dates: up to November 1, 2018). Results are reported in relation to breast, with a meta-analysis finding a significant relationship between physical activity and reductions in cancer-specific and all-cause mortality, with greater reductions associated with increases in post-diagnosis

compared with pre-diagnosis physical activity. An inverse dose-response relationships between physical activity and breast cancer-specific and all-cause mortality was also found.

Diet

One systematic review assessed the effects of diet on survival and changes in body mass index in women treated for early-stage breast cancer (Trasel et al. 2021). In relation to survival outcomes, of 12 included RCTs, only 2 reported on overall survival (OS) and disease-free survival (DFS) (Search dates: NR). A meta-analysis, reporting hazard ratios, found that there was no significant difference in OS or DFS between intervention and control groups. The authors noted that there is a lack of prospective data assessing the effects of dietary interventions in breast cancer patients.

Stress management

One systematic review aimed to evaluate the effects of physical activity, fast-mimicking diet and psychological interventions on survival in all cancers reported in RCT evidence; but retrieved no RCTs on fast-mimicking diet and findings from the 9 RCTs on physical activity were not reported in relation to breast cancer (Clark et al. 2021). Twenty-two RCTs were included on psychological interventions including counselling, cognitive and other psychotherapies (search date: up to January 2020). A meta-analysis was undertaken on the 9 RCTs specific to breast cancer (n=1,687), results of which are described as indicating a 'trend towards improved overall survival', however 95% CI for the hazard ratios crossed zero.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A patient group said that NICE guideline NG101 should have a specific focus on rehabilitation and promoting lifestyle changes. They interpreted recommendation 1.14.1 as only focusing on the association between improved lifestyle and reducing the risk of breast cancer recurrence.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence on the association between increases in physical activity after breast cancer diagnosis and survival outcomes, reinforces previous findings that physical activity increases survival in people with breast cancer.

As the systematic review on the association between improved diet after breast cancer diagnosis and survival outcomes indicates that there are no improvements from improved diet, we checked the full text for further details. The systematic review included a study used as evidence within evidence review K: lifestyle: Chlebowski et al. 2006 and the other RCT (Pierce et al. 2007) was considered and excluded from evidence review K: lifestyle. As the evidence was already considered during development of NICE guideline NG101, we do not

think there is an impact on recommendation 1.14.1, which in relation to diet, highlights that advice is around 'achieving and maintaining a healthy weight' rather than focus on specific changes to dietary intake.

Evidence review K: lifestyle also considered evidence on the impact of stress management interventions on breast cancer-specific outcomes in people treated for early and locally advanced breast cancer. It found 1 RCT that indicated there were clinically meaningful increases in OS and DFS at 11 years follow-up. These findings were not highlighted within lifestyle recommendations as stress management was considered to be already included in the recommendations on providing information and psychological support. It is unclear whether the new evidence is directly relevant to stress management or other psychological outcomes, and as the importance of improving psychological outcomes goes beyond survival outcomes (see psychological support section), it is not considered that this evidence would have an impact on current recommendations.

We do not agree with the patient group's view that recommendation 1.14.1 is not focusing on promoting lifestyle changes as it highlights existing NICE guidelines on preventing excess weight gain, obesity, physical activity for adults and stop smoking interventions and services. NICE has a large portfolio of guidelines supporting lifestyle changes, and as such we do not think recommendations specific to patients with breast cancer are required. As part of the overall update of NICE guideline NG101, we will ask the guideline committee to consider whether recommendations can be made clearer to highlight that lifestyle change should be promoted; and to consider which NICE guidelines and recommendations can be usefully cross-referenced within the guideline.

Editorial amendment

We note that the cross-reference to the NICE guideline on stop smoking interventions and services requires updating to tobacco: preventing uptake, promoting quitting and treating dependence.

Non-systemic disease modifying therapy for early and locally advanced breast cancer - radiotherapy

This section includes recommendations on:

- minimising the risk of radiotherapy to the lung and heart (NG101-1.10.1 to 1.10.2)
- radiotherapy after breast conserving surgery (NG101-1.10.3 to 1.10.9)
- radiotherapy after mastectomy (NG101-1.10.10 to 1.10.12)
- dose fractionation (NG101-1.10.13), this is not covered in the surveillance review as this is undergoing a current update
- breast boost following breast-conserving surgery (NG101-1.10.14 to 1.10.15): No relevant evidence or intelligence was identified in the 2022 or 2015 surveillance review for the

review question 'What are the indications for an external beam radiotherapy boost to the site of local excision after breast-conserving surgery?' Evidence that was identified in the 2012 surveillance review showed external beam radiation therapy to be effective, which was in line with the current guideline recommendation to offer this treatment to people with a high risk of local recurrence.

- radiotherapy to nodal areas (NG101-1.10.16 to 1.10.20): No relevant evidence or intelligence was identified in the 2022 surveillance review. This was an area updated following the 2015 surveillance review for NICE guideline NG101.
- intraoperative radiotherapy (NG101-1.10.21), this is not covered in the surveillance review as the recommendation is a cross-reference to intrabeam radiotherapy system for adjuvant treatment of early breast cancer. (NICE technology appraisal guidance TA501).
- radiotherapy after neoadjuvant chemotherapy (NG101-1.11.9 to 1.11.13)

Minimising the risk of radiotherapy to the lung and heart

NICE guideline NG101 recommendations:

- 1.10.1 Use a radiotherapy technique that minimises the dose to the lung and heart. **[2018]**
- 1.10.2 Use a deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer to reduce the dose to the heart. **[2018]**

Surveillance decision

Recommendations 1.10.1 to 1.10.2 on minimising the risk of radiotherapy to the lung and heart in NICE guideline NG101 should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review assessed the effects of deep inspiration breath-hold compared with free breathing during radiotherapy in patients with left-sided breast cancer (Lu et al. 2022). Forty-one retrospective studies (n=3,599) were included (search dates: published before 30 November 2021). A meta-analysis showed that while deep inspiration breath-hold technique had no obvious advantage over free breathing in contralateral breast mean dose, it significantly reduced heart dose, left anterior descending branch dose, ipsilateral lung dose, and heart volume; and significantly increased ipsilateral lung volume.

A systematic review assessed the effects of left-sided adjuvant radiotherapy with right-sided adjuvant radiotherapy, and radiotherapy versus no radiotherapy on cardiovascular events and mortality in breast cancer patients (Taylor et al. 2021). Seventy-two cohort studies, 3 RCTs and 1 case-control study (n=7,363) were included (search dates: database inception to July 2020). Seven of 35 studies reported an increase in cardiovascular mortality and 8 of 28 studies found an increase in cardiovascular events when left-sided radiotherapy was compared with right-sided radiotherapy. It was reported that most of the studies that found significant associations between laterality and cardiovascular mortality and events (i.e. that left-sided radiotherapy had worse outcomes compared to right-sided radiotherapy) included treatment periods that started prior to 1985, suggesting that modern radiotherapy techniques have minimised the cardiac exposure in breast cancer patients receiving radiotherapy.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No intelligence was identified.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new systematic review evidence supports existing recommendation 1.10.1 to use a radiotherapy technique that minimises the dose to the lung and heart, and recommendation 1.10.2 to use a deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer to reduce the dose to the heart.

It should be noted that while Taylor et al. 2021 found that left-sided radiotherapy caused an increased dose of radiation to the heart compared to right-sided radiotherapy, these findings are only relevant to studies which used old radiotherapy techniques. These findings have not been replicated in studies since 2015. For example, between 2014 to 2017, the mean heart dose decreased from 4.6 Gy to 2.6 Gy. This is likely to be due to several factors including the use of focal radiation (which minimises the dose to the heart and lungs compared with radiation fields, which have been phased out), the use of the deep inspiratory breath-hold technique, better positioning, and heart blocking.

Radiotherapy after breast-conserving surgery

NICE guideline NG101 recommendations:

- 1.10.3 Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins. **[2018]**

- 1.10.4 Consider partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who:
  - have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) **and**
  - have been advised to have adjuvant endocrine therapy for a minimum of 5 years. **[2018]**
- 1.10.5 When considering partial breast radiotherapy (see recommendation 1.10.4), discuss the benefits and risks, and explain that:
  - local recurrence with partial breast radiotherapy at 5 years is equivalent to that with whole-breast radiotherapy
  - the risk of local recurrence beyond 5 years is not yet known
  - there is a potential reduction in late adverse effects. **[2018]**
- 1.10.6 When delivering partial breast radiotherapy, use external beam radiotherapy. **[2018]**
- 1.10.7 Consider omitting radiotherapy for women who:
  - have had breast-conserving surgery for invasive breast cancer with clear margins **and**
  - have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) **and**
  - are willing to take adjuvant endocrine therapy for a minimum of 5 years. **[2018]**

And see Table 5 Benefits and risks of radiotherapy compared with no radiotherapy in the group of women at low risk described in recommendation 1.10.7

- 1.10.8 When considering omitting radiotherapy for the population in recommendation 1.10.7, discuss the benefits and risks, including those in table 5, and explain that:
  - without radiotherapy, local recurrence occurs in about 50 women per 1,000 at 5 years, and with radiotherapy, occurs in about 10 women per 1,000 at 5 years
  - overall survival at 10 years is the same with or without radiotherapy
  - there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer). **[2018]**
- 1.10.9 Consider adjuvant radiotherapy for women with DCIS following breast-conserving surgery with clear margins, and discuss with them the possible benefits and risks of radiotherapy (also see the section on surgery to the breast). **[2009, amended 2018]**

Surveillance decision

Recommendations in this section should not be updated at this time; evidence will be monitored.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

Two systematic reviews were identified that assessed the impact of omitting radiotherapy in older adults with breast cancer:

One systematic review evaluated the effects of omitting adjuvant radiotherapy for older adults (definition not provided in abstract) with early-stage low risk breast cancer (Palumbo et al. 2021). Nine RCTs (n=7,149) were included in a narrative synthesis of results (search dates: up to June 2020) which reported that, due to evidence of low absolute risk of local recurrence, adjuvant radiotherapy could be omitted in a group of older adult early-stage breast cancer patients with favourable prognostic factors (those with pT1-2N0M0 R0, grade 1–2, oestrogen receptor-positive, human HER2 negative tumours).

Another systematic review evaluated the effects of omitting radiotherapy (or endocrine therapy) in patients aged ≥50 years old treated with breast-conserving surgery for 'lower risk' breast cancer (Savard et al. 2021). With regards to omitting radiotherapy, 7 RCTs (n=4,604) and one prospective cohort study (n=667) were included in a meta-analysis (search dates: 1980 to April 30, 2020). The meta-analysis found that compared with no radiotherapy, adjuvant radiotherapy significantly reduced 5- and 10-year breast tumour recurrence but had no effect on 5-year survival. (To note, results for omitting endocrine therapy were not provided given small number of studies).

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

A Cochrane review assessed whether partial and/or accelerated partial breast irradiation is equivalent to or better than conventional or hypofractionated whole breast radiotherapy after breast-conserving therapy for patients with early-stage breast cancer (Hickey and Lehman 2021). Nine RCTs (n=15,187) were included (search dates: to 27 August 2020). Results of a meta-analysis indicated that for local recurrence-free survival is probably worse with partial and/or accelerated partial breast irradiation compared with whole breast radiotherapy (moderate-certainty evidence); however, the difference was small and nearly all women remained free of local recurrence. OS was similar between groups (high-certainty evidence), and little to no differences were found in other oncological outcomes. Some late

effects (subcutaneous fibrosis) may be worse with partial and/or accelerated partial breast irradiation (moderate-certainty evidence) and its use is probably associated with worse cosmetic outcomes (moderate-certainty evidence). The authors noted that limitations of the data currently available meant they could not make definitive conclusions about the efficacy and safety, or ways to deliver partial and/or accelerated partial breast irradiation. At the time of publication they were awaiting completion of 7 ongoing trials (see impact section below).

There were also 5 systematic reviews identified that compared partial with whole breast radiotherapy in patients with early-stage breast cancer (Haussmann et al. 2021, Xiang et al. 2021, Haussmann et al. 2020, Tagliaferri et al. 2020, and Viani. et al. 2020). Only 1 systematic review, Haussmann et al. 2021, included a later search period than the Cochrane review (13 RCTs (n=15,561) were included; search dates: between December 2009 and May 2021).

Results of the systematic reviews were similar to the findings reported in the Cochrane review. For local recurrence, 2 systematic reviews reported a higher local recurrence rate from partial/accelerated partial breast irradiation compared with whole breast irradiation (Xiang et al. 2021 and Haussmann et al. 2021), while another found that local recurrence was similar between techniques (Viani et al. 2020). For survival outcomes, 4 systematic reviews reported no difference overall between partial breast radiotherapy compared with whole breast radiotherapy (Xiang et al. 2021, Haussmann et al. 2020, Tagliaferri et al. 2020, and Viani et al. 2020), while Haussmann et al. 2021 found that DFS was significantly longer in patients treated with whole breast radiotherapy. Three systematic reviews also undertook subgroup analysis by partial breast radiation technique. While Haussmann et al. 2020 reported no detectable differences on any outcomes between different techniques, Viani et al. 2020 and Haussmann et al. 2021 reported that intraoperative radiotherapy appeared to be associated with a higher likelihood of local recurrences than other techniques (brachytherapy and external beam radiotherapy).

Intelligence gathering

No intelligence was identified.

Impact statement

New evidence is unlikely to change guideline recommendations.

One Cochrane review and 5 systematic reviews provide evidence relevant to recommendations 1.10.4 to 1.10.6 in NICE guideline NG101 on providing partial breast radiotherapy instead of whole-breast radiotherapy. The rationale for NG101 recommendations on radiotherapy after breast-conserving surgery says 'good evidence showed that partial breast radiotherapy led to similar results to whole-breast radiotherapy after breast-conserving surgery in women with a low risk of local recurrence. In addition, it may have fewer treatment-related adverse effects'. The Cochrane review findings suggest that treatment-related adverse effects may be greater with partial breast radiotherapy compared to whole-breast radiotherapy and that local recurrence-free survival may be worse; which is also supported by other systematic review evidence. However, the Cochrane review

authors note that definitive conclusions cannot yet be drawn and that there are some major ongoing trials whose results should help address differences in outcomes between partial and whole-breast radiotherapy. While the findings of the new evidence potentially disagree with the current content of recommendation 1.10.4, as it is too early to draw a conclusion, this will be an area actively monitored.

The 3 systematic reviews that assessed outcomes according to partial breast radiation technique indicated that only intraoperative radiotherapy might be associated with a higher likelihood of local recurrence. These findings are therefore consistent with recommendation 1.10.6: 'when delivering partial breast radiotherapy, use external beam radiotherapy'. NICE guideline NG101 does not make a direct recommendation on intraoperative radiotherapy, but instead provides a cross-reference to the NICE technology appraisal guidance on the intrabeam radiotherapy system for adjuvant treatment of early breast cancer in recommendation 1.10.21.

New evidence from 2 systematic reviews was identified in relationship to omitting radiotherapy in older breast cancer patients considered to be at low risk of local recurrence. This is relevant to recommendation 1.10.7 which says to 'consider omitting radiotherapy for women who have had breast-conserving surgery for invasive breast cancer with clear margins and have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) and are willing to take adjuvant endocrine therapy for a minimum of 5 years'. The findings of the Palumbo et al. 2021 systematic review are consistent with this recommendation. As the abstract for Savard et al. 2021 discusses patients aged 50 years and older, a check of the full text was made. The age of the participants across the studies included in the systematic review was approximately ≥65 years and they had tumours that were low risk (most studies included patients without lymph node involvement), as such the findings of this systematic review are also considered to be in line with recommendation 1.10.7.

Radiotherapy after mastectomy

NICE guideline NG101 recommendations:

- 1.10.10 Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins. **[2018]**
- 1.10.11 Consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer. **[2018]**
- 1.10.12 Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk of local recurrence (for example, most people who have lymph node-negative breast cancer). Risk can be estimated using a range of standardised tools and clinical expertise. **[2018]**

Surveillance decision

Recommendations 1.10.10 to 1.10.12 on radiotherapy after mastectomy in NICE guideline NG101 should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review assessed the effect of radiotherapy after mastectomy on survival outcomes in older patients (>65 years old) with intermediate risk breast cancer (T1-2N1 or T3N0) (Tseng et al. 2020). Two retrospective cohort studies (n=746) were included (search dates: January 2008 to December 2018). A meta-analysis indicated that, compared with no radiotherapy, radiotherapy after mastectomy was associated with a non-significant reduction in mortality and breast cancer-related death.

A systematic review assessed local recurrence in patients with DCIS breast cancer treated by mastectomy with negative margins versus positive or close margins, or close margins versus positive margins (Kim et al. 2020). Twelve retrospective studies (n=2,902) were included (search dates: to 31 January 2019). A meta-analysis found that patients with positive or close margins had a significant increase in risk of local recurrence compared with patients with a negative margin; and patients with positive margin had a significant increase in risk of local recurrence compared with patients with a close margin. While resection margin status after mastectomy was shown to have an impact on local recurrence, the authors of the systematic review said that 'the recurrence rate was insufficient to warrant a recommendation for postmastectomy radiotherapy in patients with close or positive margins.'

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No intelligence was identified.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence on the effect of radiotherapy after mastectomy on survival outcomes in older patients with intermediate risk breast cancer indicated that there was no significant

benefit from radiotherapy for this group (Tseng et al. 2020). Current recommendation 1.10.11 says to consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer. The population in the Tseng et al. 2020 systematic review included people with node negative T3 breast cancer, but also included people with T1-2N1 breast cancer, and as such is not directly relevant, but does indicate that there is no reason to consider radiotherapy after mastectomy for patients with an 'intermediate' risk breast cancer, or low risk breast cancer, as advised in recommendation 1.10.12.

