Surveillance report 2015 – Early and locally advanced breast cancer (2009) NICE guideline CG80

November 2015

Surveillance decision

We will plan an update of this guideline.

Reason for the decision

We found 176 new studies through surveillance of this guideline.

New evidence that could affect recommendations was identified.

Topic experts who helped to develop the guideline advised us about whether the following sections of the guideline should be updated and any new sections added:

Surgery to the axilla

- What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis?

From the surveillance reviews, 2 randomised controlled trials (RCTs) and 1 systematic review and meta-analysis were identified suggesting that, for some people with breast cancer and 1 or 2 micrometastases, axillary lymph node dissection (ALND) may not be necessary.

The topic experts noted that clinical practice has already moved on in response to the new evidence and the guideline should be updated to remain relevant.

Decision: This review question should be updated.

Postoperative assessment and adjuvant therapy planning

- What is the best method of adjuvant treatment planning?

The guideline did not review evidence for this question. No new evidence was identified in surveillance; however, a new UK-based method (Predict) was identified for assessing whether chemotherapy should be offered.

The topic experts advised that the current recommendation to use Adjuvant online is outdated and that Predict is now widely used in the UK. However, other methods to determine whether to offer chemotherapy are available, for example gene profiling tests such as Oncotype Dx (recommended by NICE diagnostics guidance DG10) and Prosignia (PAM50; to be assessed in the UK-based OPTIMA study).

The topic experts agreed that this area needs to be updated. The topic experts agreed that investigating the strengths and weaknesses of tools and recommending criteria that a tool should meet may be better than recommending a specific tool or test.

Decision: This review question should be updated.

Endocrine therapy

- What are the indications for hormonal treatments for the adjuvant treatment of early oestrogen-positive breast cancer?

From the surveillance review, 1 RCT and 1 systematic review and meta-analysis, and 1 individual patient data meta-analysis were identified suggesting benefits of treatment with tamoxifen for up to 10 years and with aromatase inhibitors for up to 5 years.

The topic experts agreed that clinical practice has moved on from the guideline recommendations but that several areas of uncertainty remain. One of these is the hormonal treatments that should be offered depending on the woman's menopausal status (premenopausal, perimenopausal or post-menopausal).

The overlap with NICE technology appraisal guidance TA112, which covers use of aromatase inhibitors, was discussed. It was suggested that TA112 should be updated as part of an update to this review question in the

guideline. Any decision to update NICE TA112 will be subject to consultation with the technology appraisal's stakeholders.

Decision: This review question should be updated.

Chemotherapy

- What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer?

From the surveillance review, 1 RCT, 2 individual patient data meta-analyses and 3 systematic reviews and meta-analyses were identified covering a range of chemotherapeutic regimens for early breast cancer. The guideline did not make recommendations on specific chemotherapeutic regimens to use.

The topic experts had some concerns that the guideline looks out of date because it does not reflect current clinical practice in chemotherapy. However, any update of the guideline in this area would be difficult because of the number of regimens available.

The topic experts felt that there is a risk covering specific chemotherapy regimens in guideline recommendations because they could quickly become outdated. The question about the indications for chemotherapy was thought to be best answered by what is the best method of adjuvant treatment planning? (see above).

Decision: This review question should be updated.

Radiotherapy

- Which groups of patients should receive chest wall radiotherapy after mastectomy?

From the surveillance review, 1 meta-analysis was identified suggesting that radiotherapy to the chest wall and between 1 and 3 regional lymph nodes is associated with reduced recurrence and breast cancer mortality in people with intermediate-risk disease.

The guideline recommends considering entering the person into a trial such as SUPREMO to assess the value of radiotherapy. However, recruitment to this trial has completed so the recommendation is out of date.

The topic experts thought that an update should consider which populations should be offered radiotherapy to the chest wall.

Decision: This review question should be updated.

- What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla?

From the 3- and 6-year surveillance reviews, 4 RCTs and 1 systematic review and meta-analysis of radiotherapy to the internal mammary lymph node were identified. The new evidence suggested that radiotherapy to the internal mammary node may reduce recurrence but may not increase overall survival.

The topic experts advised that these results indicate that the internal mammary lymph nodes need to be formally assessed. Current UK practice not to irradiate this target is out of step with practice in the rest of Europe, where radiotherapy of internal mammary nodes is used.

Additionally, 1 RCT (AMAROS) and an individual patient data meta-analysis of radiotherapy to the axilla were identified. The new evidence suggests that radiotherapy to the axilla may be a useful alternative to ALND in selected patients.

The topic experts agreed that this area needs to be updated. Issues that should be addressed include how to replicate the radiotherapy technique used in the AMAROS study and the risk of overtreatment with radiotherapy in people who may have adequate treatment with chemotherapy and hormonal treatments.

