NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101)

Surveillance report

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Surveillance decision

We will update the NICE guideline on early and locally advanced breast cancer.

The update will focus on recommendations on effective strategies for reducing arm and shoulder mobility problems after breast cancer surgery.

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on the NICE guideline following completion of the PROSPER trial, a National Institute for Health Research (NIHR) funded study (HTA 13/84/10), which published findings in the British Medical Journal (Bruce et al. 2021).

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Considering the evidence used to develop the guideline in 2009.
- Feedback from topic experts.
- Examining related NICE guidance and quality standards (none identified).
- A search for ongoing research.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether to update the section of the guideline on arm mobility as a complication of local treatment.

We decided that full updated literature searches were not needed because the information we had from the new evidence, original guideline and topic experts was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE

guidelines: the manual.

Study considered in this exceptional surveillance review

The PROSPER trial was a UK based multicentre, pragmatic, superiority, randomised controlled trial (RCT) comparing the effectiveness and cost-effectiveness of usual care plus a structured exercise programme compared with usual care alone in women undergoing breast cancer surgery who were at risk of postoperative upper limb morbidity (n=392 from 17 NHS cancer centres).

Participants were women aged 18 and above with newly diagnosed invasive or non-invasive breast cancer who were scheduled for surgical excision and assessed as being at high risk of upper limb disability after surgery. High risk was defined by 1 or more of the following: being scheduled for planned axillary node clearance or planned radiotherapy to the axilla and/or supraclavicular fossa or having any subsequent axillary surgery after sentinel lymph node biopsy, or having a later decision to refer for axillary and/or supraclavicular radiotherapy within 6 weeks of primary surgery; or a body mass index (BMI) indicating obesity (BMI 30 or above); or an existing shoulder problem (history of shoulder surgery, shoulder trauma injury from fracture or dislocation, frozen shoulder, osteoarthritis or rheumatoid arthritis affecting the shoulder, non-specific shoulder pain, stiffness, or weakness, restricted range of shoulder movement or decreased shoulder function).

Exclusion criteria included men, women having immediate reconstructive surgery or sentinel lymph node biopsy with or without breast surgery (unless other high risk criteria), women having bilateral breast surgery, and women with metastatic disease.

One hundred and ninety-one participants were randomised to 'best practice usual care': freely available information leaflets provided during preoperative clinics which had details on postoperative exercises and generic postoperative advice (exercises after breast cancer surgery and your operation and recovery). The intervention arm (n=191) received the same usual care plus a supervised structured physiotherapy exercise programme which aimed to 'restore range of movement in the shoulder, improve strength, and increase physical activity'. Physiotherapists were trained in trial procedures and an intervention manual was produced which included a range of possible exercises a physiotherapist could prescribe, pathways for clinical assessment and behaviour change

techniques, allowing for an individually tailored programme. At least 3 face-to-face physiotherapy sessions were delivered at 7 to 10 days, 1 month and 3 months post-operation and participants could receive up to 3 more sessions over a year, delivered by telephone or face-to-face.

The primary outcome of interest was upper limb function assessed using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at 12 months follow-up post-randomisation. The scores on DASH range from 0, indicating no disability to 100, indicating the most severe disability. The authors of the study selected a 7-point difference in DASH scores at 12 months as indicative of a clinically meaningful difference 'to account for the preventive approach rather than treatment of an established, chronic condition and to allow for the pragmatic trial design, whereby some participants in the control arm may be exposed, by serendipity, to other active interventions'. The authors noted that while the 'accepted minimally important clinical difference for people with painful disability is 10', research also indicates that a 5-to 10-point difference in DASH score indicates a moderate improvement for adults with acute or chronic upper extremity orthopaedic or rheumatological conditions (Angst et al. 2005 and Sorensen et al. 2013).

Secondary outcomes were based on self-report questionnaires and included the DASH subscales (activity limitations, impairment, and participation restriction), postoperative pain, wound-related complications, lymphoedema data and health-related quality of life (measured by SF-12 and EQ-5D-5L). Health and personal social service resource use data was also collected (postal questionnaires and hospital resource use data from NHS Digital hospital episode statistics).