The new evidence from Kim et al. 2020 highlights the positive relationship between local recurrence and presence of cancer cells in the surgical margin (aka margin of resection) in patients with DCIS breast cancer treated by mastectomy, but the authors concluded that the evidence was not sufficient to indicate that these patients should receive postmastectomy radiotherapy. It therefore does not impact on current recommendations, which do not recommend postmastectomy radiotherapy for this group.

Radiotherapy after neoadjuvant chemotherapy

NICE guideline NG101 recommendations:

- 1.11.9 Offer local treatment with mastectomy (or, in exceptional cases, breast-conserving surgery) followed by radiotherapy to people with locally advanced or inflammatory breast cancer that has been treated with neoadjuvant chemotherapy. [2009]
- 1.11.10 Offer postmastectomy radiotherapy after neoadjuvant chemotherapy if post-treatment histology shows node-positive (macrometastases) breast cancer or involved resection margins. [2018]
- 1.11.11 Offer postmastectomy radiotherapy after neoadjuvant chemotherapy if pretreatment investigations show node-positive (macrometastases) breast cancer. [2018]
- 1.11.12 Consider postmastectomy radiotherapy after neoadjuvant chemotherapy if post-treatment histology shows node-negative T3 breast cancer. [2018]
- 1.11.13 Consider postmastectomy radiotherapy after neoadjuvant chemotherapy if pretreatment investigations show node-negative T3 breast cancer. [2018]

Surveillance decision

Recommendations in this section should not be updated at this time; evidence will be monitored.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review assessed the effect of radiotherapy after mastectomy on locoregional recurrence in patients with breast cancer who had a pathologic complete response (pCR) to neoadjuvant chemotherapy or pathologically lymph node negative disease following neoadjuvant chemotherapy (Shah et al. 2020a). Seven cohort studies (n=2,432) were included (search dates: 1 January 1980 to 30 April 2019). A meta-analysis found that radiotherapy after mastectomy was associated with significantly lower odds of locoregional recurrence, with the effect 'most pronounced' in stage III/IV disease, and 'a benefit' for patients with lymph node negative disease (statistics not reported in abstract).

A systematic review compared adjuvant locoregional radiation therapy versus no radiation therapy in patients with breast cancer who had mastectomy or breast-conserving surgery and a pCR after neoadjuvant chemotherapy (Nikyar, Tegnelius and Valachis 2022). Thirteen retrospective studies (n=16,380) were included (search dates: 1990 until November 2020). A meta-analysis found a significant reduction in the risk of locoregional recurrence in patients with node positive breast cancer at diagnosis and pathologically lymph node negative disease following neoadjuvant chemotherapy compared with those who did not receive adjuvant locoregional radiation therapy. There were no significant differences for survival outcomes between groups.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

System intelligence identified that there is uncertainty about chest wall radiotherapy depending upon pathological response and/or initial stage at diagnosis as well as regional node radiotherapy. This is considered an area of clinical importance that has implications for practice. There is also a related recommendation for research on the indications for postmastectomy radiotherapy after neoadjuvant chemotherapy.

Impact statement

New evidence is unlikely to change guideline recommendations.

The systematic review evidence is consistent with recommendation 1.11.12 to consider postmastectomy radiotherapy after neoadjuvant chemotherapy if post-treatment histology shows node-negative T3 breast cancer, based on a reduction in the risk of locoregional recurrence.

Ongoing trials are being monitored for evidence on outcomes from chest wall radiotherapy depending upon pathological response, initial stage at diagnosis and regional node radiotherapy.

Non-systemic disease modifying therapy for early and locally advanced breast cancer - surgery

This section includes recommendations on:

- further surgery after breast-conserving surgery based on tissue margins (NG101-1.3.1 to 1.3.3)
- breast reconstruction surgery (NG101-1.5.1 to 1.5.4)
- Paget's disease (NG101-1.3.4): No relevant evidence or intelligence was identified in the 2022, 2015 or 2012 surveillance reviews for the review question 'what is the role of mastectomy in patients with localised Paget's disease of the nipple?'
- surgery to the axilla - invasive breast cancer (NG101-1.4.1 to 1.4.3): No relevant evidence or intelligence was identified in the 2022 surveillance review. Evidence was identified in the 2015 and 2012 surveillance reviews for the review question 'in patients with invasive breast cancer or DCIS, when is sentinel lymph node biopsy justified as a staging procedure?' which was assessed as being consistent with the 2009 recommendations.
- surgery to the axilla - ductal carcinoma in situ (DCIS) (NG101-1.4.4 to 1.4.5): No relevant evidence or intelligence was identified in the 2022 surveillance review. Evidence was identified in the 2015 and 2012 surveillance reviews for the review question 'in patients with invasive breast cancer or DCIS, when is sentinel lymph node biopsy justified as a staging procedure?' which was assessed as being consistent with the 2009 recommendations.
- surgery to the axilla – positive axillary lymph node identified by a preoperative ultrasound-guided needle biopsy (NG101-1.4.6): No relevant evidence or intelligence was identified in the 2022 surveillance review.
- surgery to the axilla - positive axillary lymph node identified by a sentinel lymph node biopsy (NG101-1.4.7 to 1.4.10)

Further surgery after breast-conserving surgery based on tissue margins

NICE guideline recommendations:

- 1.3.1 Offer further surgery (re-excision or mastectomy, as appropriate) after breast-conserving surgery where invasive cancer and/or DCIS is present at the radial margins ('tumour on ink'; 0 mm). **[2018]**

- 1.3.2 For women who have had breast-conserving surgery where invasive cancer and/or DCIS is present within 2 mm of, but not at, the radial margins (greater than 0 mm and less than 2 mm):
  - discuss the benefits and risks of further surgery (re-excision or mastectomy) to minimise the risk of local recurrence
  - take into account the woman's preferences, comorbidities, tumour characteristics and the potential use of radiotherapy (also see radiotherapy after breast-conserving surgery). **[2018]**
- 1.3.3 All breast units should audit their recurrence rates after treatment. **[2009, amended 2018]**

Surveillance decision

Recommendations in this section should be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

A systematic review assessed the association between tumour-free tissue margin width after breast-conserving surgery and recurrence (local and distant) in early-stage invasive breast cancer (Bundred et al. 2022). Sixty-eight studies (study design: NR; n=112,140) with a minimum follow-up of 5 years were included (search dates: 1 January 1980 to 31 December 2021). A meta-analysis found that tumour on ink (involved) margins were associated with a significant increase in rate of distant and local recurrence compared with negative margins (≥2 mm), but not compared with close margins (no tumour on ink but <2 mm). Close margins were also associated with a significant increase in rate of distant and local recurrence when compared with negative margins, after adjusting for receipt of adjuvant chemotherapy and radiotherapy. The authors also reported on an analysis of data from 5 studies published since 2010 which found that, compared with negative margins, both tumour on ink and close margins were associated with significantly increased distant recurrence. On the basis of their findings, the authors concluded that 'surgeons should aim to achieve a minimum clear margin of at least 1 mm'.

Studies that do not impact recommendations

A systematic review assessed how improvements over time in breast-conserving therapy for early-stage invasive cancers have affected the impact of margins on local recurrence rates over time (Shah C et al. 2020b). Thirty-eight studies (study designs=NR; n=54,502 patients) with a minimum follow-up of 50 months were included (search dates: 1995 to 2016). A Bayesian logistic regression model showed that local recurrence rates decreased over time for each margin width cohort, 'with maximum differences between negative margin groups of

less than 1% for the most recent enrolment period. However, relative rates of LR between different margin groups remained stable over time' The authors concluded that results support the guidelines of 'no tumour on ink' for most patients; and that the analysis shows that 'the impact of margin width on local recurrence rates has declined substantially over time, with very small differences between the narrowest and widest margin groups in the most recent cohort.'

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

System intelligence identified a systematic review on margin status and survival outcomes after breast cancer conservation surgery (Bundred et al. 2022) that post-dated the surveillance review search period (see details above).

Impact statement

New evidence is likely to change guideline recommendations.

The results reported by Shah C et al. 2020b are consistent with recommendation1.3.1 to offer further surgery (re-excision or mastectomy, as appropriate) after breast-conserving surgery where invasive cancer and/or DCIS is present at the radial margins ('tumour on ink'; 0 mm) and provide useful information on the importance of considering new evidence independently of older research due, probably, to changes in surgical techniques. It should however be noted that the search period for evidence in this systematic review pre-dates the search period for the NICE guideline NG101 evidence review question 'Do tumour-free tissue margins wider than 0 mm reduce local recurrence for people with invasive breast cancer and/or DCIS treated with breast-conserving surgery?' which was January 2017.

The findings of the meta-analyses reported by Bundred et al. 2022 are also consistent with recommendation1.3.1 content; but they do indicate that the wording of recommendation 1.3.2 may require amending to highlight that there does now appear to be evidence of a benefit in terms of reducing local and distant recurrence from having further surgery where invasive cancer is present within 2 mm of, but not at, the radial margins (greater than 0 mm and less than 2 mm) – including from studies published since 2010. This change would not apply to patients with DCIS as they were excluded from the Bundred et al. 2022 study. The current 'cautious' approach to the wording of recommendation 1.3.2 was based on no evidence of a clear and consistent benefit of having tumour-free tissue margins between >0 mm and 2 mm for invasive disease. 'Given this uncertainty, the committee were unable to make recommendations about whether or not further surgery was warranted to achieve margins wider than 0 mm. Instead they agreed to recommend that the risks and benefits of further surgery be discussed with person where their radial margins are between >0 mm to 2 mm. The committee discussed the balance of benefits and harms … they … noted that for people with a radial margin of >0 mm to 2 mm there was uncertainty about the effect on

local recurrence and it was possible that this could increase in the group. They balanced this potential harm by recommending more personalised care.' (evidence review A: surgery to the breast). Because there was not enough evidence to clearly define an optimum margin width between 0 mm and 2 mm to minimise local recurrence rates and minimise further surgery the committee agreed that this was an important topic for further research, and made a recommendation for research on the optimum tumour-free margin width after surgery to the breast. There appears to now be evidence that can address this recommendation for research.

Breast reconstruction surgery

NICE guideline NG101 recommendations:

- 1.5.1 Offer both breast reconstruction options to women (immediate reconstruction and delayed reconstruction), whether or not they are available locally. **[2018]**
- 1.5.2 Be aware that some women may prefer not to have breast reconstruction surgery. **[2018]**
- 1.5.3 Offer immediate breast reconstruction to women who have been advised to have a mastectomy, including those who may need radiotherapy, unless they have significant comorbidities that rule out reconstructive surgery. **[2018]**
- 1.5.4 Discuss the benefits and risks of immediate breast reconstruction and delayed breast reconstruction with women. Topics to discuss include those in table 1 and:
  - the timing of breast reconstruction surgery (at the same time as mastectomy or later)
  - different breast reconstruction surgery options and what they involve
  - how the timing of breast reconstruction surgery affects the options available
  - the uncertainty over long-term outcomes in women having radiotherapy. **[2018]**

And see Table 1 Breast reconstruction options for women who choose breast reconstruction

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review evaluated breast reconstruction options for women after mastectomy for breast cancer (or breast cancer prophylaxis) in relation to 6 key questions, one of which was on the timing of implant-based reconstruction and autologous reconstruction in relation radiation therapy (and chemotherapy) (Saldanha et al. 2021). In total 8 RCTs, 83 nonrandomized comparative studies, and 69 single group studies (n=NR) were included (search dates: from database inception to March 23, 2021). A meta-analysis (study number and sample size=NR) found that, for implant-based reconstruction undertaken before or after radiation therapy, there were comparable physical, psychosocial and sexual wellbeing outcomes and patient satisfaction with breasts (low strength of evidence); and comparable risks of implant failure and/or loss or need for explant surgery (moderate strength of evidence). There was no evidence on the timing of autologous reconstruction and radiation therapy. The authors noted a need for new high-quality research with regards to timing of breast reconstruction in relation to radiation therapy.

A systematic review compared immediate with delayed autologous reconstruction and postmastectomy radiation therapy on early and late complications in breast cancer patients requiring postmastectomy radiation therapy (Hershenhouse et al. 2021). Forty-four studies (study design=NR; n=3,473; immediate reconstruction n=1,927 and delayed reconstruction n=1,546) were included (search dates: NR). A meta-analysis found that there were no significant differences between immediate and delayed breast reconstruction for early complications of flap loss, fat necrosis, thrombosis, hematoma, infection. There were significantly lower rates of seroma in the immediate versus delayed breast reconstruction groups. Late complications not reported.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A patient group said they thought NICE guideline NG101 should 'explicitly state that patients should be offered and be able to access the different types of reconstruction, that are suitable for them even if they are not available locally'. They referenced Getting It Right First Time (GIRFT) (Association of Breast Surgery 2021) which provides information on variation in provision and access to some types of reconstruction, such as free flap. The patient group said that providing information on the different types of reconstruction available could help improve equitable access. A topic expert also said that they were aware of inequity of access to oncoplastic and autologous surgery and surgeon bias existing between regions.

The patient group also thought that recommendation 1.5.4 on discussing the benefits and risks of immediate breast reconstruction and delayed breast reconstruction with women should include types of reconstruction available. They also said it should be clear in the recommendations that this is a shared decision making process.

The breast cancer health inequalities briefing found that for older women, breast reconstruction is often not raised as a possibility by either clinicians or individuals themselves, even though they would have liked to have it as an option; and that this finding is supported by findings in the 2022 national audit of breast cancer in older patients that older women were less likely to have reconstructive surgery.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence is in line with recommendation 1.5.3 to offer immediate breast reconstruction to women who have been advised to have a mastectomy, including those who may need radiotherapy as there is no indication of worse outcomes between radiotherapy delivered after immediate reconstruction compared with radiotherapy before delayed reconstruction.

No evidence was identified on the longer-term outcomes and different types of reconstruction which could address the recommendation for research on long-term outcomes for breast reconstruction in women having radiotherapy to the chest wall.

With regards to patient group feedback and findings concerning older women not being offered/discussing breast reconstruction, recommendation 1.5.4 highlights that discussions should involve 'different breast reconstruction surgery options and what they involve'. Specific types of breast reconstruction are not listed as these can change over time and the evidence reviews do not cover evidence on comparison of different surgical options. It would therefore not be appropriate to list all options within the recommendations. As with all recommendations within NICE guidelines, shared decision making is a fundamental principle, highlighted on the overview page of all guidance, which says 'when exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. The guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.' NICE guideline NG101 recommendation 1.2.1 on requirements expected of all members of a breast cancer clinical team also cross-references to recommendation section 1.5 enabling patients to actively participate in their care in patient experience in adult NHS services (NICE guideline CG138) which includes shared decision making.

Surgery to the axilla - positive axillary lymph node identified by a sentinel lymph node biopsy

NICE guideline recommendations:

- 1.4.7 Offer further axillary treatment (axillary node clearance or radiotherapy) after SLNB to people who have 1 or more sentinel lymph node macrometastases. **[2018]**

- 1.4.8 Discuss the benefits and risks of having no further axillary treatment after primary breast-conserving surgery (within clinical trials where available) with women who:
  - have 1 or 2 sentinel lymph node macrometastases **and**
  - have been advised to have whole-breast radiotherapy with systemic therapy (which may be endocrine therapy). **[2018]**
- 1.4.9 Do not offer further axillary treatment after primary surgery to people with invasive breast cancer who have only micrometastases in their sentinel lymph nodes. **[2018]**
- 1.4.10 Do not offer further axillary treatment after primary surgery to people with invasive breast cancer who have only isolated tumour cells in their sentinel lymph nodes. Regard these people as having lymph node-negative breast cancer. **[2018]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review assessed survival outcomes, recurrence rate and lymphoedema in patients with early-stage breast cancers and 1 or 2 positive sentinel lymph node (SLN) metastasis who had SLN biopsy (SLNB) alone or SLNB plus axillary lymph node dissection (ALND) (Huang et al. 2021). One RCTs and 6 retrospective studies (n=8,864) were included (search dates: NR). Meta-analysis found that there were no significant differences in OS, DFS or recurrence rates between patients receiving SLNB alone compared with SLNB plus ALND; but there was a significantly lower incidence of lymphoedema in SLNB alone compared with SLNB plus ALND group.

A systematic review compared observation or axillary radiotherapy with completion axillary lymph node dissection (cALND) in the management of positive SLN in clinically node negative women with breast cancer on survival outcomes, recurrence and morbidity (Castelo et al. 2020). Three RCTs comparing observation with cALND, and 2 RCTs comparing axillary radiotherapy with cALND were included (search dates: database inception to July 2019). Results were presented as a narrative summary: there was no statistical difference in axillary recurrences, 5- or 8-year OS or DFS between either observation or axillary radiotherapy compared with cALND. Four RCTs reported on morbidity outcomes, with all showing significantly more lymphoedema, paraesthesia, and shoulder dysfunction in cALND compared with observation or axillary radiotherapy groups.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A topic expert said that changes in axillary management after neoadjuvant chemotherapy (targeted axillary biopsy) is an area requiring update in NICE guideline NG101.

Impact statement

New evidence is unlikely to change guideline recommendations.