Decision: This review question should be updated.

Assessment and treatment of bone loss

- What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer?

From the surveillance review, 1 RCT, 5 systematic reviews and meta-analyses and 1 individual patient data meta-analysis were identified suggesting that bisphosphonates may have beneficial effects on recurrence in postmenopausal women.

The topic experts agreed that adjuvant bisphosphonates showed benefits in postmenopausal women, with some studies showing an effect on survival.

Decision: This review question should be updated.

Other clinical areas

We also found new evidence relating to other areas, but it was not deemed to have an effect on current recommendations. These areas were: referral, diagnosis and preoperative assessment; providing information and psychological support; surgery to the breast; breast reconstruction; biological therapy; primary systemic therapy; complications of local treatment and menopausal symptoms; and follow-up.

Overall decision

After considering all the new evidence and the views of topic experts, we decided that a full update is necessary for this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

Surgery to the axilla

We selected the systematic review by Ram et al. (2014) for a full commentary because it includes results from the ACSOG Z0011 and IBCSG 23-10 trials

along with other results. This gives a wider view of the relevant evidence than including only 1 RCT for this area.

What the guideline recommends

NICE guideline CG80 recommends offering further axillary treatment to patients with early invasive breast cancer who:

- have macrometastases or micrometastases shown in a sentinel lymph node
- have a preoperative ultrasound-guided needle biopsy with histologically proven metastatic cancer.

The preferred technique is ALND because it gives additional staging information.

NICE CG80 additionally states: ‘Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.’

Methods

Ram et al. (2014) conducted a systematic review and meta-analysis of sentinel lymph node biopsy (SLNB) compared with ALND in people with node-positive breast cancer. Three RCTs (n=2058) and 5 retrospective studies were included in the systematic review although the primary analysis included only data from the RCTs. The primary outcomes of interest were disease-free survival and overall survival. Secondary outcomes were local recurrence and surgical morbidity.

Results

Overall survival was reported in 2 RCTs (n=1822): the ACSOG Z0011 trial (Giuliano et al. 2011) and the IBCSG 23-10 trial (Galimberti et al. 2013). Overall survival did not differ significantly between treatments (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.60 to 1.14, p=0.25), suggesting that SLNB was non-inferior to ALND.

Disease-free survival also showed no significant difference between treatments (HR 0.94, 95% CI 0.79 to 1.13, p=0.52; 3 studies, n=2020).

Meta-analysis was not done for disease recurrence, but each of the studies showed no difference between groups for this outcome.

Surgical morbidity was reported to be higher in the ALND group, including wound infections, lymphoedema, axillary seroma, motor neuropathy and paraesthesia, although statistical analysis was not reported for adverse events.

Strengths and limitations

Strengths

Strengths of the review were use of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and assessing individual studies with the Cochrane risk of bias tool.

Limitations

A potential limitation of the systematic review was that no meta-analysis was done for the secondary outcome of recurrence. It was not clear whether this was because meta-analysis of secondary endpoints was not planned or was not possible.

The authors of the systematic review reported several potential limitations of the included studies, such as differences in populations within and between trials. The Z0011 trial included people with up to 2 positive nodes who were having breast-conserving surgery, whereas the IBCSG 23-10 trial included people with micrometastases including isolated tumour cells who could have breast-conserving surgery or mastectomy. Both trials stopped early because low numbers of events meant that very large numbers of participants or follow-up of more than 20 years would be needed to reach the necessary number of events to prove non-inferiority.

In 2 of the 3 trials, more participants had micrometastases than had macrometastases, which could have affected the results in favour of non-inferiority.

The Z0011 trial had differences between the randomised groups that were not accounted for in analysis. About 20% of participants in the ALND group had 3 or more positive nodes (more than the protocol allowed) compared with about 4% of participants in the SLNB group.

Impact on guideline

The new evidence suggests that SLNB may result in survival and recurrence outcomes similar to those with ALND, but with less morbidity in people with 1 or 2 positive lymph nodes, particularly those with micrometastases. This finding may have a potential impact on NICE CG80, which recommends ALND as the preferred treatment for micrometastases and macrometastases.

Radiotherapy* – *targeting the axilla in lymph-node positive breast cancer

We selected the AMAROS study for a full commentary because the guideline refers to this study in a research recommendation and the full results of the study are now available.

What the guideline recommends

NICE CG80 recommends:

- ALND as the preferred treatment for people who have metastases detected in their sentinel lymph nodes
- that adjuvant radiotherapy to the axilla should be offered to patients with early breast cancer if ALND is not possible.