Due to the nature of the intervention, participants and physiotherapists were aware of which procedure they received. Analysis was undertaken by researchers who were masked to intervention allocation.

A sample size analysis was undertaken to ensure recruitment of enough patients for identifying a 7-point difference in DASH score at 12 months follow-up and considering the pragmatic trial design which meant some participants receiving usual care may be exposed to other interventions. The authors reported that a sample size of 242 patients was required 'at 80% power and 5% type 1 error rate on a two-sided test'. This was then increased to account for 'therapist effects', resulting in 256 participants. At 12 months follow-up the total sample size was 274 (n=139 in usual care and n=135 in the intervention arm).

Most participants had axillary node clearance (86%) and/or axillary/supraclavicular radiotherapy (83%). At baseline, 45% were obese, 27% overweight (BMI between 25 and 30) and 25% had a healthy BMI (25). Only 21% had a history of shoulder problems. The mean baseline DASH score was 19 (median=12 and interquartile range=2 to 30), indicating that most participants did not have pre-existing severe upper limb dysfunction. Prevalence of baseline characteristics and surgery type was similar between participants in the usual care and intervention arms.

Ninety-five percent of participants in the intervention arm attended at least 1 physiotherapy appointment and 75% attended 3 or more sessions.

At 12 months follow-up questionnaire data was available from 139/196 participants allocated to usual care and 135/196 allocated to the intervention.

At 12 months follow-up, the mean DASH score was 16.3 in the exercise group and 23.7 in the usual care group. An intention to treat (ITT) analysis found that compared with usual care, the exercise programme led to a clinically significant improvement in upper limb function at 12 months follow-up: unadjusted mean difference in DASH score was 7.34 (95% confidence interval [CI]=2.44 to 12.23, p<0.01) and adjusted mean difference was 7.81 (95% CI=3.17 to 12.44, p=0.001; adjusted for age, baseline DASH, breast surgery, axillary surgery, radiotherapy, and chemotherapy).

Compared with usual care, the exercise group also reported significant improvements in all the DASH subscales, lower postoperative pain, fewer arm disability symptoms and higher physical health-related quality of life scores. There were no differences between the groups on neuropathic pain, wound-related complications, surgical site infection, lymphoedema, or other complications, nor on mental health-related quality of life scores.

Compared with usual care, the exercise programme cost an average of £129 more per participant. When healthcare and personal social services costs were considered, the incremental average cost was -£387 (95% CI=-£2,491 to £1,718). When baseline utility values were controlled for, there was a small but statistically significant increase in QALYs in the exercise programme compared with usual care: average of 0.029 QALYs accrued (95% CI=0.001 to 0.056, p=0.04). The authors reported that at the cost-effectiveness threshold values of £20,000 and £30,000 per QALY, the probability that exercise was more cost-effective than usual care was 78% and 84%, respectively; and 'the probability of cost-effectiveness at a willingness to pay threshold of £20,000 per QALY increased to 97% when we excluded the high cost cancer treatment (chemotherapy, radiotherapy), which

had driven much of the uncertainty from the primary analysis. These findings remained robust to pre-specified sensitivity analyses' (see supplementary information for details of the economic evaluation).

Ongoing research

We checked for relevant ongoing research. Of the ongoing studies identified, 2 were assessed as having the potential to change recommendations. We will regularly check whether these studies have published results and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Effect of the pilates method on the range of shoulder movement in women with breast cancer: a systematic review and meta-analysis
- Meta-analysis of different forms of exercise effects on rehabilitation effects of affected limb in patients with breast cancer.

Information considered when developing the guideline

During development of the original NICE guideline in 2009, RCT evidence published up to May 2007 was searched for the review question: 'What strategies are effective in reducing arm and shoulder mobility problems after breast cancer surgery?'

Evidence from 10 RCTs suggested that physiotherapy or exercise interventions could improve arm and shoulder function in patients who had received surgery for breast cancer, with no increase in long-term complications. Evidence from 7 RCTs indicated that instructed physiotherapy or instructed exercise interventions were associated with improved patient compliance, a better range of arm movement and lower rates of lymphoedema compared with control groups in which patients received booklets or other education for unsupervised exercise.