On the basis of the abstracts of the new evidence it is not possible to draw any conclusions concerning the impact of findings that women with clinically node negative breast cancer and positive SLNs could safely be managed without ALND or axillary radiotherapy as the systematic reviews' abstracts do not differentiate between people with SLN macrometastases or micrometastases. NICE guideline NG101 is clear about different treatment decisions between SLN macrometastases or micrometastases, with recommendations 1.4.7 and 1.4.8 saying to 'offer further axillary treatment (axillary node clearance or radiotherapy) after SLNB to people who have 1 or more sentinel lymph node macrometastases' and to 'discuss the benefits and risks of having no further axillary treatment after primary breast-conserving surgery (within clinical trials where available) with women who have 1 or 2 sentinel lymph node macrometastases and have been advised to have whole breast radiotherapy with systemic therapy (which may be endocrine therapy).' These recommendations were based on the finding of unclear benefits and risks of further axillary treatment after primary surgery in people with only 1 or 2 sentinel lymph node macrometastases who have had breast-conserving surgery and have been advised to have whole-breast radiotherapy and systemic therapy, so the committee agreed that the risks and benefits of further treatment should be discussed with this group.

For people with invasive breast cancer who have only SLN micrometastases, recommendation 1.4.9 says 'do not offer further axillary treatment after primary surgery'. This was because the guideline committee agreed that current evidence shows that further axillary treatment after primary surgery does not improve survival for people with micrometastases and there are risks such as lymphoedema, therefore further treatment should not be offered to this population.

The full texts of the new evidence were therefore checked for reporting and/or analysis of SLN macrometastases or micrometastases of studies included within the systematic reviews. Within Huang et al. 2021 only 1 of 7 included study reports SLN on basis of macrometastases or micrometastases, all other studies have SLN metastatic status described in terms of number of affected nodes. Within Castelo et al. 2020, the 3 RCTs comparing observation with cALND included 2 RCTs with only SLN micrometastases and 1 RCT with a mix of women with SLN macrometastases or micrometastases. Castelo et al. 2020 report that the 2 RCTs with only SLN micrometastases 'demonstrated 5-year overall survival of greater

than 97% in all groups, and no statistically significant increase in axillary recurrence at 5 years', which is consistent with recommendation 1.4.9 to not offer further axillary treatment after primary surgery. The 2 RCTs include in Castelo et al. 2020 comparing axillary radiotherapy with cALND included women with SLN macrometastases or micrometastases, limiting conclusions that can be drawn concerning the impact of findings on recommendations 1.4.7 and 1.4.8. Further research is therefore required in this area to clarify the benefits and risks of further axillary treatment (axillary node clearance or radiotherapy) after primary surgery in people with 1 or 2 SLN macrometastases.

With regards to changes in axillary management after neoadjuvant chemotherapy, what to do to the axilla after neoadjuvant chemotherapy if, at diagnosis (usually on ultrasound with or without biopsy) the lymph nodes were involved, is an important area for clinical practice and there is a debate as to whether, after neoadjuvant therapy a SLNB can be considered rather than ALND. However no evidence was identified in this area. We are aware that this is an area of ongoing research and will monitor this area.

Systemic disease modifying therapy - chemotherapy

This section includes recommendations on:

- chemotherapy for advanced breast cancer (CG81-1.3.2 and 1.3.8 to 1.3.11)
- adjuvant chemotherapy for early and locally advanced breast cancer (NG101-1.8.1 to 1.8.3)
- neoadjuvant chemotherapy for early and locally advanced breast cancer (NG101-1.11.1 to 1.11.3)
- neoadjuvant chemotherapy regimens for early and locally advanced breast cancer (NG101-1.11.4 to 1.11.5)

Chemotherapy for advanced breast cancer

- 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]**
- 1.3.8 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. (This recommendation is from NICE's technology appraisal guidance on gemcitabine for the treatment of metastatic breast cancer.) **[2009]**

Surveillance decision

This section should be updated.

Previous surveillance

The 2018 surveillance review found evidence relating to both monotherapy and combination chemotherapy therapy for advanced breast cancer, finding that taxane-based chemotherapy was more effective than non-taxane-based chemotherapy. However none of the evidence found was conclusive enough to change the focus of the guideline recommendations. Eribulin and gemcitabine were also discussed, however these were largely covered by technology appraisals. No new evidence was found relating to combination versus sequential single agent chemotherapy at the 2018 review, however topic experts noted that not stipulating the order of use may make the recommendations less restrictive.

2023 surveillance

Studies that impact recommendations

Two meta-analyses and one Cochrane review assessed the efficacy and safety of platinum containing chemotherapy regimes for women with triple-negative metastatic breast cancer.

- Yang et al. 2021, included 11 trials (study type: NR), n=1,222, search dates: up to November 2020.
- Lu et al. 2021, included 4 RCTS, n=590, search dates: up to June 1st 2020.
- Egger et al. 2021, 10 trials (study type: NR), n=1,349, search dates: up to 27th September 2019.

The Cochrane review (Egger et al. 2021) found that for women with triple-negative metastatic breast cancer, there was moderate-quality evidence of a small survival benefit from platinum-based regimens compared to non-platinum regimens. There was also a benefit to progression free survival, time to progression, and tumour response to platinum containing

regimes. They highlighted however that there are known toxicities associated with platinum containing regimes, and found increased rates of nausea and vomiting, and anaemia in their analysis. Both meta-analyses (Yang et al. 2021 & Lu et al. 2021) found that platinum containing regimes were associated with significant improvements in progression free survival, but no significant differences in OS. Yang et al. also reported that platinum containing regimes are not associated with an increased incidence of adverse side effects compared with non-platinum-containing chemotherapies, with the exception of nausea and vomiting. Lu et al. found that for the 2 studies in their meta-analysis that reported side effects, platinum containing regimes were associated with increased thrombocytopenia, whereas non-platinum containing regimes were associated with increased fatigue.

Two meta-analyses looked at the efficacy of capecitabine combination therapy on DFS and progression-free survival (PFS) in women with metastatic breast cancer.

- Zhang et al. 2021, included 12 RCTs, n=4,854, search dates: NR
- Alsaloumi et al. 2020, included 9 trials (study type: NR), n=6,714, search dates: NR

Both meta-analyses found that capecitabine combination therapy results in significant increases in DFS, with Zhang et al. also reporting significant increases in OS for women with triple-negative breast cancer. Reports of toxicity profile differed between the 2 meta-analyses with Zhang et al. reporting that the addition of capecitabine was associated with a much higher risk of hand-foot syndrome, diarrhoea and mucositis or stomatitis. In contrast Alsaloumi et al. reported that while haematological side effects were increased with capecitabine combination therapy, non-haematological adverse effects such as hand-foot syndrome were fewer.

A Cochrane review also assessed whether capecitabine is more useful in hormone receptor-positive or hormone receptor-negative breast cancer, and whether this differs depending on how advanced the cancer is (Hoon et al. 2021). Twenty-six RCTs (n=20,934) were included (search dates: up to June 4 2019). It found that a moderate PFS benefit from including capecitabine was seen only in hormone receptor-positive cancers in metastatic breast cancer studies. No benefit of capecitabine for pCR was noted overall or in hormone receptor subgroups when included in neoadjuvant therapy. In contrast, the addition of capecitabine in the adjuvant setting led to improved outcomes for OS and DFS in hormone receptor-negative breast cancer.

One Cochrane review compared taxane-containing chemotherapy regimens with regimens not containing a taxane in the management of women with metastatic breast cancer (Ghersi et al 2015). Twenty-eight RCTs (n=6,871) were included (search dates: up to February 14 2013). This found that taxane-containing regimens appear to improve OS, time to progression, and tumour response rate in women with metastatic breast cancer. Taxanes were also associated with an increased risk of neurotoxicity, but less nausea and vomiting compared to non-taxane containing regimens. The considerable heterogeneity encountered across studies probably reflects the varying efficacy of the comparator regimens used in these studies and indicates that taxane-containing regimens are more effective than some, but not all, non-taxane containing regimens.

Studies that do not impact recommendations

A systematic review and meta-analysis evaluated docetaxel schedule in patients with metastatic breast cancer on treatment tolerability and efficacy (van Eijk et al. 2022). In total 4 RCTs (n=459) were included (search dates: to January 2021). No significant differences were found in efficacy outcomes between docetaxel scheduling of weekly, or 3 weekly dosing. Side effects varied with the 2 weekly dosing schedules, with a weekly schedule having significantly lower risk of neutropenia, febrile neutropenia and neuropathy, and higher risk of onycholysis, epiphora, and treatment discontinuation.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

A systematic review and meta-analysis evaluated nab-paclitaxel monotherapy in women with metastatic breast cancer (Lu et al. 2021). Included studies looked at any dose, schedule or regime of nab-paclitaxel monotherapy, across all lines of treatment. In total 22 studies (study type: NR; n=3,287) were included (search dates: NR). Subgroup analyses revealed that first-line nab-paclitaxel monotherapy shows greater beneficial effects in overall response rate, and progression free survival, than nab-paclitaxel monotherapy used during any other line of treatment.

Intelligence gathering

The health inequalities briefing identified that there is variation in treatment by age. In those under 50 years the most common treatment is a combination of tumour resection, radiotherapy, and chemotherapy (Figure 17). But as age increases the use of active treatments involving a combination of chemotherapy, tumour resection, and radiotherapy declines. This is in line with the 2018 national breast cancer audit which found that chemotherapy use declines with increasing age regardless of tumour characteristics. As the age of an individual increases, clinicians are more likely to state that comorbidities and frailty are reasons that chemotherapy is not offered, even though these factors are not recorded in a third of cases.

During our searches evidence was found to support the use of everolimus with exemestane for treating advanced breast cancer after endocrine therapy, as recommended in NICE technology appraisal TA421. Evidence was also found which may impact recommendations made on the use of eribulin for treating locally advanced or metastatic breast cancer after 1, or 2 chemotherapy regimens (NICE technology appraisals TA515 and TA423). This information will be passed on to the relevant teams in Centre for Health and Technology Evaluation (CHTE).

Topic experts were contacted regarding areas of the guideline that they considered in need of an update. Multiple topic experts raised the issue of systemic anticancer therapies, and the sequence in which agents are delivered. This includes chemotherapeutic, endocrine and biological treatments.

A recommendation for research for chemotherapy is included in NICE guideline CG81, regarding the clinical and cost effectiveness of different sequences of chemotherapy for advanced breast cancer.

Impact statement

New evidence is likely to change guideline recommendations.

Two meta-analyses and one Cochrane review were identified that looked at the benefits of a platinum containing chemotherapy regime for women with triple-negative breast cancer. Currently NICE guideline CG81 does not make any recommendations on platinum containing chemotherapy regimes, nor does it specify any chemotherapy regimes for women with triple-negative metastatic breast cancer. Triple-negative breast cancer has some of the worst outcomes for patients, and new evidence regarding the use of platinum containing regimes should be assessed for benefit.

Evidence was also identified in favour of capecitabine combination therapy for hormone receptor-positive cancers, which contradicts current NICE guidance. Currently NICE guideline CG81 recommends capecitabine monotherapy as either a second or third-line chemotherapy regime. Combination therapy is also recommended if it is expected there will be a greater probability of response for people who have hormone receptor-positive cancers. An update should be conducted in this area to assess whether capecitabine combination therapy for people with hormone receptor-positive cancers is preferential to the currently recommended monotherapies.

New evidence, including a Cochrane review (Ghersi et al 2015), was also identified in favour of the use of taxanes as first-line chemotherapeutic agents. Currently NICE guideline CG81 recommends docetaxel as a treatment for people with breast cancer who are not suitable for anthracyclines (recommendation 1.3.10). The new evidence, including the Cochrane review suggests that taxanes should be considered as first line treatment.

There does not appear to be new evidence to fulfil research recommendation 3 on clinical and cost effectiveness of different sequences of chemotherapy, as such this research recommendation should be retained.

Topic experts highlighted systemic anticancer therapies as an area of the guideline that required an update, the identification of new evidence for platinum containing regimes, for combination capecitabine, and for the use of first-line nab-paclitaxel monotherapy indicate that evidence in this area has moved on since recommendations were written in 2009, and therefore an update should be done.

Adjuvant chemotherapy for early and locally advanced breast cancer

NICE guideline NG101 recommendations:

- 1.8.1 For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications. **[2018]**
- 1.8.2 Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens. Topics to discuss include those in table 4 and:
  - the benefits of reduced cardiac toxicity and reduced nausea
  - the risks of additional side effects, including neuropathy, neutropenia and hypersensitivity
  - the different side effects and dosing frequencies of different docetaxel and paclitaxel regimens, and the additional clinic visits that may be needed
  - that absolute benefit is proportional to absolute risk of recurrence.

    Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications. **[2018]**

And see Table 4 Benefits and risks of adding a taxane to anthracycline-containing regimens and comparison of different taxane regimens

- 1.8.3 Weekly and fortnightly paclitaxel should be available locally because these regimens are tolerated better than 3-weekly docetaxel, particularly in people with comorbidities. **[2018]**

Surveillance decision

Recommendations in this section should not be updated at this time; evidence will be monitored.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A Cochrane review evaluated the sequencing of anthracyclines and taxanes in people with early breast cancer receiving adjuvant therapy (Zaheed et al. 2019). Four RCTs (n=208) were included (search dates: 1st February 2018). No studies reported on OS and DFS, and only one study collected the data. Administration of taxanes before anthracyclines resulted in significant reductions in grade 3/4 neutropenia and caused no significant difference to grade 3/4 neurotoxicity. There was no evidence suggesting a change to the number of people

experiencing a dose delay when taxanes were given before anthracyclines. One study reported that there was no difference in QoL in both groups, however no numerical data was provided in the original study text.

A systematic review evaluated the role of cytotoxic agents, including chemotherapy regimes which used anthracyclines and taxanes, for breast cancer and colon cancer patients on post-chemotherapy cognitive impairment (Huehnchen et al. 2020). In total 30 RCTs (n=3,473; 23/30 of studies looked at breast cancer patients) were included (search dates: 2006 to 2016). The breast cancer patients in most studies were treated with various combinations of cyclophosphamide, epirubicin or doxorubicin (anthracyclines), docetaxel or paclitaxel (taxanes), and 5-fluorouracil (FEC or FEC-T regimen). Review of the articles within the systematic review found that in 21 out of the 23 studies looking at breast cancer patients, chemotherapy did cause post-chemotherapy cognitive impairment, this occurred in regimes that did, and did not include a taxane.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

The equalities impact assessment for NG101 highlighted the lack of older women in clinical trials, and this was considered to be of particular relevance for the current review question. During development the committee used formal consensus methods to try and ascertain if specific recommendations could be made for older people, but this was not possible.

The health inequalities briefing for breast cancer also identified that there is variation in treatment by age. In those under 50 years old the most common treatment is a combination of tumour resection, radiotherapy, and chemotherapy. But as age increases the use of active treatments involving a combination of chemotherapy, tumour resection, and radiotherapy declines. This is consistent with the findings in the National Audit of Breast Cancer in Older Patients (NABCOP) 2018 Annual Report that chemotherapy use declines with increasing age regardless of tumour characteristics. As the age of an individual increases, clinicians are more likely to state that comorbidities and frailty are reasons that chemotherapy is not offered, even though these factors are not recorded in a third of cases.

A topic expert said that de-escalation of chemotherapy (omission of anthracyclines) in lower risk disease should be an area for update within NICE guideline NG101.They referenced the 2021 customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021.

System intelligence was received highlighting an ongoing meta-analysis on anthracycline and taxane-based chemotherapy, which is likely to raise questions about taxane without anthracycline chemotherapy, numbers of chemotherapy cycles and scheduling of chemotherapy.

System intelligence was also received on areas to consider for update as practice has changed:

- While existing recommendations do only talk about anthracycline and taxane, it was noted that 5-fluorouracil (an antimetabolite) is now generally not given with anthracycline. 5-fluorouracil is however mentioned in some NHS guidance and by the European Society for Medical Oncology (ESMO). There is also a MHRA safety alert 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity.
- Information on anthracycline and taxane-based chemotherapy dose density is not provided within the recommendations, but evidence supports scheduling and use of dose dense chemotherapy (giving every 2 weeks or sometimes weekly) rather than every 3 weeks (a patient level meta-analysis of RCTs (Early Breast Cancer Trialists' Collaborative Group 2019) was provided as a reference in support of this).

Impact statement

New evidence is unlikely to change guideline recommendations.

A Cochrane review and systematic review were identified as being relevant to the review question 'Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline-based adjuvant chemotherapy?' The Cochrane review found that relevant studies did not report on the critical outcomes of OS, DFS or treatment-related morbidity. The Cochrane review looked at the sequencing of taxanes and anthracyclines, but overall did not find sufficient evidence to move away from current practice of delivering anthracyclines followed by taxanes. NICE guideline NG101 does not specify the sequence in which an anthracycline and taxane regimen should be administered.

Intelligence indicates that a more currently relevant review question would be 'which people with early and locally advanced breast cancer would benefit from the addition of anthracyclines to taxane-based adjuvant chemotherapy?' and we are aware of ongoing research in this area that will be monitored.

There was also intelligence received on areas not covered by current recommendations that may be of clinical importance to consider (i.e. update): not giving fluorouracil and anthracycline, and scheduling and use of dose dense chemotherapy.

The systematic review outcomes were considered to be relevant to HRQoL, as cognitive functioning had been included as an outcome for the review question (see evidence review E: Adjuvant chemotherapy). There was evidence found on cognitive functioning that 'there is very low-quality evidence from 1 RCT (N=113) that there is no clinically meaningful effect of the addition of docetaxel on cognitive functioning at 5.4 year follow-up for people with invasive breast cancer.' As the Huehnchen et al. 2020 included multiple different types of chemotherapy regimes, the full text was checked to determine possible impact of findings. This reported that 'most patients' cognitive function improved within 1 year after completing chemotherapy, depending on age and cognitive reserve.' As the impact of an anthracycline

and taxane regimen on cognitive function is not considered long-term, and recommendation 1.8.2 states that the risks of adding a taxane to a chemotherapy regimen should be discussed with people (information on side effects is available from the British National Formulary), we do not consider the evidence to have an impact on current recommendations.