Methods

Donker et al. (2014) reported results of a non-inferiority RCT (AMAROS) assessing axillary radiotherapy compared with ALND in people with lymph-node positive breast cancer. Initially the study included people with breast tumours of up to 3 cm in size. However, the protocol was later amended to

include tumours of up to 5 cm in size and at the same time isolated tumour cells were no longer regarded as positive sentinel nodes. Exclusion criteria were previous malignancy, neoadjuvant chemotherapy, or previous surgery or radiotherapy to the axilla.

Participants (n=4806) were randomly assigned to treatment groups before undergoing SLNB, and those with negative or unidentified lymph node status were excluded from the analysis. This left an intention-to-treat population of 744 people in the ALND group and 681 people in the radiotherapy group.

The primary end point was 5-year axillary recurrence, defined as tumour recurrence in lymph nodes in the ipsilateral axilla, infraclavicular fossa or interpectoral area. Recurrence at the supraclavicular lymph nodes was classed as distant metastasis. Secondary end points were axillary recurrence-free survival, disease-free survival, overall survival, shoulder mobility, lymphoedema and quality of life.

Treatment of the breast tumour was by breast-conserving surgery with whole-breast radiotherapy, or by mastectomy with or without chest-wall radiotherapy. Adjuvant chemotherapy was used at the discretion of the multidisciplinary team. Radiotherapy targeted 3 levels of the axilla plus the medial part of the supraclavicular fossa and was delivered in 25 fractions of 2 Gy. In the ALND group, adjuvant radiotherapy was allowed if 4 or more positive nodes were detected.

Results

The primary end point, 5-year axillary recurrence, was seen in 0.43% of the ALND group, 1.19% of the radiotherapy group and 0.72% of people who were assessed as node-negative.

ALND did not differ significantly from radiotherapy for the outcomes of disease-free survival and overall survival.

Disease-free survival at 5 years was 86.9% in the ALND group and 82.7% in the radiotherapy group (HR 1.18, 95% CI 0.93 to 1.51, p=0.18). In participants with negative sentinel nodes, 5-year disease-free survival was 87.9%.

Overall survival at 5 years was 93.3% in the ALND group and 92.5% in the radiotherapy group (HR 1.17, 95% CI 0.85 to 1.62, p=0.34). In participants with negative sentinel nodes, 5-year overall survival was 95.4%.

ALND was associated with more cases of lymphoedema and more increases in arm circumference of more than 10% at 5 years.

Strengths and limitations

Strengths

Strengths of this study included use of central computerised allocation and that all primary and secondary outcomes specified in the trial protocol were reported.

Limitations

The authors noted potential limitations of their study, including that the extent of radiotherapy may be considered as overtreatment, and that more people were assigned to ALND than to radiotherapy. The imbalance in treatment groups was investigated by the independent data monitoring committee, which found no plausible cause for the imbalance. No bias was detected.

Although the protocol was amended during the study so that isolated tumour cells were not considered to be metastases, 12% of people in the ALND group and 10% of the radiotherapy group had only isolated tumour cells. In the UK, these people would not have had either of these treatments. Additionally, 95% of participants in both groups had only 1 or 2 positive nodes, so the results may not be applicable to people with 3 or more positive nodes.

The non-inferiority design of the trial assumed that 5-year axillary recurrence would be seen in 2% of people in the ALND group and in no more than 4% of people in the radiotherapy group. However, the lower than expected event rates in both groups meant that the non-inferiority test was underpowered.

Impact on guideline

The new evidence suggests that radiotherapy may be comparable to ALND in people with early breast cancer and positive lymph nodes. This may have a

potential impact on the guideline, which currently recommends radiotherapy only for people who cannot have ALND.

The population eligible for radiotherapy will also be affected by the findings reported in the previous section on surgery to the axilla in lymph-node positive breast cancer. Those results suggested that SLNB may be sufficient treatment for micrometastases in the lymph nodes.

Assessment and treatment of bone loss* – *bisphosphonates for people with early breast cancer

We selected an individual patient data meta-analysis of bisphosphonates for people with early breast cancer for a full commentary because it contained data from more than 18,000 women. Many other studies on this topic were identified but had conflicting results; the large size of this analysis may strengthen its findings.

What the guideline recommends

NICE CG80 recommends a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density for patients with early breast cancer if they:

- are starting adjuvant aromatase inhibitor treatment or
- have treatment-induced menopause or
- are starting ovarian ablation/suppression therapy.

Bisphosphonates should be offered according to the person's risk of fracture.

