Surveillance report – Advanced breast cancer (2009; CG81.1 addendum 2014) NICE guideline CG81

November 2015

Surveillance decision

We will plan a partial update of this section of the guideline:

- Reassessment of oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) on disease recurrence.

Reason for the decision

We found 263 new studies through surveillance of this guideline.

New evidence that could affect recommendations was identified.

Topic experts, including those who helped to develop the guideline advised us about whether the following sections of the guideline should be updated:

Diagnosis and assessment

- Reassessment of ER and HER2 on disease recurrence.

From the surveillance review, 2 studies were identified examining discordance between primary and recurrent breast cancer in terms of ER, HER2 and progesterone receptor status. The 2 studies found there could be discordance in receptor status between the primary tumour and metastases, which led to altered management in 14.2–20% of cases.

The topic experts agreed with the need to reassess receptor status on disease recurrence. They noted that the NICE quality standard on breast cancer already states that 'People with newly diagnosed invasive breast cancer and those with recurrent disease (if clinically appropriate) have the ER and HER2 status of the tumour assessed'. The topic experts felt that there is

evidence to update the recommendation which would then align the guideline (which currently states that, if disease recurs, further biopsy just to reassess ER and HER2 status should not be done) with the quality standard.

Decision: This review question should be updated.

Other clinical areas

We also found new evidence relating to the following areas, but it was not deemed to have an effect on current recommendations. These areas were: assessing disease extent and monitoring the response to treatment; providing information and support for decision making; hormone treatment; chemotherapeutic treatment; biological treatment; combination treatments; management in the community; lymphoedema; managing complications; surgery of the primary tumour; and predictors of treatment response.

We did not find any new evidence related to: choice of first line treatment (endocrine therapy or chemotherapy); or interventions to support young families.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision.

Overall decision

After considering all the new evidence and the views of topic experts, we decided that a partial 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.

Diagnosis and assessment – PET-CT for diagnosing distant metastases in breast cancer

We selected systematic reviews by Hong et al. (2013) and Rong et al. (2013) for full commentary. Although they suggest that PET-CT is better than conventional imaging for detecting distant metastases, the evidence is unlikely to affect current recommendations to use PET-CT only for following up suspicious conventional imaging, rather than as first-line investigation.

What the guideline recommends

NICE CG81 recommends:

- Assessing the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI).
- Assessing 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.
- 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.

Methods

Two systematic reviews assessed PET-CT for diagnosing distant metastases in breast cancer:

- Hong et al. (2013) analysed 5 retrospective and 3 prospective studies (n=748) to compare PET-CT with conventional imaging (CT, ultrasonography, radiography and bone scintigraphy) for detecting various distant metastases.
- Rong et al. (2013) analysed 5 retrospective and 2 prospective studies (n=668) to compare PET-CT with bone scintigraphy for detecting bone metastases.

Of the studies included across the 2 reviews, 5 were the same.

Results

In both reviews, PET-CT had higher sensitivity and higher specificity than conventional imaging based on a reference standard of histopathological analysis and clinical and imaging follow-up.

In Hong et al. (2013), only 6 of the 8 included studies directly compared PET-CT and conventional imaging. The performances of the 2 imaging strategies in detecting various metastases from a meta-analysis of these 6 studies (n=664) were:

- PET-CT:
  - sensitivity 0.97 (95% confidence interval [CI] 0.84 to 0.99)
  - specificity 0.95 (95% CI 0.93 to 0.97)
  - positive likelihood ratio 20.8 (95% CI 13.1 to 32.9)
  - negative likelihood ratio 0.03 (95% CI 0.01 to 0.18).

- Conventional imaging:
  - sensitivity 0.56 (95% CI 0.38 to 0.74)
  - specificity 0.91 (95% CI 0.78 to 0.97)
  - positive likelihood ratio 6.5 (95% CI 2.5 to 17.2)
  - negative likelihood ratio 0.48 (95% CI 0.31 to 0.72).

In Rong et al. (2013) the performances of the 2 imaging strategies in detecting bone metastases from a meta-analysis of 7 studies (n=668) were:

- PET-CT
  - sensitivity 0.93 (95% CI 0.82 to 0.98)
  - specificity 0.99 (95% CI 0.95 to 1.00)
  - positive likelihood ratio 149.8 (95% CI 19.6 to 1149.3)
  - negative likelihood ratio 0.07 (95% CI 0.02 to 0.19)

- Bone scintigraphy:
  - sensitivity 0.81 (95% CI 0.58 to 0.93)
  - specificity 0.96 (95% CI 0.76 to 1.00)

- positive likelihood ratio 22.0 (95% CI 2.7 to 180.3)
- negative likelihood ratio 0.20 (95% CI 0.08 to 0.50).

The authors of both reviews stated that they considered a positive likelihood ratio of greater than 10 as convincing evidence to rule in disease, and a negative likelihood ratio of less than 0.1 as convincing evidence to rule out disease.