Neoadjuvant chemotherapy for early and locally advanced breast cancer

NICE guideline NG101 recommendations:

- 1.11.1 Offer neoadjuvant chemotherapy to people with ER-negative invasive breast cancer as an option to reduce tumour size. **[2018]**
- 1.11.2 Offer neoadjuvant chemotherapy to people with HER2-positive invasive breast cancer in line with the NICE technology appraisal guidance on pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. **[2018]**
- 1.11.3 Consider neoadjuvant chemotherapy for people with ER-positive invasive breast cancer as an option to reduce tumour size if chemotherapy is indicated. **[2018]**

Surveillance decision

This section should be updated, with a focus on neoadjuvant chemotherapy for people with HER2-positive invasive breast cancer and triple-negative invasive breast cancer.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

HER2 positive invasive breast cancer

A systematic review reported on a network meta-analysis (NMA) comparing neoadjuvant treatment regimens for HER2-positive early and locally advanced breast cancer on efficacy (achieving pCR) and safety (Gunasekara et al. 2022). Twenty-one RCTs (n=4,092) which covered 11 different regimens of neoadjuvant anti-HER2 therapy were included (search dates: to November 2021). The NMA found that the optimal balance between efficacy and safety was for trastuzumab emtansine plus pertuzumab plus chemotherapy (T-DM1PC), trastuzumab emtansine alone (T-DM1), and pertuzumab plus trastuzumab plus chemotherapy followed by trastuzumab emtansine plus pertuzumab regimens; and that DFS was highest for the pertuzumab plus trastuzumab plus chemotherapy regimen. However, the authors do note that results were based on a small number of studies, and 'additional RCTs assessing the efficacy of regimens with T-DM1 are still needed to confirm these findings'.

Another systematic review reported on a NMA comparing neoadjuvant treatment regimens for HER2-positive early breast cancer (Zhang et al. 2021). Thirty-six phase II/III RCTs which had targeted therapy in at least one arm (n=10,379) were included (search dates: to November 2020). The NMA showed that dual-target therapy is better than single-target therapy, and combination chemotherapy is better than mono-chemotherapy in achieving pCR; but there were no additional benefits to combining anthracycline with dual-target therapy or single-target therapy. A conjoint analysis of the pCR rate and safety endpoints showed that 'trastuzumab plus pertuzumab' and 'T-DM1 containing regimens' were well balanced in terms of efficacy and toxicity in all target regimens. Trastuzumab plus pertuzumab-based dual-target therapy with combination chemotherapy regimens showed the highest efficacy of all assessed regimens. They also achieved the best balance between efficacy and toxicity. Based on the NMA results the authors recommended docetaxel + carboplatin + trastuzumab + pertuzumab (TCbHP) as the preferred choice for neoadjuvant treatment of HER2-positive breast cancer.

Triple-negative invasive breast cancer

Four systematic reviews assessed the efficacy and safety of immune checkpoint inhibitors plus neoadjuvant chemotherapy compared with neoadjuvant chemotherapy in people with early-stage triple-negative breast cancer:

- Sternschuss et al. 2021 included 5 RCTs, n=2,075; search dates: 1 January 2010 to 30 October 2020
- Xin et al. 2021 included 6 RCTs, n=2,142; search dates: to 30 January 2021
- Rizzo et al. 2022 included 5 RCTs, n=1,639; search dates: 15 June 2008 to 10 April 2022
- Tarantino et al. 2021 included 5 RCTs, n=1,496; search dates: to 25 November 2020

All the systematic reviews reported that, compared with neoadjuvant chemotherapy alone, a combination of immune checkpoint inhibitors plus neoadjuvant chemotherapy resulted in a significant improvement in pCR. Two systematic reviews (Sternschuss et al. 2021, Xin et al. 2021) found that a combination of immune checkpoint inhibitors plus neoadjuvant chemotherapy was associated with a significant improvement in event-free survival, although follow-up was reported as 'short' in Xin et al. 2021. Two systematic reviews reported an increased incident in adverse events associated with the addition of immune checkpoint inhibitors (Sternschuss et al. 2021, Xin et al. 2021), while 1 reported no significant association with the addition of immune checkpoint inhibitors and 'toxicity' (Tarantino et al. 2021).

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

We identified an in-development NICE technology appraisal on neoadjuvant chemotherapy for early and locally advanced triple-negative breast cancer that includes immune checkpoint inhibitors (also described as a type of monoclonal antibody or targeted treatment; these include pembrolizumab, ipilimumab, nivolumab and atezolizumab):

- Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of early and locally advanced non-metastatic triple-negative breast cancer (NICE technology appraisal GID-TA10399)

Impact statement

New evidence is likely to change guideline recommendations.

ER-negative invasive breast cancer

No new evidence was identified on the effect of neoadjuvant chemotherapy on reducing tumour size in people with ER-negative invasive breast cancer, so there is no indication of the need for an update of recommendation 1.11.1.

HER2-positive invasive breast cancer

Two systematic reviews on neoadjuvant treatment regimens for HER2-positive early and locally advanced breast cancer supports recommendation 1.11.2 which cross-references to pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (NICE technology appraisal TA424). This recommends pertuzumab, in combination with trastuzumab and chemotherapy, within its marketing authorisation (which includes in combination with docetaxel), as an option for the neoadjuvant treatment of adults with HER2-positive breast cancer (locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence). The new evidence also indicates that neoadjuvant regimes containing trastuzumab emtansine are also effective in achieving a pCR in patients with HER2-positive early and locally advanced breast cancer. Evidence also indicated that neoadjuvant regimes containing carboplatin (a platinum-based chemotherapy drug) may be an effective treatment. As there are no NICE technology appraisals for trastuzumab emtansine as a neoadjuvant treatment, or carboplatin-containing regimens, in HER2-positive early and locally advanced breast cancer, evidence on this should be considered in an update.

ER-positive invasive breast cancer

No new evidence was identified on the effect of neoadjuvant chemotherapy on reducing tumour size in people with ER-positive invasive breast cancer, so there is no indication of the need for an update of recommendation 1.11.3.

Triple-negative invasive breast cancer

The new evidence indicates that immune checkpoint inhibitors plus neoadjuvant chemotherapy may be an appropriate treatment for achieving pCR in people with triple-negative invasive breast cancer. However none of the RCT evidence from the

systematic reviews would have met the inclusion criteria for the evidence review question on the effectiveness of neoadjuvant chemotherapy on which recommendations in NICE guideline NG101 were made (see evidence review J: neoadjuvant treatment). To be included an RCT had to assess neoadjuvant chemotherapy ± biological therapy compared with no neoadjuvant chemotherapy ± biological therapy, whereas all the evidence in the above systematic reviews had neoadjuvant chemotherapy as the comparator. There is also an in-development NICE technology appraisal GID-TA10399. Expert input will be requested to determine whether this should be an area for update or whether existing and anticipated NICE technology appraisal guidance addresses whether immune checkpoint inhibitors plus neoadjuvant chemotherapy should be recommended to people with triple-negative invasive breast cancer.

Neoadjuvant chemotherapy regimens for early and locally advanced breast cancer

NICE guideline NG101 recommendations:

- 1.11.4 For people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline. **[2018]**
- 1.11.5 Discuss the benefits and risks of adding a platinum to an anthracycline-containing neoadjuvant chemotherapy regimen. Topics to discuss include those in table 6, and particularly the risk of increased toxicity. **[2018]**

And see Table 6 Benefits and risks of adding a platinum to anthracycline-containing neoadjuvant chemotherapy for triple-negative invasive breast cancer

Surveillance decision

This section should be updated, with a focus on whether the addition of a platinum to anthracycline (± taxanes)-based neoadjuvant chemotherapy leads to improvements in survival outcomes in people with triple-negative early and locally advanced breast cancer; plus an updated check for RCT evidence that includes people with BRCA germ line mutation.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

Two systematic reviews reported on survival outcomes in people with triple-negative breast cancer receiving platinum-based neoadjuvant chemotherapy (anthracycline ± taxane) compared with neoadjuvant chemotherapy alone (Pathak et al. 2022 and Saleh et al. 2021):

Pathak et al. 2022 included 8 RCTs (n=2,425) which compared carboplatin-based neoadjuvant or adjuvant chemotherapy with standard anthracycline and taxane (search dates:

1 January 2004 to 30 January 2022). A meta-analysis using individual patient data from included RCTs found that carboplatin-based neoadjuvant/adjuvant chemotherapy was associated with significant improvements in DFS and OS in people with triple-negative non-metastatic breast cancer.

Saleh et al. 2021 included 9 RCTs and 5 retrospective studies (n=3,518) assessing platinum-based agents plus anthracycline and taxane-based chemotherapy compared with anthracycline and taxane-based chemotherapy alone in the neoadjuvant or adjuvant setting in people with early-stage triple-negative breast cancer (search dates: to 1 July 2021). A meta-analysis found that platinum-based neoadjuvant chemotherapy significantly improved DFS, but not OS.

BRCA germ line mutation

A systematic review assessed the relationship between BRCA1/2 (and homologous recombination deficiency) in the prediction of pCR rates of patients with triple-negative breast cancer treated with platinum-based neoadjuvant chemotherapy (Chai et al. 2022). Thirteen trials with 1,266 patients with triple-negative breast cancer and BRCA or HRD status were included (search dates: January 2000 to September 2021). A meta-analysis of data from 12 trials reporting on BRCA status, found that there was no significant difference in achieving pCR with platinum-based neoadjuvant chemotherapy between patients with BRCA1/2 mutation and BRCA wildtype patients.

Studies that do not impact recommendations

Two systematic reviews evaluated pCR rates in people with triple-negative non-metastatic breast cancer receiving platinum-based neoadjuvant chemotherapy (anthracycline ± taxane) compared with neoadjuvant chemotherapy alone (Pathak et al. 2022 and Li et al. 2020). In Pathak et al. 2022 a meta-analysis found a significant improvement in pCR in the carboplatin-based neoadjuvant chemotherapy compared with standard anthracycline taxane. Li et al. 2020 included 8 RCTs (n=1,345; search dates: to 2 February 2020). A meta-analysis found a significant improvement in pCR from platinum-based neoadjuvant chemotherapy compared with neoadjuvant therapy based on anthracyclines, cyclophosphamide, taxanes, and fluorouracil.

Three systematic reviews reported on treatment-related morbidity (Pathak et al. 2022, Saleh et al. 2021 and Li et al. 2020); with all reporting a significant increase in thrombocytopaenia in the platinum-based neoadjuvant chemotherapy groups compared with neoadjuvant chemotherapy alone. Pathak et al. 2022 also reported that anaemia was higher in the carboplatin compared with anthracycline and taxane arm; and Saleh et al. 2021 reported a significant increase in all-grade neuropathy, but non-significant increases in neutropenia and grade 3–4 neuropathy associated with platinum-based neoadjuvant/adjuvant chemotherapy, although they noted that the reporting of toxicity in studies was 'suboptimal'.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No intelligence was identified.

Impact statement

New evidence is likely to change guideline recommendations.

The new evidence is consistent with the content of recommendation 1.11.4 to consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline for people with triple-negative invasive breast cancer as it supports previous findings that, compared with anthracycline ± taxane-based neoadjuvant chemotherapy, platinum-containing neoadjuvant chemotherapy regimens improve pCR rate, but are also associated with an increase in adverse events, in particular thrombocytopenia.

The literature search for the NICE guideline NG101 review question 'do people with triple-negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?' was up to 28 September 2017 (see evidence review J: neoadjuvant treatment). For evidence review J, there was low-quality evidence from 1 RCT (N=91) of no clinically important effect (no statistically significant difference) of addition of platinum to anthracycline ± taxane-based neoadjuvant chemotherapy on OS or relapse-free survival at 5 years for people with triple-negative invasive breast cancer. The new evidence from 2 systematic reviews indicates that the addition of platinum to anthracycline ± taxane-based neoadjuvant chemotherapy is associated with a significant increase in DFS, and possibly OS, at least for carboplatin-based neoadjuvant chemotherapy, in people with invasive triple-negative cancer. Of particular interest is the systematic review by Pathak et al. 2022 which included only RCT data published to 30 January 2022. A check of the full text for included RCTs revealed that the RCT on which the evidence statement for evidence review J was made on OS and DFS was included in Pathak et al. 2022 (Zhang et al. 2016), plus 5 new RCTs reporting on survival outcomes (2 additional RCTs were on adjuvant chemotherapy). Currently Table 6 in NICE guideline NG101 on the 'benefits and risks of adding a platinum to anthracycline-containing neoadjuvant chemotherapy for triple-negative invasive breast cancer' says that there is 'no increase in overall survival with platinum-based chemotherapy', however new evidence indicates that there may be increases in DFS and/or OS from platinum-based neoadjuvant chemotherapy. It is therefore proposed that evidence on survival outcomes is considered in an update and that this area is monitored for publication of ongoing studies.

Evidence review J reported that no evidence was available for the BRCA germ line mutation subgroup, however the systematic review by Chai et al. 2022 indicates that there is now available trial data for this subgroup, some of which comes from RCTs. An update should therefore also include a check for new evidence on the relationship between BRCA status in people with triple-negative and pCR rates with platinum-based neoadjuvant chemotherapy compared with neoadjuvant chemotherapy alone. The evidence on homologous

recombination deficiency has not been reported in this surveillance review as this was not considered within evidence review J.

Systemic disease modifying therapy – endocrine therapy

This section includes recommendations on:

- endocrine therapy for advanced breast cancer (CG81-1.3.1, and 1.3.4 and 1.3.7)
- adjuvant endocrine therapy for invasive breast cancer (NG101-1.7.1 to 1.7.3)
- ovarian function suppression (CG81-1.3.5 to 1.3.6 and NG101-1.7.4 to 1.7.5)
- extended endocrine therapy for early and locally advanced breast cancer (NG101-1.7.6 to 1.7.9)
- ductal carcinoma in situ (DCIS) (NG101-1.7.10 to 1.7.12): No relevant evidence or intelligence was identified in the 2022 surveillance review for the evidence review question 'what is the role of chemoprevention in women following initial treatment for DCIS?'
- neoadjuvant endocrine therapy (NG101-1.11.6 to 1.11.8): No relevant evidence or intelligence was identified in the 2022 surveillance review for the NICE guideline NG101 review question 'Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?' nor the recommendations for research on the safety of neoadjuvant endocrine therapy in premenopausal women and postmenopausal women with early breast cancer.

Endocrine therapy for advanced breast cancer

NICE guideline CG81 recommendations:

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

Surveillance decision

Recommendations in this area should be updated to be in line with relevant NICE technology appraisals.

Previous surveillance

Previous surveillance looked for new evidence regarding systemic disease modifying therapy in advanced breast cancer. In the 2012 surveillance, new evidence was identified looking at fulvestrant for the treatment of advanced breast cancer. However the use of fulvestrant is covered in NICE technology appraisal TA239, and so evidence did not change guideline recommendations. Further evidence regarding fulvestrant was found in the 2015 surveillance, but did not impact on recommendations. In 2018 surveillance, new evidence was found that was in line with current recommendations.

The 2018 surveillance review identified an RCT which suggested benefit of endocrine therapy modulation with ribociclib. This is covered by technology appraisal TA496. Topic experts highlighted populations where endocrine therapy is not offered however the review concluded that this was covered in the breast cancer pathway. Developments in chemotherapy was raised by topic experts, however it was concluded that this was already covered by NICE technology appraisals.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

There are 4 NICE technology appraisals related to endocrine therapy plus cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors:

- palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (NICE technology appraisal TA836)
- alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (NICE technology appraisal TA816)
- abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (NICE technology appraisal TA725)

- ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (NICE technology appraisal TA687)
- ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (NICE technology appraisal TA496).

Nineteen articles were identified that assessed the efficacy of endocrine therapy plus cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. This surveillance information will be shared with the CHTE team at NICE.

Systemic anticancer therapies, including endocrine agents, alone or in combination with chemotherapeutic or biological agents were also raised by topic experts as an area of NICE guideline CG81 that was in need of an update, in particular the use of CDK4/6 inhibitors in combination with endocrine therapy.

NICE guideline CG81 also has a recommendation for research regarding clinical trials for endocrine therapy for postmenopausal women with ER-positive tumours who progress on treatment with an aromatase inhibitor.

The health inequalities briefing identified information from an All-Party Parliamentary Group (2018) which identified geographical variations in spending on hormone therapies to prevent cancer recurrence.

Impact statement

New evidence is likely to change guideline recommendations.

A large volume of evidence was identified relating to 4 NICE technology appraisals. These technology appraisals concern the use of CDK4/6 inhibitors with endocrine therapy, either fulvestrant or an aromatase inhibitor. This area was also raised by topic experts when asked to identify areas of the guideline in need of an update. Current recommendations in NICE guideline CG81 state that for postmenopausal women an aromatase inhibitor should be offered, for pre- and peri-menopausal women tamoxifen and/or ovarian function suppression should be offered, and for men tamoxifen should be offered. The inclusion into NICE guideline CG81 of NICE technology appraisal TA496, may lead to post- menopausal women being offered ribociclib and an aromatase inhibitor as their first-line treatment.