Methods

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2015) reported an individual patient data meta-analysis of treatment with adjuvant bisphosphonates compared with control (no bisphosphonates) in women with early breast cancer. The primary outcomes were breast cancer recurrence, distant recurrence and breast cancer mortality. Secondary outcomes included bone recurrence. Of 38 identified trials, 32 had been completed (n=19,291),

and the authors were able to obtain individual patient data for 18,766 women from 26 trials.

Results

In the whole population:

- The 10-year rate of any breast cancer recurrence was not significantly different for bisphosphonate treatment (24.9%) compared with control (25.9%; rate ratio [RR] 0.94, 95% CI 0.87 to 1.01, p=0.08).
- The 10-year risk of distant recurrence as the first event was significantly lower with bisphosphonates at 20.4% compared with control (21.8%; RR 0.92, 95% CI 0.85 to 0.99, p=0.03)
- The 10-year breast cancer mortality was significantly lower with bisphosphonates (16.6%) compared with control (18.4%; RR 0.91, 95% CI 0.83 to 0.99, p=0.04).
- The 10-year bone recurrence rate was significantly lower for bisphosphonates (7.8%) compared with control (9.0%; RR 0.83, 95% CI 0.73 to 0.94, p=0.004).

In subgroup analyses, significant effects of bisphosphonates on bone recurrence were seen in postmenopausal women (RR 0.72, 95% CI 0.57 to 0.90) but not in premenopausal or perimenopausal women. Bone recurrence was significantly lower with bisphosphonates in women aged 55–69 years (RR 0.74, 95% CI 0.56 to 0.98), but not in younger women. However, the authors could not determine whether age or menopausal status was most relevant because these factors are closely related. Sensitivity analysis excluding 2 studies that initially generated the hypothesis that menopause may be a factor (the ABCSG-12 and AZURE trials) still showed a significant effect of bisphosphonates in postmenopausal women.

Breast cancer mortality showed a significant reduction with bisphosphonates in postmenopausal women (RR 0.82, 95% CI 0.73 to 0.93, p=0.002) but no effect in premenopausal women (RR 1.00, 95% CI 0.86 to 1.15, p=0.96).

Distant recurrence outside bone was not significantly affected by bisphosphonates in either premenopausal women (RR 1.08, 95% CI 0.92 to 1.26, p=0.35) or postmenopausal women (RR=0.90, 95% CI 0.79 to 1.02, p=0.1).

No significant effect on the results was seen with dose, type or duration of bisphosphonate treatment or the characteristics of breast cancer such as node status, hormone-receptor status or use of chemotherapy.

Fracture rates were known for 71% of the total population analysed, and were significantly lower with bisphosphonates (6.3%) compared with control (7.3%; RR 0.85, 95% CI 0.75 to 0.97, p=0.02).

Strengths and limitations

Strengths

A strength of this study is that it included data from 85% of all people who participated in trials of bisphosphonates in early breast cancer. Additionally, the use of individual patient data means that outcomes were standardised across the dataset.

Limitations

The analysis did not assess adverse effects of bisphosphonates; the authors noted that they were unable to assess the incidence of osteonecrosis of the jaw. They referred to previously reported estimates of 1–2%. In the AZURE trial (Coleman et al. 2014) the rate of confirmed osteonecrosis of the jaw was reported to be 1.7%.

For many outcomes, the absolute improvements seen with bisphosphonates were similarly small. For example, bone recurrence was reduced by 1.4% in postmenopausal women.

Impact on guideline

NICE CG80 recommends bisphosphonates only for bone loss associated with treatments for breast cancer. The new evidence indicates that

bisphosphonate treatment may have benefits in a wider population of postmenopausal women with early breast cancer.

However, the benefits of bisphosphonate treatment must be weighed against the risks, particularly of osteonecrosis of the jaw. The Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update on the risk of osteonecrosis of the jaw. It noted: 'The risk of developing osteonecrosis of the jaw in association with oral bisphosphonates seems to be low. The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.'

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 6 years after the publication of Early and locally advanced breast cancer (2009) NICE guideline CG80.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 100 new studies in a search for systematic reviews published between 1 October 2011 and 15 January 2015. We also considered 7 additional studies identified by members of the Guideline Committee who originally worked on this guideline. A further 10 studies were identified from other correspondence we have received since the publication of the guideline.

Evidence identified in previous surveillance 3 years after publication of the guideline was also considered. This included 55 studies identified by search and 4 studies identified in comments received during consultation on the 3-year surveillance update decision.

From all sources, 176 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline, and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 6-year review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

NICE Surveillance Programme project team

Sarah Willett
Associate Director

Philip Alderson
Consultant Clinical Adviser

Emma McFarlane
Technical Adviser

Lynne Kincaid
Technical Analyst

The NICE project team would like to thank the topic experts who participated in the surveillance process.