There was conflicting evidence for regimes offered directly after surgery. Evidence from 6 RCTs indicated that the timing of physiotherapy within the first 2 postoperative weeks did not affect outcomes assessed 1 month or later from the date of surgery, while physiotherapy given in the first postoperative week to patients with surgical drains in situ was associated with a larger drainage volume, compared with delayed physiotherapy, or

compared with other interventions (for example, massage). One RCT on an exercise intervention that started between 6 and 26 weeks after surgery, reported that the precise timing of the exercises did not influence outcomes.

The evidence review from 2009 reported that although there were several studies assessed at being a 'high level' of quality, 'most sample sizes were very small making it unlikely that statistically significant effects could be demonstrated, the method to generate the sequence of randomisation, the allocation concealment procedure, blinding, ITT and withdrawals were rarely mentioned making it difficult to assess the validity of the trials'. It was also noted that patients with pre-existing shoulder problems were often excluded from the RCTs even though these may be the patients most at risk of complications, so the best strategy for treating those patients was not clear.

The guideline development group (GDG) did not consider the topic as a health economic priority and so cost-effectiveness literature on this topic was not reviewed.

A set of recommendations on arm mobility were developed based on GDG consensus and the RCT evidence described above. While the current NICE guideline updated and replaced the original, the recommendations on arm mobility remain the same as those developed in 2009 as a surveillance review in 2015 found no systematic review evidence in this area and hence this was not considered for update. The recommendations are:

1.12.5: All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy.

1.12.6: Identify pre-existing shoulder conditions preoperatively in people with breast cancer, as this may inform further decisions on treatment.

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.

1.12.8: Refer people to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.

Topic expert feedback

In this exceptional review we contacted 8 topic experts who were members of the GDG for

the current NICE guideline or recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty and had an interest in breast cancer. Five topic experts responded: 2 consultant clinical oncologists, a consultant oncoplastic breast surgeon, a GP (and cancer clinical lead) and an advanced nurse practitioner.

All topic experts responded that, based on the new evidence reported in the PROSPER trial, the recommendations on arm mobility in the NICE guideline should be updated. One topic expert highlighted that 'upper limb and/or shoulder morbidity is commonly under-appreciated, develops at times when patients are discharged from regular breast clinic follow-up and may become more prominent with increased use of axillary radiotherapy'. Topic experts thought that updating the NICE guideline with recommendations on content and timing of a structured physiotherapy care programme would provide benefits for at least patients at high risk of arm and shoulder mobility problems. They suggested that improvements may include prevention of long-term shoulder morbidity, minimising postoperative complications, prevention of delays in delivering radiotherapy for those with severe restrictions, a reduction in late interventions outside the planned treatment pathway which can be harder to access and/or coordinate, improved long-term physical function and quality of life. A topic expert also thought that a physiotherapist programme offering guided support and follow-up, instead of the usual care of a leaflet/reading list on exercise, would improve health inequalities, adherence to exercise and patient empowerment (by enabling them to feel they had done what they could to address long-term outcomes).

One topic expert did raise concerns about only using the PROSPER trial as a basis for updating recommendation content; however the update will consider the cumulative impact of previous evidence and new RCT evidence published since recommendations 1.12.5 to 1.12.8 were developed in 2009, in line with the previous search strategy and inclusion criteria (see information considered when developing the guideline).

One topic expert highlighted that consideration should be made and/or further research may be needed to consider different delivery models: group classes, virtual assessment, virtual classes, and potential use of exercise Apps.

Equalities

Three topic experts highlighted equalities issues which will be considered when the NICE guideline is updated, in line with NICE's equality scheme. Two topic experts noted that the use of leaflets or written information can lead to inequalities for people who are non-

English speakers, are not literate, have sensory or learning disabilities; and that these patients may benefit from physiotherapy input for instructions. One topic expert also noted how these factors can also lead to a lack of awareness of resources and reduced access to diagnostic and surveillance facilities. They also reported that 'patients who do not want to be exposed to men (due to abuse or religious reasons) will be less likely to present and may encounter difficulties in the healthcare system when they do, due to limited female staff availability to undertake the assessments and/or interventions indicated'.