No specific evidence was found at this review to address research recommendation 2 regarding postmenopausal women with ER-positive tumours who progress on aromatase inhibitors, as such this research recommendation should be retained.

Adjuvant endocrine therapy for invasive breast cancer

NICE guideline NG101 recommendations:

- 1.7.1 Treat people with invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. **[2009]**
- 1.7.2 Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer. **[2009, amended 2018]**
- 1.7.3 Offer an aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated. Risk can be estimated using a range of standardised tools and clinical expertise. (Please refer to the summary of product characteristics for individual aromatase inhibitors because there are differences in their licensed indications.) **[2009, amended 2018]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

Previous surveillance reviews assessed new evidence for the review question 'what are the indications for hormonal treatments for the adjuvant treatment of early oestrogen-positive breast cancer?' New evidence was identified in the 2012 that reported anastrozole was cost effective in postmenopausal women with hormone receptor-positive breast cancer compared with tamoxifen. This was in line with the recommendations. The 2015 surveillance review identified evidence which indicated that longer duration of treatment with endocrine treatments, specifically tamoxifen, is associated with better outcomes in women with early breast cancer. An update on the use of tamoxifen and the populations who most benefit from tamoxifen, for example by menopausal status was also recommended.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

We received feedback from a topic expert and patient group concerning enhanced endocrine treatment with adjuvant abemaciclib.

The topic expert referenced the MONARCH-E trial which assessed the efficacy and safety outcomes of adjuvant treatment with abemaciclib plus endocrine therapy compared with endocrine therapy alone in patients with hormone receptor-positive, HER2-negative (now known as ERBB2-negative), high-risk early breast cancer (Martin et al. 2022). Patients received standard endocrine therapy for at least 5 years with or without abemaciclib (150 mg, twice daily) for 2 years (treatment period) or until criteria were met for discontinuation. At follow-up (median of 19 months; n=5,637), treatment with adjuvant abemaciclib plus endocrine therapy resulted in a significant improvement in invasive DFS and distant relapse-free survival

The patient group said recommendations should reflect the content of abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (NICE technology appraisal TA810). The evidence for abemaciclib with endocrine therapy for this technology appraisal came from the MONARCH-E trial.

System intelligence identified the PALbociclib CoLlaborative Adjuvant Study (PALLAS) as relevant. The results of this RCT are reported by Gnant et al. 2022: 5,796 patients with hormone receptor-positive, HER2-negative early breast cancer received either 2 years of palbociclib with adjuvant endocrine therapy or adjuvant endocrine therapy alone (for at least 5 years). There was no difference between the groups for invasive DFS at follow-up (median of 31 months), nor for any secondary time-to-event end points (invasive breast cancer-free survival, distant recurrence-free survival, locoregional cancer-free survival, and OS).

There is a NICE technology appraisal awaiting development on palbociclib for treating high-risk early breast cancer after neoadjuvant chemotherapy (GID-TA10723).

Impact statement

New evidence is unlikely to change guideline recommendations

As abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node positive early breast cancer at high risk of recurrence is already recommended in NICE technology appraisal TA810, this will be presented alongside relevant recommendations from NICE clinical guideline NG101 as part of the guideline on breast cancer, which is being designed to reflect the treatment pathway. The findings of the PALLAS trial on palbociclib with adjuvant endocrine therapy do not impact on current recommendations as they did not find a survival benefit from this combination over adjuvant endocrine therapy alone in hormone receptor-positive, HER2-negative early breast cancer; and, once published, NICE technology appraisal GID-TA10723 will be linked to this recommendation section in the guideline.

Ovarian function suppression

NICE guideline NG101 recommendations:

- 1.7.4 Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer. **[2018]**
- 1.7.5 Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER-positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy. **[2018]**

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

Recommendations in this section should be updated to consider ovarian function suppression with aromatase inhibitors in premenopausal women with hormone receptor-positive advanced breast cancer; and clarification should be made in recommendations for premenopausal women with ER-positive invasive breast cancer as to whether either tamoxifen or aromatase inhibitors are a suitable endocrine therapy to combine with ovarian function suppression.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

No new evidence on the effectiveness of ovarian suppression in addition to endocrine therapy in premenopausal or perimenopausal women with oestrogen-positive advanced breast cancer was identified in the 2012 or 2018 surveillance reviews for NICE guideline CG81.

2023 surveillance

Studies that impact recommendations

A NMA compared ovarian function suppression with tamoxifen or aromatase inhibitors, against tamoxifen alone, in premenopausal women with hormone receptor-positive breast cancer for survival outcomes (Jiang et al. 2021). Thirty-two articles (study design=NR; n=37,224) were included (search dates: January 1980 to November 2020). NMA found that ovarian function suppression with tamoxifen significantly improved both 5-year DFS and OS when compared with tamoxifen monotherapy. Ovarian function suppression with an aromatase inhibitor also significantly improved 5-year DFS when compared to tamoxifen monotherapy, however 5-year OS was not significantly improved. When subgroup analyses

were conducted, it was found that improvements in DFS, or in OS were seen in patients with stage I to III, but not in patients with stage I to II breast cancer.

An individual patient data meta-analysis compared ovarian function suppression with tamoxifen, against ovarian function suppression with aromatase inhibitors (anastrozole, exemestane, or letrozole) in premenopausal women with early-stage oestrogen receptor-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group 2022). Primary outcomes were breast cancer recurrence, breast cancer mortality, death without recurrence, and all-cause mortality. Individual patient data was collected from 4 randomised trials (n=7,030; enrolment dates: June 17 1999 to August 4 2015; median follow-up was 8 years). The rate of breast cancer recurrence was significantly reduced for women taking an aromatase inhibitor compared with tamoxifen, with the main benefit being seen between years 0 – 4, with either no further benefit or a loss of benefit from year 5 onwards. Rate of distant recurrence was also significantly reduced in women taking an aromatase inhibitor compared with tamoxifen. There were no significant differences observed in breast cancer mortality, death without recurrence, or all-cause mortality.

A meta-analysis compared ovarian function suppression with tamoxifen, against ovarian function suppression with aromatase inhibitors in premenopausal women with early-stage hormone receptor-positive breast cancer on survival outcomes (Meng et al. 2020). Three RCTs (n=7,203) were included (search dates: to May 2019). No significant differences were seen in either DFS or OS between the groups.

Studies that do not impact recommendations

A Cochrane review compared the addition of ovarian function suppression to another treatment (including chemotherapy and endocrine therapy with tamoxifen), or to no further adjuvant treatment in premenopausal women with hormone receptor-positive early breast cancer (Bui et al 2020). 15 randomised trials (n=11,538) were included, with 6 RCTs (n=NR) comparing ovarian function suppression plus tamoxifen with tamoxifen alone (search dates: to 26 September 2019). There was high-certainty evidence that the addition of ovarian function suppression to treatment resulted in a reduction in mortality. This effect was seen when the comparator was observation, tamoxifen alone or tamoxifen and chemotherapy. It was not seen when treatment was chemotherapy alone. The addition of ovarian function suppression also resulted in a significant increase in DFS. This effect was seen for all treatment groups, but was non-significant when ovarian function suppression was added to chemotherapy alone.

A meta-analysis compared ovarian function suppression with tamoxifen against tamoxifen alone in premenopausal women with breast cancer (type/stage: NR) on survival outcomes (Azim et al. 2020). Five clinical trials (n=7,557) were included (search dates: NR). Meta-analysis found that adding ovarian function suppression to tamoxifen significantly increased both DFS and OS, when compared to tamoxifen alone. The benefits were primarily seen in women under the age of 40, and who had also received adjuvant chemotherapy. The use of ovarian function suppression significantly increased the incidence of musculoskeletal symptoms and hot flushes.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

The health inequalities briefing reported that the All-Party Parliamentary Group (2018) identified geographical variations in spending on primary care prescribing for breast cancer, hormone therapies to prevent cancer recurrence and whether people were informed about treatment implications on fertility.

A topic expert said that data from the Suppression of Ovarian Function Trial (SOFT) is now available. Data from this RCT was included in the individual patient data meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group 2022 (see above). However, the topic expert noted that the results of SOFT suggest a 'broader population of premenopausal patients benefit from ovarian suppression', i.e. not just those who have oestrogen-positive invasive breast cancer as the trial included oestrogen receptor and/or progesterone receptor positive-breast cancer. The 2 publications that post-date the search period for evidence review D (28 September 2017) reporting on data from SOFT report results overall for hormone receptor-positive breast cancer, not separately for oestrogen receptor and progesterone receptor positive-breast cancer (Francis et al. 2018 and Pagani et al. 2020).

We received an external enquiry requesting that we consider naming leuprorelin acetate (a luteinising hormone-releasing hormones) as an ovarian function suppression treatment, however guideline recommendations do not name any ovarian function suppression treatments as these may change and there is an assumption that clinicians will know what these are. Evidence review D included studies assessing the effectiveness of leuprorelin acetate and oophorectomy for ovarian function suppression in addition to endocrine therapy in premenopausal women with oestrogen-positive breast cancer.

System intelligence was received that the recommendations on ovarian function suppression for people with advanced breast cancer are out-of-date.

Impact statement

New evidence is likely to change guideline recommendations.

Currently tamoxifen is recommended as the first-line choice for endocrine therapy for premenopausal women with ER-positive invasive breast cancer (see recommendation 1.7.2). Therefore, an assumption might be made that tamoxifen is the endocrine therapy of choice to combine with ovarian function suppression.

Three studies were identified which are consistent with recommendation 1.7.4 to consider ovarian function suppression in addition to endocrine therapy for premenopausal women with oestrogen receptor-positive invasive breast cancer. The Cochrane review, and a meta-analysis (Azim et al. 2020), found that ovarian function suppression plus tamoxifen resulted in

reduced mortality and increased DFS. A NMA (Jiang et al. 2021) found that ovarian function suppression with either tamoxifen or an aromatase inhibitor has beneficial outcomes, with ovarian function suppression plus tamoxifen showing slightly better results. While the recommendation does not name tamoxifen as the endocrine therapy of choice, the rationale and impact section on ovarian function suppression only discusses tamoxifen, as only evidence on tamoxifen was identified.

There is however also new evidence that ovarian function suppression with an aromatase inhibitor may result in better outcomes for disease recurrence (local and distant) compared with ovarian function suppression plus tamoxifen in premenopausal women with hormone receptor-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group 2022). It should be noted that this individual patient data meta-analysis is only indirectly relevant to the review question 'What is the effectiveness of ovarian suppression in addition to endocrine therapy in premenopausal women with oestrogen-positive breast cancer?' as the included studies compared the efficacy of ovarian function suppression with different endocrine therapy regimes, which differs from the original inclusion criteria in evidence review D: endocrine therapy for invasive disease, which included studies comparing ovarian function suppression plus endocrine therapy with endocrine therapy alone. While this study, and the meta-analysis reported in Meng et al. 2020 found no differences in survival outcomes between ovarian function suppression plus aromatase inhibitor compared with ovarian function suppression plus tamoxifen, the NMA reported by Jiang et al. 2021 did find that, compared with tamoxifen monotherapy, ovarian function suppression with an aromatase inhibitor improves 5-year DFS (but not 5-year OS). The committee discussion in evidence review D says that DFS, along with treatment-related morbidity and HRQoL, were critical outcomes and prioritised over OS 'due to the significant side-effect profile associated with ovarian suppression, including menopausal symptoms and the fact that conception is not possible or not advised for the duration of treatment. This meant that the DFS benefits would need to be balanced against the side effects. Overall survival, local recurrence rate, compliance with treatment, and treatment-related mortality were selected as important outcomes'. Given the new evidence on ovarian function suppression with an aromatase inhibitor in premenopausal women with hormone receptor-positive breast cancer it is therefore proposed that this is an area for update.

Evidence on the effectiveness of ovarian suppression in addition to endocrine therapy in premenopausal women with breast cancer other than oestrogen-positive breast cancer was not considered as this was not part of the original review question. There are a small group of people with oestrogen receptor-negative but progesterone receptor positive-breast cancer where benefits from endocrine therapies are less certain. If sufficient evidence is available for this population, this may be an area that the guideline committee could consider in an update.

While no new systematic review evidence was identified on ovarian function suppression with endocrine therapy in premenopausal or perimenopausal women with advanced breast cancer, as system intelligence indicates current recommendations for this population are out-of-date it is proposed that the update also considers whether there is any relevant RCT evidence for this population that can inform recommendations.

Any update should also consider how recommendations are worded to narrow inequalities in access to services; and whether recommendations can be developed that support primary care in decisions around when to stop endocrine therapy and manage adverse effects.

Extended endocrine therapy

NICE guideline NG101 recommendations:

- 1.7.6 Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Medium or high risk may include people who have lymph node-positive breast cancer, with tumours that are T2 or greater and higher grade. [2018]
- 1.7.7 Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at low risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

  Low risk may include people with lymph node-negative breast cancer, with smaller or lower-grade tumours. [2018]
- 1.7.8 Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer. [2018]
- 1.7.9 Discuss the benefits and risks of extended endocrine therapy with women. Topics to discuss include those in table 2. [2018]1.1.7 Do not use bone scintigraphy to monitor the response of bone metastases to treatment. **[2009]**

And see Table 2 Effects of extended endocrine therapy

Surveillance decision

Recommendations in this section should not be updated at this time; evidence will be monitored.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

System intelligence identified an upcoming meta-analysis on extended aromatase inhibitors, results of which will be assessed for impact on publication (results reported in a conference abstract (Gray and Early Breast Cancer Trialists' Collaborative Group 2019), awaiting full publication).

The external reference group reported that people with breast cancer are taking endocrine therapy for many years and that this is often managed within primary care. They said that general practitioners don't know when endocrine treatment should be stopped or how to appropriately manage side effects. Breast cancer specialists reported spending a lot of time supporting queries from GPs.

Impact statement

New evidence is unlikely to change guideline recommendations.

No relevant evidence was identified in the 2022 surveillance review for the review question 'What is the optimal duration of adjuvant endocrine therapy for people with oestrogen receptor-positive breast cancer?' We are aware that there is a need to clarify under what circumstances endocrine treatments can be stopped and we await the publication of further research in this area to inform an update in this area.

Ductal carcinoma in situ (DCIS)

NICE guideline NG101 recommendations:

- 1.7.10 Offer endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is recommended but not received. **[2018]**
- 1.7.11 Consider endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is not recommended. **[2018]**
- 1.7.12 Discuss the benefits and risks of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS. Topics to discuss include those in table 3. **[2018]**

And see Table 3 Effects of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

This was an area updated following the 2015 surveillance review for NICE guideline NG101.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A patient group referenced Early Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2019) which recommends that 'in patients treated conservatively for ER-positive DCIS, both tamoxifen and aromatase inhibitors decrease the risk of invasive and non-invasive recurrences and reduce the incidence of second primary (contralateral) breast cancer, albeit without an effect on OS'. The references provided to support this recommendation all pre-date the search period of up to 9 March 2017 in evidence review D for the review question 'what is the role of chemoprevention in women following initial treatment for DCIS?'

The rationale and impact section on endocrine therapy for DCIS says there was no evidence available for aromatase inhibitors … is there now evidence on AI? RQ: "What is the role of chemoprevention in women following initial treatment for DCIS?"

Impact statement

New evidence is unlikely to change guideline recommendations.

A patient group highlighted guidelines from the ESMO which recommends both tamoxifen and aromatase inhibitors used after conservative local treatment of DCIS to prevent local recurrence and to decrease the risk of development of a second primary breast cancer. While this differs from the information in NICE guideline NG101 Table 3, which recommends either tamoxifen or an aromatase inhibitor for 5 years after breast-conserving surgery for women with ER-positive DCIS, the evidence on which the ESMO recommendations pre-dates the evidence review searches for NICE guideline NG101 and is therefore not considered as new evidence. The rationale and impact section on endocrine therapy for DCIS says there was no evidence available for aromatase inhibitors that met inclusion criteria.

Systemic disease modifying therapy – biological therapy

This section includes recommendations on:

- biological therapy for advanced breast cancer (CG81-1.3.12)
- biological therapy for early and locally advanced breast cancer (NG101-1.8.4 to 1.8.8)

Biological therapy for advanced breast cancer

NICE guideline CG81 recommendations:

- 1.3.12 For patients who are receiving treatment with trastuzumab 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. (Recommendations on the use of trastuzumab are covered by NICE's technology appraisal guidance on the use of trastuzumab for the treatment of advanced breast cancer). **[2009]**

Surveillance decision

Previous surveillance

No evidence was identified in the 2018 surveillance review for NICE guideline CG81 for this topic area. The previous surveillance review identified several treatment options, however many were single studies, concluding that further research was required. Guidance for the treatment options identified is largely covered by the following technology appraisals: TA257, TA34, TA263. TA214, TA421, TA458. A stakeholder raised that this recommendation be changed to mirror clinical practice, as many oncologists continue with treatment at the point of disease progression however the 2018 review found reiterated that the decision to discontinue use of trastuzumab was based on evidence that it doesn't not cross the blood-brain barrier and is therefore not effective for metastatic disease treatment.

2023 surveillance

Studies that impact recommendations

A systematic review evaluated anti-HER2 antibody treatment regimes, for women with HER2 positive metastatic breast cancer, on OS and progression free survival (Chen et al. 2021). In total 28 trials (study type: NR; n=10,928) were included (search dates: January 1999 - November 2017). The study did not report different results for different anti-HER2 antibody treatments, but found that when an anti-HER2 antibody was used within a treatment arm, there was increased OS and progression free survival, and that OS was increased by a greater degree than progression free survival.