Strengths and limitations

Strengths

Strengths common to both reviews included:

- Data extraction was carried out by 2 reviewers, and clear inclusion and exclusion criteria were reported.
- References in the articles retrieved by the original systematic search were screened for additional studies.
- Studies were quality assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Limitations

Limitations common to both reviews included:

- Only 2 databases were searched.
- Several studies in the 2 reviews were retrospective (introducing the possibility that observers may have been aware of the outcome of other imaging before interpreting PET-CT).
- There was no single clinical and imaging follow-up strategy across the studies, which may have affected the evaluation of PET-CT.
- Funnel plot analysis was not used to check for publication bias because of the small number of included studies.

Additionally, in Hong et al. (2013) conventional imaging varied across the studies, so PET-CT was not compared to 1 standard imaging strategy.

Impact on guideline

NICE CG81 does not currently recommended PET-CT for initially assessing the presence and extent of visceral or bone metastases. PET-CT is only recommended for making a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

From the new evidence, PET-CT appears better at detecting distant metastases in people with breast cancer than conventional imaging techniques (namely, CT, ultrasonography, radiography and bone scintigraphy). However, topic experts noted that, in the UK, metastatic disease is predominantly investigated only when it is suspected. Therefore the current recommendation, that 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, remains valid.

***Managing complications* – surgical resection of the primary tumour in stage 4 breast cancer**

We selected a systematic review and meta-analysis by Harris et al. (2013) for full commentary because although it appears to indicate the efficacy of surgical resection of the primary tumour, study limitations are likely to reduce the impact of the evidence. RCTs are ongoing in this area, which in future could affect the guideline recommendations because surgery to the primary tumour is not currently discussed by the guideline.

What the guideline recommends

Although NICE CG81 includes recommendations on surgery for bone and brain metastases, the guideline does not discuss surgery of the primary breast tumour.

Methods

A systematic review and meta-analysis by Harris et al. (2013) compared surgical resection of the primary breast tumour with conventional systemic treatment in stage 4 breast cancer. The review found 10 studies: 9 were

retrospective cohort studies and 1 was a case–control study. Of the 28,693 patients in the 10 studies, 53% had surgery and 47% had systemic therapy.

Of all the surgeries, 61% were mastectomy and 39% were breast conserving. Data on systemic therapy were limited and it was not always reported whether all patients who had surgery also had systemic therapy. In 4 studies that did provide this information, it was reported that the majority of patients had some form of systemic therapy. The primary outcome was 3-year survival.

Results

Survival at 3 years was significantly higher in patients who had surgery compared with those who had no surgery (40% versus 22%; odds ratio=2.32, 95% CI 2.08 to 2.60, $p<0.01$). In subgroup analyses, patients were more likely to be selected for surgery if they had smaller primary tumours, fewer comorbidities and fewer metastases ($p<0.01$). Patients undergoing surgery were also younger in all but 2 studies.

The odds ratio for the between-group difference in 3-year survival was based on a random effects model, but was not adjusted to take into account the differences between the surgical and non-surgical groups. It was reported that the surgical and systemic treatment groups did not differ significantly in terms of metastatic disease location, tumour grade or receptor status.

Strengths and limitations

Strengths

- To be included in the review, studies had to have staged cancer according to the TNM (primary tumour, regional lymph nodes, distant metastasis) or AJCC (American Joint Committee on Cancer) staging manuals.
- References in the articles retrieved by the original systematic search were screened for additional studies.
- Seven of the included studies were multicentre.

Limitations

- Only 2 databases were searched.
- All studies in the review were retrospective and no studies were randomised. Additionally, patients undergoing surgery were younger and had less severe disease, which may have confounded the results. Therefore although surgery of the primary tumour was associated with prolonged survival, the relationship may not definitely be causal.
- Patients could have had excision of metastatic sites that may not have been recorded in retrospective studies.
- Data on the types of systemic therapy used across the studies were limited.
- Three studies were from the 1970s, since when clinical management strategies are likely to have changed.
- Quality of the included studies was not assessed.

Impact on guideline

NICE CG81 does not discuss surgery of the primary breast tumour. The new evidence suggests an association of surgical excision of the primary tumour with prolonged survival when compared with systemic treatment. Topic experts noted that surgery to the primary tumour in patients with established advanced or metastatic disease is a rare intervention that is more likely to be performed in patients in relatively better health, for example to improve quality of life. It was felt that the use of this treatment would be decided on a case by case basis, and may not have a biological basis for improving survival.

Although these data could indicate a potential impact on the current guideline, limitations of the evidence, particularly the retrospective nature of the studies analysed, mean that more robust evidence is needed. The authors noted that 5 RCTs in this area are in progress. Preliminary results from 2 of these trials (Badwe et al. 2013 and Soran et al. 2013) indicated no effect on overall survival of surgery to the primary tumour.

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 Advanced breast cancer (2009; CG81.1 addendum 2014) NICE guideline CG81.

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 39 new studies in a search for systematic reviews published between 1 October 2011 and 22 January 2015. We also considered 9 additional studies identified by members of the Guideline Committee who originally worked on this guideline, and 2 additional studies 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 213 studies identified by search.

From all sources, 263 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 surveillance 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.

Date of next surveillance

Our next surveillance to decide whether the guideline should be updated is scheduled for 2017.

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