Recommendation 1.12.7 in the NICE guideline does allow for physiotherapy input as it says that instructions on functional exercises should be given, while it highlights that this should be accompanied by written information, this does not preclude verbal instruction; and the requirement to ensure the needs of all adults are met by NHS services are addressed in NICE's guideline on patient experience in adult NHS services and others, including NICE's guideline on learning disabilities and behaviour that challenges.

One topic expert said that it was important to recognise that 'patients who are elderly and frail, those who are homeless and from lower socioeconomic groups appear to present for diagnoses at later stages and will have poorer prognoses in view of this'.

A topic expert also highlighted that while male patients were not included in the PROSPER trial, male patients with breast cancer are also at risk of shoulder morbidity and that the recommendations should also be applied to men with breast cancer.

Overall decision

The PROSPER trial addresses many of the concerns raised with the evidence base in 2009: it is an adequately powered RCT with a suitable sample size, included patients with pre-existing shoulder problems, undertook an ITT analysis and researchers analysing the data were blinded to intervention allocation. While the pragmatic design of the RCT may be considered as having less internal validity than a 'standard' RCT, it has the benefit of providing results that are more generalisable to the real world (greater external validity) and the pragmatic design of the intervention, allowing for tailoring of the intervention, is important for meeting the individual needs of patients.

The UK based study found that leaflets plus a structured exercise programme delivered at 7 to 10 days, 1 month and 3 months post-operation with up to 3 more sessions over a year, led to a significant improvement in upper limb function at 12 months postoperative follow-up; and was cost-effective in comparison with leaflets (usual care) in women undergoing

breast cancer surgery at risk of postoperative upper limb morbidity. The intervention was safe, with no serious adverse events and no increase in complications.

With regards to the intervention leading to a clinically meaningful improvement in upper limb function, there is no agreed change score for DASH. The developers of DASH suggest that a minimal clinically meaningful difference in DASH scores is 15 for discriminating between improved and unimproved patients (see what is considered to be a clinically important change for the DASH/QuickDASH?), however they note that there is considerable variability between studies, ranging from 3.9 to 15 being considered as a clinically meaningful difference. They also highlight that the minimal detectable change at the 95% confidence level, which the minimal clinically meaningful difference could be at, or below, also varies across studies they assessed, ranging from 8 to 17, with a mean of 13. The authors of the PROSPER study provide a justification for choosing 7 as the minimal clinically meaningful difference in DASH scores between groups (which is what the analysis found): the study was about preventing arm mobility issues rather than treating pre-existing issues; most of the study participants did not have severe upper limb dysfunction before their surgery as the mean baseline DASH score was 19, whereas in studies of other conditions such as shoulder arthroplasty or elbow arthroplasty baseline mean DASH scores were 64 and 59 respectively; it took into account the pragmatic trial design and long follow-up period. Importantly, at 12 months follow-up, the mean DASH score had reduced to 16.3 in the exercise group, while it increased to 23.7 in the usual care group. The developers of DASH report that 'there are no divisions to categorise scores as excellent, good or fair or mild, moderate or severe disability' but they do provide information on normative data for DASH in a US general population (n=1,800): the general population mean score was 10.1 (standard deviation=14.68) (Hunsaker et al. 2002). Consideration of what is considered a clinically significant improvement in arm mobility should be considered during the update.

All topic experts thought that the findings of the PROSPER trial indicated that recommendations on arm mobility in the NICE guideline should be updated.

The current recommendations highlight that pre-existing shoulder conditions may inform treatment decisions, but do not provide details of potential interventions; and they focus on referring people for physiotherapy only when a persistent reduction in arm and shoulder mobility has been identified after breast cancer treatment, rather than considering how to prevent arm and shoulder mobility problems from occurring.

Based on the results of the PROSPER trial and topic expert feedback we are proposing

that recommendations 1.12.5 to 1.12.8 on arm mobility in the NICE guideline are updated in relation to the content and timing of exercise programmes offered to people who have undergone axillary node clearance or radiotherapy to the axilla or supraclavicular fossa for breast cancer or who are considered at high risk of a reduction in arm or shoulder movement.

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