A systematic review and meta-analysis evaluated dual anti-HER2 antibody treatment regimes, for women with HER2 positive metastatic breast cancer on OS and rate of

intracranial metastatic disease (Erickson et al. 2021). In total 19 RCTs (n=32,572) were included (search dates: to 25th March 2020). They found that dual HER2-targeted therapy was associated with improved OS and PFS compared to single HER2-targeted therapy, with no change in the rate of intracranial metastatic disease.

A systematic review and Bayesian NMA assessed the efficacy of second-line treatments for women with HER2 positive breast cancer after trastuzumab based treatment on survival benefits (Chen et al. 2021). In total 12 RCTS (n=4022) were included (search dates: NR). For OS trastuzumab emtansine + atezolizumab, pertuzumab + trastuzumab + capecitabine, and trastuzumab emtansine had similar effectiveness, with capecitabine or neratinib alone providing the least benefit.

A systematic review and NMA considered the clinical effectiveness and safety of HER-2 targeted treatment regimes following previous treatment with trastuzumab and a taxane in women with unresectable or metastatic HER2 positive breast cancer (Paracha et al. 2020). In total 7 RCTS (n=NR) were included (search dates: January 1998 – January 2018). Progression free survival and OS benefits were both highest with trastuzumab emtansine, and trastuzumab emtansine ranked highest for all efficacy outcomes. Additionally, discontinuation due to adverse events was less likely with trastuzumab emtansine than other treatment regimes.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

There are 2 NICE technology appraisals related to the immune checkpoint inhibitor drugs: for Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer (NICE technology appraisal TA639); and for Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer (NICE technology appraisal TA801). During our literature searches, 6 articles were identified that assessed the efficacy of immune checkpoint inhibitors, plus chemotherapy, in women with triple-negative breast cancer.

Two articles were found that related to the use of bevacizumab, which relate to 2 NICE technology appraisals: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (NICE technology appraisal TA214); and for Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (NICE technology appraisal TA263).

One article was found that related to the use of tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer, as covered in tucatinib with trastuzumab

and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies (NICE technology appraisal TA786).

One article was found that related to the use of trastuzumab emtansine, as covered in Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (NICE technology appraisal TA458).

Topic experts highlighted the FeDeriCa trial (Tan et al. 2020) which looks at the efficacy of pertuzumab and trastuzumab subcutaneous injection as opposed to intravenous infusion, and found that subcutaneous injection was non-inferior, and may be more tolerable for patients. This study relates to pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (NICE technology appraisal 509).

This surveillance information will be shared with the CHTE team at NICE.

Two recommendations for research are included in NICE guideline CG81. These relate to the continued use of trastuzumab in patients with progressive metastatic disease which should be investigated as part of an RCT, and whether patients who have adjuvant trastuzumab should be offered further biological response modifiers.

When topic experts were asked about the areas of NICE guideline CG81 that needed an update, multiple individuals highlighted the number of biological therapeutic agents, beyond trastuzumab, which are now available on the NHS, and which NICE has technology appraisals specific to. They highlighted the need for the technology appraisal guidance to be integrated, and the recommendations in this area to be updated.

Impact statement

New evidence is likely to change guideline recommendations.

New evidence was identified regarding anti-HER2 antibody treatment regimes, and second-line therapies, following trastuzumab based treatments. Currently NICE guideline CG81 only has one recommendation about biological therapy, stating that treatment with trastuzumab should be discontinued following disease progression outside of the central nervous system. Since this recommendation was written in 2009, there has been an increase in the number of available biological therapies on the market. This gap in the guideline was highlighted by topic experts who were asked about areas in which an update may be necessary. There is emerging evidence assessing the efficacy of different treatment regimes, beyond trastuzumab, which may impact on recommendations in NICE guideline CG81. This may also partially fulfil research recommendation 4 and 5 above, as it provides evidence for the use of other therapies either following or in conjunction with trastuzumab.

Evidence was also identified that related to a number of technology appraisals which detail the conditions in which different biological therapies should be offered.

Biological therapy for early and locally advanced breast cancer

NICE guideline NG101 recommendations:

- 1.8.4 Offer adjuvant trastuzumab for people with T1c and above HER2-positive invasive breast cancer, given at 3-week intervals for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate. [2009, amended 2018]
- 1.8.5 Consider adjuvant trastuzumab for people with T1a/T1b HER2-positive invasive breast cancer, taking into account any comorbidities, prognostic features and possible toxicity of chemotherapy. [2018]
- 1.8.6 Assess cardiac function before starting treatment with trastuzumab. [2009]
- 1.8.7 Use trastuzumab with caution in people with HER2 positive invasive breast cancer who have any of the following:
  - a baseline left ventricular ejection fraction (LVEF) of 55% or less
  - a history of, or current, congestive heart failure
  - a history of myocardial infarction
  - angina pectoris needing medication
  - cardiomyopathy
  - cardiac arrhythmias needing medical treatment
  - clinically significant valvular heart disease
  - haemodynamic effective pericardial effusion
  - poorly controlled hypertension. [2009, amended 2018]
- 1.8.8 Repeat cardiac function assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50%, suspend trastuzumab treatment. Restart trastuzumab only after reassessing cardiac function and discussing the possible benefits and risks. Cardiac function assessments should also be repeated every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. [2009, amended 2018]

Surveillance decision

Recommendations in this section should not be updated, but we are monitoring the area for research on duration of trastuzumab treatment.

Previous surveillance

A 2020 exceptional surveillance assessed impact of the PERSEPHONE trial (HTA 06/303/98; see Earl et al. 2019). The PERSEPHONE trial (n=4,089) compared 12 months (standard treatment length) with 6 months of adjuvant trastuzumab in early breast cancer. The Lancet publication referenced several other studies comparing shorter and longer treatment durations; therefore a focused search was performed for RCTs and systematic reviews **on** adjuvant trastuzumab in adults with early or locally advanced HER2-positive breast cancer, comparing trastuzumab treatment over any designated time period with any shorter period of

treatment for RCTs published from 1 July 2008 to 30 November 2019 and systematic reviews published in 2019. Two systematic reviews and 12 publications originating from 9 individual RCTs were included.

Among the new evidence identified by surveillance, 2 meta-analyses suggested that DFS was improved with the standard 12 months of trastuzumab compared to shorter regimens. New evidence from RCTs for non-inferiority of shorter regimens was mixed, in particular there was disagreement between 2 large similarly designed trials. Most studies were unable to demonstrate non-inferiority. Heterogeneity of individual RCTs (such as varying lengths of the short trastuzumab regimen, various accompanying chemotherapy regimens, and different definitions of non-inferiority) also makes it difficult to make any conclusions based on this evidence. A subgroup analysis of an RCT did find that in people at very low risk of metastasis, 6 months of trastuzumab appeared to be similarly effective as 12 months; but this analysis was not prospectively planned, which limits any firm conclusions. An expert noted that individual patient level meta-analysis and longer follow-up is ideally needed to help draw clearer conclusions, therefore based on the survival data it was concluded that there was no impact on the guideline.

Safety data from meta-analyses and RCTs consistently show that shorter trastuzumab regimens are less cardiotoxic, and there is some limited evidence that the lowest risk patients may have similar survival outcomes with shorter regimens. This suggests that there may be subgroups (for example, people with cardiac disease, or at lower risk of recurrence) for whom shorter trastuzumab regimens may be appropriate. Topic experts also raised this point. However, the studies were not set up to prospectively examine these issues, and further research specifically looking at these areas is needed to confirm findings before an impact on the guideline can be considered.

2023 surveillance

Studies that impact recommendations

Not applicable (see intelligence gathering below).

Studies that do not impact recommendations

Not applicable.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

Not applicable.

Intelligence gathering

Following publication of the exceptional surveillance review we were made aware of an ongoing patient-level data meta-analysis exploring the efficacy of trastuzumab for 1 year versus less than 1 year being undertaken by the Early Breast Cancer Trialists Collaborative Group. As we are awaiting publication of this research, systematic review evidence in this

area was not searched for. We have received information that indicates that the work will not be published until November 2023 at the earliest.

System intelligence was received that indicates duration of trastuzumab treatment remains an area of clinical uncertainty and that there may therefore be a need to consider RCT evidence now in relation to the duration trastuzumab (i.e. an update).

A topic expert questioned whether the treatment pathway for people with HER2 breast cancer needs updating with regards to using trastuzumab emtansine in those who do not achieve a pCR following neoadjuvant therapy. A patient group also noted the new treatments recommended in NICE technology appraisals, including trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (NICE technology appraisal TA632) pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer (NICE technology appraisal TA569), neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab (NICE technology appraisal TA612).

The patient group also said the guideline should include Phesgo as an available option for patients as listed in the national Cancer Drugs Fund list (the rationale in the Cancer Drugs Fund for offering this is NICE technology appraisal TA424); and they said there are new treatments which can apply to those with locally advanced breast cancer which should be reflected here, such as the CDK 4/6 inhibitors.

Impact statement

New evidence is unlikely to change guideline recommendations.

Recommendations on trastuzumab for people with HER2-positive invasive breast cancer are based on evidence for the review question 'Which people with T1N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?' and as such other treatments for patients with HER2-positive breast cancer have not been included; however the guideline on breast cancer will be presenting recommendations from all NICE guidance that is relevant to breast cancer care and that reflects the treatment pathway, so all relevant technology appraisals will be presented alongside relevant recommendations from NICE clinical guideline NG101 for the treatment of people with HER2-positive breast cancers.

There are NICE technology appraisal guidelines for CDK4/6 inhibitors, but not for patients with HER2-positive early or locally advanced breast cancers: Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (NICE technology appraisal TA810) and Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (NICE technology appraisal TA495).

New evidence on the duration of trastuzumab treatment was not searched for as we are awaiting the publication of a patient-level data meta-analysis in this area.

Complications

This section includes recommendations on:

- lymphoedema (CG81-1.5.1 to 1.5.7 and NG101-1.12.1 to 1.12.4)
- arm mobility (NG101-1.12.5 to 1.12.8)
- menopausal symptoms (NG101-1.12.9 to 1.12.13)
- cancer-related fatigue (CG81-1.5.8 to 1.5.10)
- uncontrolled local disease (CG81-1.5.11 to 1.5.13)
- adjuvant bisphosphonates (NG101-1.9.1 to 1.9.3) and bone health (NG101-1.9.4 to 1.9.6)
- bone metastasis (CG81-1.5.14 to 1.5.17)
- brain metastasis (CG81-1.5.18 to 1.5.21)

Lymphoedema

NICE guideline NG101 recommendations:

- 1.12.1 Inform people with breast cancer about the risk of developing lymphoedema, and give them relevant written information before treatment with surgery and radiotherapy. **[2009]**
- 1.12.2 Give advice on how to prevent infection that may cause or exacerbate lymphoedema to people who have had treatment for breast cancer. **[2009, amended 2018]**
- 1.12.3 When informing people with breast cancer about the risk of developing lymphoedema, advise them that:
  - they do not need to restrict their physical activity
  - there is no consistent evidence of increased risk of lymphoedema associated with air travel, travel to hot countries, manicures, hot-tub use or sports injuries
  - there is no consistent evidence of increased risk of lymphoedema associated with medical procedures (for example, blood tests, injections, intravenous medicines and blood pressure measurement) on the treated side, and the decision to perform medical procedures using the arm on the treated side should depend on clinical need and the possibility of alternatives. **[2018]**
- 1.12.4 Ensure that people with breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service. **[2009]**

NICE guideline CG81 recommendations:

- 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]

Surveillance decision

Recommendations in this section for both NICE guideline NG101 and CG81 should be updated.

Previous surveillance

For NICE guideline NG101, this was an area updated following the 2015 surveillance review.

For NICE guideline CG81, recommendations 1.5.1 and 1.5.2 were added following the 3-year surveillance review. The 2015/16 evidence update concentrated on oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) on disease recurrence. Other clinical areas were identified including lymphoedema, however it was deemed not to have an impact on the guideline recommendations. The 2018 review found mixed evidence regarding manual lymphatic drainage, and topic experts highlighted potential issues with terminology. The terminology issue was explored with the British Lymphology Society and decided not to update at that time.

2023 surveillance

Studies that impact recommendations

Surveillance strategies plus early intervention

Two systematic reviews assessed the impact of surveillance strategies plus early intervention on chronic breast cancer-related lymphoedema. One systematic review assessed the effect of prospective surveillance with early management for cancer-related lymphoedema programs

on preventing chronic lymphoedema (Rafn et al. 2022). Twenty-three studies (RCTs and observational studies) were included (search date: published up to February 26, 2021). Pooled relative risk (RR; from RCT data) of chronic lymphoedema was calculated. Data from 2 RCTs (n=106) indicated that, compared with usual care, participation in prospective surveillance with early management significantly reduced the risk of chronic breast cancer-related lymphoedema. The rate of chronic breast cancer-related lymphoedema in observational studies was also reported: pooled rate was 4% (95% CI=3 to 6; 15 observational studies; n=3,545) and when restricted to participants with ALND it was 6% (95% CI=4 to 9; 12 studies; n=1,527).

Another systematic review (Whitworth et al. 2022) included 4 RCTs (n=1,203) and 8 'prospective studies' (n=1,704) on prospective surveillance with early intervention. The abstract is limited in its reporting of data and statistics, but does report on an RCT described as having 'the strongest data': the PREVENT trial (Ridner et al. 2022). This found that early detection of lymphoedema with bioimpedance spectroscopy (BIS) plus early intervention (a compression garment applied for 12 h a day over 4 weeks) led to a significant reduction in the rate of chronic breast cancer-related lymphoedema when compared with lymphoedema assessed by tape measurement plus the early intervention.

Vascularised lymph node transfer

A systematic review (Ward et al. 2021) of 31 studies examined vascularised lymph node transfer (VLNT) for the reduction in limb volumes by reconstructing lymphatic flow, with the primary outcomes of upper limb and lower limb volume, and episodes of cellulitis in patients with lymphoedema following cancer treatment. Included studies used lymphoedema specific QoL measurements, volumetric limb and infection rate to determine the circumferential reduction rate (CRR) via meta-analysis. A reduction in cellulitis was seen with VLNT at a rate of 2.1 episodes per year. Upper and lower limb volume was significantly reduced when VLNT was used. Categories used to determine upper and lower limb scores were as follows: upper limb included above elbow pooled CRR=42.7%, (95% CI=36.5-48.8) and below elbow CRR=34.1% (95% CI=33.0 to 35.1). Lower limb included above knee CRR=46.8% (95% CI=43.2 to 50.4) and below knee CRR=54.6% (95% CI=39.0 to 70.2). Greater volume reduction was seen with VLNT flaps from extra abdominal donor sites compared to either intra-abdominal donor sites or synchronous autologous breast reconstruction. VLNT was effective for all primary outcomes in reducing limb volume, however the authors note significant heterogeneity in outcome reporting and state there is currently a lack of standardised reporting procedures.

A systematic review (Winters et al. 2022) of 17 studies aimed to examine the primary outcomes of volume change between arms and QoL in patients with breast cancer-related unilateral lymphoedema following VLNT. A meta-analysis was undertaken on 8 of the included studies, which found an average reduction rate of 40.13% between the healthy and affected arms. QoL was significantly increased in the 5 studies which reported this outcome. Three studies reported on annual infection rates before and after surgery, finding significant decreases in the rate of infection. Compression garment use was discontinued as a result of

VLNT in 27 of 60 patients from 3 studies. The authors, however, note complication rates of 12.1% in donors and 7.3% in recipients.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

Exercise interventions

A systematic review assessed the effect of resistance exercise interventions on breast cancer-related lymphoedema (and upper and lower extremity strength) in breast cancer survivors (Hasenoehrl et al. 2020). Twenty-nine trials (RCTs and uncontrolled trials) were included (search dates: 1966 to 31st January 2020). A meta-analysis was undertaken on data from 6 trials. The meta-analysis reported a significant reduction in lymphoedema after resistance exercise, as measured by BIS.

A systematic review (Rangon et al. 2022) of 14 studies examined the effects of complex physical therapy and multimodal approaches compared to usual care for patients with lymphoedema secondary to breast cancer. Outcomes included pain, total volume and upper limb function. A meta-analysis was completed for 11 studies. For volume reduction a small effect was seen (SMD, -0.18; 95% confidence interval [CI], -0.35 to 0.00) and for pain reduction in the short-term a moderate effect was seen (SMD, -0.61; 95% CI=-1.19 to -0.02), no results are noted in the abstract for physical function of the upper limb.

Manual lymphatic drainage

A systematic review (Thompson et al. 2021) of 17 studies examined the effect of manual lymphatic drainage (MLD) on lymphoedema. Some studies reported positive effects of MLD on QoL, symptom related outcomes and volume reduction however others found no benefit to MLD as part of CDT. Similarly, some studies reported preventative effects of MLD on lymphoedema whereas others did not. The authors note that methodological issues impacted the findings in some studies and as such further investigational studies are required in this area.

A systematic review (Lin et al. 2022) of 11 RCTs, (10 of which were suitable for meta-analysis) was performed to analyse the effectiveness of MLD for patients with breast cancer-related lymphoedema (BCRL). Significant improvements were seen in incidence of lymphoedema and pain intensity (RR=0.58, 95% CI=0.37 to 0.93; P=0.02 and (SMD=-0.72, 95% CI=-1.34 to-0.09; P=0.02 respectively). The effect of MLD on QoL and volumetric changes of lymphoedema was not significant.

A meta-analysis (Qiao et al. 2022) of RCTs (457 patients) examined the effect of MLD on BCRL. MLD was found to reduce upper limb circumference significantly compared to control or no MLD groups, but only when greater than 20 sessions were undertaken. There was no significant effect of MLD on any other reported outcome including lymphoedema volume.

A systematic review (Liang et al. 2020) of 17 RCTs and meta-analysis of 8 RCTs examined the impact of MLD on patients with BCRL. No significant difference in lymphoedema reduction was seen with MLD when compared to control groups (SMD: -0.09, 95% confidence interval (CI): [-0.85 to 0.67]), however in certain patient groups, such as those under the age of 60 with treatment periods of 1 month and improvement may be seen (SMD: -1.77, 95% CI: [-2.23 to -1.31). Four RCTs also found that MLD could not significantly prevent the risk of BCRL. Overall results from the meta-analysis of 12 studies found that MLD did not prevent or improve BCRL.

Laser therapy

A systematic review (Wang et al. 2022) of 7 systematic reviews and 10 RCTs investigated the use of low-level laser therapy (LLLT) in BCRL. Improvements were seen with LLLT when compared with bandage compression, pneumatic compression, placebo laser or no treatment. However, when LLLT was compared to any other type of intervention, no significant improvement was seen. The GRADE and AMSTER 2 analysis found low or very low-quality evidence due to critical weaknesses in the methods used in some studies. The authors state that higher quality data from larger trials is required in this area.

Extracorporeal shockwave therapy

A systematic review (Tsai et al. 2021) of 8 studies and meta-analysis of 4 studies aimed to examine the effect of ESWT with CDT in patients with BCRL for the primary outcomes of arm circumference and volume of lymphoedema. The GRADE appraisal for the studies was very low, however significant improvements may be seen with ESWT for the outcome of volume reduction (MD=-76.44; 95% CI: -93.21 to -59.68; $p < 0.00001$). For the secondary outcomes of shoulder range of motion (MD=7.03; 95% CI: 4.42, 9.64; $p < 0.00001$) and skin thickness (MD=-1.65; 95% CI: -3.27 to -0.02; P=0.05), significant improvements were also seen. The authors state that although there was not enough evidence for ESWT to replace CDT, that the combination of the 2 led to significant improvements in people with breast cancer associated lymphoedema.

Intelligence gathering

For NICE guideline NG101 neither topic experts nor the patient group made comments in relation to the prevention of lymphoedema.

For NICE guideline CG81, topic experts raised the issue of specialist lymphoedema care as an area of concern. An expert highlighted a lack of consistency between NICE guidelines CG81 and NG101, particularly as there is no reference to specialist care in NICE guideline CG81. A patient group highlighted the need for more detailed information to be given to patients regarding the extent of treatment options for lymphoedema. The patient group also highlighted that further details could be added to clarify recommendations 1.5.5 (state hosiery is for moderate to severe lymphoedema) and 1.5.6 (measurement of compression garments should be done by a specialist lymphoedema practitioner). NICE guideline CG81 has a recommendation for research regarding the assessment of the roll of exercise, aimed to prompt research on the role of arm and shoulder specific exercises for lymphoedema

treatments. This does not appear to have been fully addressed by the current evidence base, and is therefore still relevant to this guideline.

The breast cancer health inequalities briefing reported that as well as treatment-related (number of nodes removed and radiation to axilla) and disease-related risk factors (stage and location of the tumour) for developing lymphoedema, there are also patient-related risk factors such as age, obesity, and comorbid conditions (hypertension). While younger women with breast cancer more frequently report impaired arm movement and lymphoedema, objective measurements show that arm function is more affected in older women and that older age is a risk factor. It was also reported that the presence of lymphoedema 'may disrupt returning to work after cancer, and people may need additional support, which could significantly impact people from disadvantaged groups because they are more likely to be in insecure employment and less likely to have sick leave entitlement'. These are considered significant findings as 'for example, more deprived groups have a higher risk of factors such as being overweight and hypertension, and may be more susceptible to developing lymphoedema. Also, people from ethnic minority family backgrounds and deprived groups are likely to present with more advanced stage disease requiring combination treatment, making them more susceptible to developing lymphoedema'.

Impact statement

New evidence is likely to change guideline recommendations.

Studies that included surveillance for BCRL plus early intervention would have been excluded from the evidence review for NICE guideline NG101 on preventing lymphoedema as they include management. By contrast, NICE guideline CG81 has recommendations on managing lymphoedema, but does not make any recommendations concerning surveillance and early intervention. The 2017 evidence review considered the diagnostic accuracy of specific investigations to recognise lymphoedema early in patients with advanced/metastatic breast cancer however no evidence was found at that time and as such no recommendations were made.

Given that lymphoedema is known to result in limited physical function and/or adverse psychological and social effects, means by which lymphoedema can be identified and managed as early as possible, would appear to be of benefit to all people with breast cancer who have undergone axillary intervention. It is therefore proposed that the evidence review question for NICE guideline NG101 is expanded to include management of lymphoedema; and that management of lymphoedema is an area for update in NICE guidelines NG101 and CG81.

For NICE guideline CG81, evidence indicates that specialist lymphoedema care could be explored as an area for update along with the potential to include new treatment options such as VLNT.

The update should consider whether recommendations apply to all people with breast cancer, and whether recommendations on lymphoedema across NICE guideline NG101 and

NICE guideline CG81 can be combined into a set of recommendations on prevention, surveillance, early management and further intervention.

Areas for monitoring of evidence were also identified:

For NICE guideline CG81, laser therapy was assessed in 1 systematic review. This reported improvements from laser therapy compared with compression, placebo laser and no treatment, but no improvement compared with other active treatments. The authors also stated there were critical weaknesses within some study methodologies and as such more work is needed in this area. Therefore, it is unlikely that laser therapy will have any impact on the recommendations in NICE guideline CG81 at this time.

Four systematic reviews reported on MLD for NICE guideline CG81, however results varied from no effect, mixed effects, lower pain to improvements in upper limb circumference, and only having an effect in a very specific subgroup of people. The evidence in this area is inconclusive and is unlikely to impact the guideline recommendations at this time. One systematic review compared extracorporeal shockwave therapy to complex decongestive therapy (CDT), finding significant improvements in skin thickness, shoulder range of mobility and volume reduction. The authors state however that there is currently not enough evidence to replace CDT with extracorporeal shockwave therapy, and as such no impact is anticipated at this time. This is an area not currently covered by CG81 and as such should be monitored.

One systematic review on the management of BCRL using extracorporeal shockwave therapy (EST) with or without CDT found that while the combination of extracorporeal shockwave therapy and CDT could lead to significant improvements in outcomes, there was insufficient evidence to support the use of EST on its own. As there was no comparison of EST plus CDT with CDT alone, there is currently insufficient evidence to consider updating recommendation 1.5.4 in NICE guideline CG81 which advises offering all patients with lymphoedema CDT as the first stage of lymphoedema management.

Findings on exercise interventions are in line with recommendation 1.12.3 in NICE guideline NG101 that physical activity does not have a negative effect on lymphoedema. However, there is some evidence that exercise may decrease BCRL, which would be in contrast to recommendation 1.5.1 in NICE guideline CG81 which says there is ‘no indication that exercise prevents’ BCRL. While the evidence from these systematic reviews is not sufficient to indicate that exercise should be considered as a strategy for preventing or managing BCRL, this is an area that should be monitored. This area is also highlighted by research recommendation 1 which focuses on the need for more evidence on arm and shoulder exercises for people with breast cancer related lymphoedema, as such this research recommendation should be retained.

Arm mobility

NICE guideline NG101 recommendations:

- 1.12.5 All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy. **[2009]**
- 1.12.6 Identify pre-existing shoulder conditions preoperatively in people with breast cancer, as this may inform further decisions on treatment. **[2009]**
- 1.12.7 Give instructions on functional exercises, which should start the day after surgery, to people with breast cancer. This should include relevant written information from a member of the breast or physiotherapy team. **[2009]**
- 1.12.8 Refer people to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment. **[2009]**

Surveillance decision

Not applicable as there is an ongoing update of this recommendation section in NICE guideline NG101.

Previous surveillance

2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) proposed that this is an area for update.

Menopausal symptoms

NICE guideline NG101 recommendations:

- 1.12.9 Stop systemic hormone replacement therapy (HRT) in women who are diagnosed with breast cancer. **[2009]**
- 1.12.10 Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. In exceptional circumstances, offer HRT to women with severe menopausal symptoms and with whom the associated risks have been discussed. **[2009]**

  In July 2018, this was an off-label use of HRT, and HRT is contraindicated in women with a history of breast cancer. See NICE's information on prescribing medicines.
- 1.12.11 Offer women information and counselling about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment. **[2009]**
- 1.12.12 Consider selective serotonin reuptake inhibitor (SSRI) antidepressants for women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not for those taking tamoxifen. For guidance on safe prescribing of antidepressants (such as SSRIs) and managing withdrawal, see NICE's guideline on medicines associated with dependence or withdrawal symptoms. **[2009, amended 2018]**

  In July 2018, this was an off-label use of SSRIs. See NICE's information on prescribing medicines.

- 1.12.13 Do not offer soy (isoflavone), red clover, black cohosh, vitamin E or magnetic devices to treat menopausal symptoms in women with breast cancer. **[2009]**

Surveillance decision

Recommendations in this section should be updated.

Previous surveillance

The 2015 surveillance review did not identify any new evidence in relation to the management of menopausal symptoms.

The 2012 surveillance review found evidence that neither black cohosh nor flax significantly reduce menopausal symptoms. This evidence was not considered as impacting on the content of the 2009 recommendations (see recommendation 1.12.13).

2023 surveillance

Studies that impact recommendations

Acupuncture

Four systematic reviews were identified that assessed the effectiveness of acupuncture as a treatment for menopausal symptoms.

A systematic review assessed the effectiveness of acupuncture on treatment-related symptoms among breast cancer survivors (Li et al. 2021). Twenty-six RCTs were included, of which 20 RCTs (n=1,709) were included in the meta-analysis (search date: through June 2021). The meta-analysis found that compared with waitlist control and usual care groups, acupuncture was associated with significant improvements in hot flash severity (this was not significant when acupuncture was compared with sham acupuncture control groups). There were no serious adverse events reported, but some mild adverse events were reported from acupuncture (11 RCTs), including bruising, pain, swelling, skin infection, hematoma, headache, menstrual bleeding.

Another systematic review assessed the effectiveness of acupuncture on breast cancer-related hot flushes and menopausal symptoms (Chien et al. 2020). Thirteen RCTs (n=943) were included (search date: published up to February 2019). A meta-analysis reported that acupuncture significantly reduced menopausal symptoms at 3 months but had no significant 'long-term maintenance on the frequency or severity of hot flushes' (long-term not defined in abstract). No adverse effects of acupuncture were reported.

A systematic review assessed the effectiveness of non-hormonal treatments (lifestyle changes, mind-body techniques, dietary and/or supplements, Selective serotonin reuptake inhibitors and/or serotonin-norepinephrine reuptake inhibitors, other medications, and acupuncture) on hot flashes in breast cancer survivors (Liu et al. 2020). Sixteen RCTs (n=2,349) were included (search date: published up to May 2018). A pairwise meta-analysis showed that, compared with no treatment, placebo or sham control, non-hormonal treatments overall resulted in a significant reduction in hot flash frequency and hot flash

score. A NMA found that acupuncture was ranked as the optimal non-hormonal therapy for hot flash frequency and hot flash score. A safety analysis found few adverse events associated with acupuncture. Results for other types of non-hormonal treatments on hot flashes were not reported in the abstract. The authors do however report that there was 'a pronounced placebo response' and that overall, the evidence of safety for non-hormonal therapies was insufficient.

Another systematic review assessed the efficacy of acupuncture on hormone therapy-related side effects in breast cancer patients reported in RCTs (n=NR; search date: published through to April 2020; Yuanqing et al. 2020). The authors report that 'pooled results suggested that acupuncture led to moderate improvements in hot flashes' (plus other side effects of fatigue and stiffness). They report on where there were also no significant improvements, including QoL (no other outcomes relevant to menopausal symptoms). The authors also note that there is a lack of adequately powered, multicentre, prospective RCTs on the effects of acupuncture hormone therapy-related side effects in breast cancer patients.

Studies that do not impact recommendations

Hormone replacement therapy (HRT)

A Cochrane review evaluated the effectiveness and safety of tibolone (an HRT) as a treatment for postmenopausal and perimenopausal women (databases searched for relevant RCTs in October 2015) (Formoso et al. 2016). It was reported that in women with a history of breast cancer, tibolone was associated with a significant increase in the risk of breast cancer (based on evidence from 2 RCTs; n=3,165 women; assessed as moderate-quality evidence).

One systematic review reported on the safety of systemic HRT (oestrogen/progestogen combination or tibolone) in survivors of breast cancer (Poggio et al. 2022). Four RCTs (n=4,050) were included (search date: published up to April 20, 2021). A random-effect model calculated the risk of breast cancer recurrence, reported as pooled hazard ratio: HRT was associated with a significant increase in the risk of breast cancer recurrence compared to placebo; and the risk of recurrence was significantly higher in patients with hormone receptor-positive disease, but not in those with hormone receptor-negative tumours (the 95% CI crossed over 1).

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A topic expert highted that management of the menopause associated with treatment and menopausal symptoms should be a focus of surveillance due to high levels of public interest.

There is existing NICE guidance on the menopause: menopause: diagnosis and management (NICE guideline NG23) which has recommendations on managing short-term menopausal symptoms for women with breast cancer (recommendations 1.4.25 and 1.4.26), which align with the content of recommendations in NICE guideline NG101. NICE guideline NG23 is

currently being updated to consider evidence on CBT for the management of menopausal symptoms in women, including those with breast cancer (see history tab for final scope). CBT for menopausal symptoms has therefore not been considered within this surveillance review.

Impact statement

New evidence is likely to change guideline recommendations.

Topic expert feedback indicates that the management of menopausal symptoms in breast cancer patients is a high priority area.

The only evidence indicating that there may be alternative treatment options for menopausal symptoms beyond currently recommended counselling and selective serotonin reuptake inhibitor (SSRI) antidepressants (recommendations 1.12.11 and 1.12.12), is in relation to acupuncture. While the evidence is mixed concerning the effectiveness of acupuncture for managing menopausal symptoms, there is sufficient evidence to indicate that this should be considered as an area for update, especially given that it does not appear to be associated with any major adverse effects. In relation to counselling, there is an ongoing update considering evidence on the effectiveness of CBT in the management of menopausal symptoms in people with breast cancer as part of an update of NICE guideline NG23. It will therefore be important to ensure that the breast cancer guideline links to any new recommendations in NICE guideline NG23 and that there is consistency between the 2 guidelines' content.

The Cochrane review on the effectiveness and safety of tibolone and the systematic review on the safety of systemic HRT, supports current recommendation 1.12.9 to stop systemic HRT in women who are diagnosed with breast cancer and current recommendation 1.12.10 to not routinely offer HRT to women with menopausal symptoms and a history of breast cancer and to only offer HRT in exceptional circumstances to women with severe menopausal symptoms and with whom the associated risks have been discussed.

Cancer-related fatigue

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

The recommendations in this section are unlikely to need updating at this time.

Previous surveillance

The 2015 surveillance review found evidence relating to the effects of exercise, psychosocial, and pharmacological treatments for cancer-related fatigue, which was considered to be in line with the guideline recommendations. The 2018 surveillance review found no new evidence for cancer-related fatigue.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review (Ficarra et al 2022) examined the effect of exercise interventions versus usual care in patients with breast cancer and breast cancer survivors for the outcomes of cardiorespiratory fitness, strength and fatigue. Twenty-two RCT's with a mean exercise frequency of 3 sessions per week and mean duration of 19 weeks found that decline in fitness, strength and fatigue in breast cancer patients could be avoided by using exercise interventions, with resistance training and combined exercise interventions providing the most positive results. The evidence found at this review supports the current guideline recommendations, no impact is anticipated.

A systematic review (Floyd et al 2021) assessed non-pharmacological interventions for post-chemotherapy, breast cancer-related fatigue. Mixed evidence was found regarding the interventions used (cognitive training, complementary therapies and exercise), with no studies covering multi-domain interventions. There was no strong evidence of a beneficial effect of non-pharmacological interventions specifically for post-chemotherapy breast cancer patients across all 83 included studies.

A systematic review evaluated physical exercise versus usual care for people with advanced cancer in palliative care. The outcomes were QoL, fatigue, aerobic fitness, and lower body strength (Toohey et al. 2022). In total 20 RCTs (n=1,840) were included (search dates: All to 14 April 2021). 3 RCTs involved people with breast cancer, which represents 14% of the people included. Meta-analyses were in favour of exercise for QoL SMD 0.27 (95%CI=0.14 to 0.39), fatigue SMD=0.30 (95%CI=0.13 to 0.47), aerobic fitness SMD 0.30 (95%CI=0.12 to 0.49), and lower body strength SMD=0.48 (95%CI=0.12 to 0.84). There was no difference between the arms for grade 2–4 adverse events. No overall effects were observed for pain SMD=0.24 (95%CI=−0.01 to 0.48), depression SMD=0.33 (95%CI=−0.07 to 0.72), and anxiety SMD=0.11 (95%CI=−0.13 to 0.35). Overall median recruitment, retention and adherence rates were 56%, 80% and 69%, respectively.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No information for cancer-related fatigue was raised by topic experts.

Impact statement

New evidence is unlikely to change guideline recommendations.

Evidence found at this surveillance review is consistent with that of the previous reviews in this area. Two studies found that a variety of exercise methods such as resistance training and cardio fitness led to a decline in breast cancer-related fatigue. One study also examined cognitive therapies however no significant effect was seen. The evidence found supports the current guideline recommendations. A third study found that quality of life, cancer-related fatigue, aerobic fitness and lower body strength were improved by physical exercise in patients with advanced cancer receiving palliative care.

Uncontrolled local disease

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

The 2015 surveillance review found a Cochrane review relating to quality of life experienced by those who required wound care, concluding that 6% miltefosine solution applied topically to people with superficial fungating breast lesions who have previously received radiotherapy, surgery, hormonal therapy or chemotherapy for their breast cancer, may slow disease progression.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No topic expert information identified.

A recommendation for research suggests that relevant research organisations should be encouraged to address the topic of uncontrolled local disease and devise appropriate research studies.

Impact statement

New evidence is unlikely to change guideline recommendations.

No new evidence or information has been found in this area since the 2015 surveillance review. With no new evidence identified, the above research recommendation should be retained. As such no impact on the recommendations in this section is anticipated.

Adjuvant bisphosphonates and bone health

Surveillance decision

We will not update recommendations in the section on bisphosphonate therapy which covers the use of adjuvant bisphosphonates and recommendations on bone health.

Previous surveillance

A 2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) recommended the section on bisphosphonate therapy in the NICE guideline on early and locally advanced breast cancer, in relation to the use of adjuvant bisphosphonates in people with early or locally advanced breast cancer should not be updated.

The exceptional surveillance review highlighted that there is no review question for NICE guideline NG101 on bone health, only on adjuvant bisphosphonates. The evidence review on the use of adjuvant bisphosphonates in people with early and locally advanced breast cancer was concerned with the effect of bisphosphonates on breast cancer-specific outcomes. Bone health, treatment-related mortality and HRQoL were identified as important outcomes; however bone health was only included to check whether the new evidence was consistent with existing 2009 recommendations for the use of bisphosphonate treatment for bone loss. As such evidence on adjuvant bisphosphonates and/or bone health in people with early or locally advanced breast cancer has not been considered withing this surveillance review.

NICE internal feedback was received as part of the exceptional surveillance review indicating that the recommendations on bone health should not be included in NICE guideline NG101, and would be more appropriate in a NICE guideline on managing osteoporosis. There is no current NICE clinical guideline on the management of osteoporosis, only NICE guideline CG146 on osteoporosis: assessing the risk of fragility fracture; however this is being updated with an expanded scope that will include treatments to reduce fracture risk, treatment monitoring and review (see osteoporosis: risk assessment, treatment, and fragility fracture prevention (update) in development [GID-NG10216]). This is due to publish January 2025. In the interim, there are several technology appraisals on interventions for prevention and treatment of osteoporosis that could be cross-referenced as part of the breast cancer guideline (see NICE's product page on osteoporosis).

Studies that impact recommendations

Not applicable

Studies that do not impact recommendations

Not applicable

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

Not applicable (see 2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) for details on monitoring of emerging prospective evidence on MAF (a biomarker for bone metastasis) diagnostic testing for predicting outcomes in people with early and locally advanced breast cancer on adjuvant bisphosphonates).

Intelligence gathering

Not applicable.

Impact statement

Not applicable.

Bone metastasis

NICE guideline CG81 recommendations:

- 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 8 Gy 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]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

The 2015 surveillance review found evidence for a number of medications for bone metastases, mainly covering bisphosphonates and denosumab (a rank ligand inhibitor). Both medications had advantages in reducing the risk of skeletal-related events. The 2018 surveillance review found 2 trials, one covering dosing schedules for zoledronic acid for breast cancer bone metastases and one that found no improvement with zoledronic acid when compared to pamidronate for palliative care patients with bone metastases.

It was concluded that the evidence on denosumab had no impact because there is NICE technology appraisal TA265 on denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours which recommends denosumab as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours (other than prostate if): bisphosphonates would otherwise be prescribed and the manufacturer provides denosumab with the discount agreed in the patient access scheme.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A topic expert highlighted that the use of bisphosphonates is currently recommended for patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain, whereas in practice denosumab has been the first-line treatment.

Impact statement

New evidence is unlikely to change guideline recommendations.

No new evidence was identified relating to the prevention of skeletal-related events or reducing pain in patients with bone metastasis, nor on the treatment of bone metastasis for patients with advanced breast cancer. The information from a topic expert, that denosumab has been a first-line treatment in clinical practice for some time is consistent with the recommendation in NICE technology appraisal TA265.

Brain metastasis

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

Recommendations in this section should be checked for consistency against NICE guideline NG99 recommendations on management of confirmed brain metastases.

Previous surveillance

The 2015 surveillance review found evidence on the following areas: safety profile of temozolomide, efficacy safety and tolerability of concurrent cisplatin and radiotherapy, concurrent trastuzumab with whole brain radiotherapy. The 2015 review concluded that the new evidence was heterogenous with all studies stating further research was required and as such no impact was noted at the time. The 2018 surveillance review identified 1 RCT which found prophylactic cranial irradiation did not significantly reduce the incidence of central nervous system metastases in the HER2 positive metastatic breast cancer population.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A systematic review (Garsa et al 2021) compared radiation therapies for brain metastases in patients with various cancer types including breast cancer. Ninety-seven studies were included evaluating whole brain radiotherapy and stereotactic radiosurgery alone or in

combination. OS was not improved with radiation therapy following surgery compared to surgery alone. Data for other outcomes was insufficient for analysis (QoL, functional status, cognitive effects). No significant differences were seen in adverse events.

A systematic review (Koniali et al 2020) of 69 studies investigated the risk factors for breast cancer brain metastases. In HER2 positive patients, the most important risk factors for brain metastases were young age, hormone receptor-negative status, higher presenting stage, nodal involvement and development of liver metastases. The following factors were found to be independent risk factors of breast cancer brain metastases: young age, oestrogen receptor-negative status, HER2 over expression, higher presenting stage, tumour grade and size.

A systematic review (Brown et al 2020) investigated the association between stereotactic radiosurgery for breast cancer brain metastases and cases of leptomeningeal disease. Eight studies covering 2555 patients with breast cancer brain metastases who were treated with stereotactic radiosurgery were included. When compared to other cancer types, breast cancer brain metastases were significantly associated with risk of developing leptomeningeal disease (pooled HR=2.22; 95% CI=1.69 to 2.93; P<0.001). the authors state further work is required to improve outcome certainty, and allow for risk stratification to be included in treatment planning.

A systematic review evaluated stereotactic ablative radiotherapy (SABR) to treat breast cancer oligometastases (no comparator was reported). The outcomes were survival and safety (Viani et al. 2021). In total 3 prospective cohort studies and 7 retrospective cohort studies (n=467) were included (search dates: 1990 to June 2021). Meta-analyses showed that in the 1- and 2-year group, local control rates were 97% (95% CI=95 to 99%), and 90% (95% CI=84–94%), respectively. OS was 93% (95% CI=89 to 96%) at 1 year, 81% (95% CI=72–88%) at 2 years. The rate of any grade 2 or 3 toxicity was 4.1 % (95% CI=0.1 to 5%), and 0.7% (0 to 1%), respectively. SABR was found to be safe and effective for patients with breast cancer brain metastases and was associated with high rates of local disease control.

A systematic review evaluated ablative stereotactic radiotherapy versus control for people with oligometastatic cancer. The outcomes were adverse events, PFS, and OS. (Lehrer et al. 2021). In total 21 prospective cohort studies (n=943) were included. However, people with breast cancer only accounted for 13% of this population (search dates: All to 23 December 2019). Meta-analyses showed that the estimate for acute grade 3 to 5 toxic effect rates under the random-effects models was 1.2% (95% CI=0% to 3.8%, and the estimate for late grade 3 to 5 toxic effects was 1.7% (95% CI=0.2% to 4.6%). The random-effects estimate for 1-year local control was 94.7% (95% CI=88.6% to 98.6%). The estimate for 1-year OS was 85.4% (95% CI=77.1% to 92.0%) and 51.4% (95% CI=42.7% to 60.1%) for 1-year PFS. SABR was found to be relatively safe in this patient group, with acceptable clinical impact on progression free survival and one-year local control.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A topic expert highlighted that this section of the guideline is lacking information on stereotactic radiosurgery for breast cancer brain metastases.

Brain tumours (primary) and brain metastases in over 16s (NICE guideline NG99) has a recommendation section on management of confirmed brain metastases which includes recommendations 1.7.3 to 1.7.8 on stereotactic radiosurgery.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new systematic review evidence does not have an impact on recommendations on brain metastasis in patients with advanced breast cancer. One study identified risk factors for breast cancer brain metastases, such as young age, oestrogen receptor-negative status, HER2 over expression, higher presenting stage, tumour grade and size. One study found the risk of developing leptomeningeal disease was significantly associated with breast cancer brain metastases compared to other cancer types in patients treated with stereotactic radiosurgery. A third study found OS was not improved with radiation therapy following surgery compared to surgery alone. Two further studies found SABR to be relatively safe for use in breast cancer patients with brain metastases, and was associated with high rates of local control, although both studies stated that further work was necessary in this area. System intelligence suggested that SABR is being used for oligometastases outside the brain in patients with breast cancer.

Previous surveillance found mixed results spread over different therapy options for breast cancer brain metastases, however there is now NICE guideline NG99, published in 2018, which has a set of recommendations on when to consider stereotactic radiosurgery for managing confirmed brain metastases, including for patients whose primary tumour was breast cancer. The guideline committee should consider whether NICE guideline CG81 recommendations should be withdrawn and replaced by NICE guideline NG99 recommendation section on the management of confirmed brain metastases, or whether to present the recommendations across the guidelines 'together'.

Follow-up

This section includes recommendations on:

- follow-up imaging (NG101-1.13.1 to 1.13.3)
- clinical follow-up (NG101-1.13.4)
- monitoring disease status (CG81-1.1.7 to 1.1.8)

Follow-up imaging

NICE guideline NG101 recommendations:

- 1.13.1 Offer annual mammography to all people with breast cancer, including DCIS, until they enter the NHS Breast Screening Programme (NHSBSP) in England or the Breast Test Wales Screening Programme (BTWSP) in Wales. People diagnosed with breast cancer who are already eligible for screening should have annual mammography for 5 years. **[2009]**
- 1.13.2 Do not offer mammography of the ipsilateral soft tissues after mastectomy. **[2009]**
- 1.13.3 Do not offer ultrasound or MRI for routine post-treatment surveillance in people who have had treatment for invasive breast cancer or DCIS. **[2009]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

No relevant evidence identified was identified in the 2015 surveillance review for the 2009 evidence review question 'What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer or DCIS?'. The 2012 surveillance review identified evidence on fluorodeoxyglucose PET for detecting recurrence using tumour markers which was not considered to have an impact on the 2009 recommendations; and evidence on the sensitivity and specificity of MRI and mammography at identifying disease recurrence, which had no impact as it supported the recommendations to offer annual mammography, not MRI.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

A Cochrane review assessed the effectiveness of different policies of follow-up for distant metastases on mortality, morbidity and QoL in women treated for stage I, II or III breast cancer (Moschetti et al. 2016). This was an update of a Cochrane review first published in 2000. The update included 1 additional RCT resulting in 5 RCTs (n=4,023) being included. This additional evidence did not change previous conclusions: 'follow-up programs based on regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on regular performance of laboratory and instrumental tests in terms of timeliness of recurrence detection, OS and QoL.'

A systematic review assessed the test performance of surveillance breast MRI in women with a personal history of breast cancer (Haas et al. 2020). Eleven diagnostic assessment studies were included (search dates: 2000 to 2019). The studies included a total of 8,338 women with a personal history of breast cancer and 12,335 surveillance breast MRIs. Measures of

heterogeneity from a meta-analysis are reported in the abstract, including the: predicted interval (PI) which provides the range of true effects that can be expected in future settings. The PI for cancer detection rate of second cancer events by breast MRI per 1,000 examinations was 9 to15 (I^2=10%), recall rate PI=5 to 31% (I^2=97%), sensitivity PI=58 to 95% (I^2=47%), specificity PI=76 to 97% (I^2=97%), and biopsy-proven predictive value (PPV3) PI=16 to 40% (I^2=44%). The findings indicate that the performance of surveillance breast MRI in women with a personal history of breast cancer is widely variable; and the authors concluded that the evidence is currently insufficient to recommend either for or against the use of breast MRI for surveillance.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

The patient group provided feedback that recommendations on 'surveillance for women with a personal and family history of breast cancer' and 'recommendations for all women having surveillance' in familial breast cancer (NICE guideline CG164) should be cross-referenced to in NICE guideline NG101.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence supports recommendation 1.13.1 to offer annual mammography to all people with breast cancer, including DCIS, until they enter the NHS Breast Screening Programme (NHSBSP) in England or the BTWSP in Wales.

We will recommend that relevant recommendations in NICE guideline CG164 are presented alongside recommendations 1.13.1 to 1.13.3.

Clinical follow-up

NICE guideline NG101 recommendations:

- 1.13.4 People who have had treatment for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals). A copy should be sent to the GP and a copy given to the person. This plan should include:
  - designated named healthcare professionals
  - dates for review of any adjuvant therapy
  - details of surveillance mammography
  - signs and symptoms to look for and seek advice on
  - contact details for immediate referral to specialist care **and**

- contact details for support services, for example, support for people with lymphoedema. **[2009]**

Surveillance decision

Recommendations in this section should not be updated.

Previous surveillance

No evidence was identified in either the 2015 or 2012 surveillance review that was relevant to the 2009 evidence review question 'What is the best setting for clinical follow-up of patients treated for breast cancer?'

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

The Cochrane review described in follow-up imaging also reported that evidence from 2 RCTs (including the newly identified RCT) indicated that there was no difference in OS, recurrence detection, or QoL in follow-up care delivered by trained and not trained GPs working in an organised practice setting compared with follow-up care delivered by hospital-based specialists (Moschetti et al. 2016).

A systematic review assessing the effects of nurse-led interventions on HRQoL symptom burden, self-management and behavioural outcomes in women with breast cancer (Chan et al. 2020). Thirty-one RCTs (n=4,651) were included (search dates: January 1999 to May 2019). It was reported that there were no differences in any outcomes for patients when nurse-led surveillance care was compared with physician-led or usual discharge care (also see providing information and support).

A systematic review evaluated the impact of different frequencies of routine follow-up of early-stage breast cancer patients (Surujballi et al. 2021). Seven studies were included (6 RCTs and 1 prospective cohort study; total n=NR; search date: up to July 16, 2020). It was reported that the evidence showed that reductions in follow-up frequency had no adverse effects on QoL (based on data from 5 RCTs and 1 prospective cohort study), DFS(1 RCT), or OS (1 RCT); but resulted in improved cost-effectiveness (1 RCT). There was also no significant difference in QoL between people with early-stage breast cancer whose follow-up was scheduled versus on demand (4 RCTs; n =544).

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A patient group highlighted that written care plans provide the opportunity to ensure patients are aware of their risks of disease recurrence after treatment, based on their family history or known harmful genetic variants. They suggested that the recommendation on clinical follow-up should be expanded to include reference to familial breast cancer and specify which services a patient should contact if they become aware of previous or new cancers in a family member which could increase their risk of disease recurrence.

The patient group also noted in previous stakeholder consultation on NICE guideline NG101 that patients should be provided with information on the signs and symptoms to look out for in relation to secondary cancer and metastatic breast cancer. They shared the report secondary breast cancer part one: diagnosis (breast cancer care) which referenced research that indicated only 22% of women with secondary breast cancer knew what signs and symptoms to look for.

The NHS long-term plan says that by 2019, for breast cancer, all trusts should have a follow-up pathway after breast cancer treatment that suits the needs of patients, and ensures they can get rapid access to clinical support where they are worried that their cancer may have recurred.

Impact statement

New evidence is unlikely to change guideline recommendations.

The new evidence and NHS long-term plan goals are in line with existing recommendation 1.13.4 on clinical follow-up. While we recognise the concern that patients may not be aware of the signs and symptoms of disease recurrence or metastatic cancer, the recommendation does say that the care plan should include 'signs and symptoms to look for and seek advice on'. The healthcare professional(s) who are working with the patient on the agreed care plan should know what these signs and symptoms are and provide this information accordingly. As this should be part of standard clinical care, this recommendation will not be updated.

Monitoring disease status

NICE guideline CG81 recommendations:

- 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]**

Surveillance decision

The recommendations in this section do not require updating.

Previous surveillance

The 2015 surveillance review found evidence for positron emission tomography fused with computed tomography (PET-CT) from 3 studies. Of these, 2 found PET-CT to be helpful for monitoring disease status however further evidence was required comparing PET-CT with other imaging modalities. Evidence was also found on the correlation between carcinoembryonic antigen (CEA) and cancer antigen (CA). Results also suggested that CEA and CA could be used as markers to predict treatment response. However, the studies were primarily of retrospective design with small sample sizes. One study concluded that MRI was superior to PET-CT for monitoring the effect of neoadjuvant chemotherapy in advanced breast cancer.

The 2018 surveillance review found no new evidence or topic expert input.

2023 surveillance

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

No information raised by topic experts at the 2022 surveillance review.

System intelligence highlights that PET scans are being used frequently for monitoring patients with advanced breast cancer in many settings, so the current recommendations may be out of line with practice.

Impact statement

New evidence is unlikely to change guideline recommendations.

No new evidence was found at this, or previous surveillance reviews on monitoring disease status, as such no impact is anticipated at this time. However system intelligence suggests that the use of PET scans may be more widely used. The breast cancer committee may therefore want to consider whether recommendation 1.1.8 remains current.