6-year surveillance 2015 – Early and locally advanced breast cancer (2013) NICE guideline CG80

Appendix A: decision matrix

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Referral, diagnosis and preoperative assessment			
80 – 1 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? (1.1.1, 1.1.2)			
No relevant evidence identified.	An individual patient data (IPD) meta-analysis[1] of 4 studies of preoperative MRI in people with breast cancer suggested that local recurrence-free survival or distant recurrence did not differ between the group that had preoperative MRI and the group that did not (p=0.87) at 8 years. A meta-analysis[2] of 85 studies suggested that HER2 overexpression is associated with the following imaging features: presence of microcalcifications on mammography or ultrasound; branching or fine linear microcalcifications, or extremely dense breasts on mammography; and washout or fast initial kinetics on MRI. Maximum fluorodeoxyglucose standardised uptake value was higher in the presence of HER2 overexpression.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The new evidence suggested that using MRI in staging of breast cancer has no effect on recurrence at 8 years. This evidence is unlikely to affect the current recommendation that routine MRI in preoperative assessment is not recommended. Additionally, some features of tumours seen on MRI and other imaging modalities may be associated with HER2 overexpression; however, the evidence does not provide any information about using these features as part of diagnosis. CG80 does not recommend MRI routinely for assessing breast cancer or DCIS, but in specific circumstances such as if there are discrepancies between clinical examination, mammography and ultrasound assessments.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
80 – 2 What is the role of pretreatment ultrasound assessment in staging the axilla? (1.1.3)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** When considering the need to update the guidance on ALND 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.
Providing information and psychological support			
80 – 3 What are the effective strategies to prevent and manage psychological distress in patients with early stage breast cancer? (1.2.1, 1.2.2, 1.2.3)			
No relevant evidence identified.	**Psychological interventions** A Cochrane review[3] of 30 RCTs assessed psychosocial interventions to improve quality of life and general psychological distress in the 12-months after initial cancer diagnosis. No significant effects were observed for quality of life at 6-month follow up; however, a small improvement was observed in quality of life using cancer-specific measures. General psychological distress assessed by 'mood measures' improved, but no significant effect was observed for measures of depression or anxiety. Psychoeducational and nurse-delivered interventions that were administered face to face and by telephone with breast cancer patients had small significant effects on quality of life (2 studies).	None identified relevant to this question.	New evidence is consistent with guideline recommendations. Evidence was identified for several interventions for psychological distress including mindfulness-based stress reduction, exercise such as yoga and tai chi, individualised care plans. 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 shows promise for reducing depression and anxiety, and yoga shows promise for increasing quality of life. Several systematic reviews found important differences between studies in the specifications of the interventions, so further rigorous research is needed to define the effectiveness of interventions.

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	Significant variation in study participants, mode of delivery, discipline of 'trained helper' and intervention was noted. **Mindfulness-based stress reduction** Two meta-analyses[4,5] (3 studies and 9 studies respectively) of mindfulness-based stress reduction in people with breast cancer indicated that this intervention significantly reduced depression symptoms. However, one of the meta-analyses[5] included only 2 RCTs out of the 9 included studies and 6 studies were single group before-and-after studies, so there is no good comparator to show that these outcomes wouldn't improve naturally over time. **Individualised care plans** A systematic review[6] assessed the impact of individualised care plans on the quality of life of adult female breast cancer survivors. Studies had significant heterogeneity between populations, interventions and outcomes so meta-analysis was not possible. 1 RCT and 1 other pilot study in older breast cancer survivors were included. The RCT found no significant or clinically important differences between individualised care plans and control for cancer-related distress or quality of life. In the pilot study, symptoms of distress significantly decreased and symptom management behaviours positively increased in the intervention group and negative mood symptoms significantly decreased. There was no statistically significant change in specific quality of life measures.		Overall, these findings are consistent with the CG80 recommendations that people with breast cancer should have support and access to specialist psychological support, but does not recommend specific interventions. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Exercise interventions A meta-analysis[7] of 25 trials of exercise interventions on the quality of life of breast cancer survivors was identified. Participants in the exercise intervention groups had higher overall and cancer-specific quality of life than those in the control group. A meta-analysis[8] of 12 RCTs (n=742) of yoga on health-related quality of life and psychological health in breast cancer patients and survivors found short-term effects on global health-related quality of life, functional wellbeing, social wellbeing, and spiritual well-being. However, these effects were only present in studies with unclear or high risk of selection bias. Another meta-analysis[9] of 6 RCTs (n=382) of yoga on psychological function and quality of life in women with breast cancer was identified. A statistically significant effect favouring yoga for the outcome of quality of life was found. The effects of yoga on psychological function outcomes, such as anxiety, depression, distress, sleep, and fatigue were not statistically significant. A meta-analysis[10] of 5 RCTS (n=407) assessed the effect of tai chi on quality of life in breast cancer survivors. Tai chi did not improve BMI, bone mineral density, or muscle strength, physical wellbeing, social or family wellbeing, emotional wellbeing or functional wellbeing. A meta-analysis[11] of 12 comparative		

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	studies (n=1014) of aerobic exercise for cancer-related fatigue in people with breast cancer receiving chemotherapy. Revised Piper Fatigue Scale scores were significantly lower in the intervention group than those in the control group. However, there was no significant difference in the Functional Assessment of Chronic Illness Treatment-Fatigue scale (FACIT-F). Subgroup analysis showed that exercise significantly affected fatigue measured in both measures in Asian populations but not in white populations.		
Surgery to the breast			
80 – 4 What is the optimal tumour-free tissue margin to achieve in patients who undergo wide local excision for DCIS? (1.3.1, 1.3.2, 1.3.3)			
3-year surveillance (2011) A study[12] reviewing the evidence on surgical margins in breast-conserving therapy for early-stage invasive breast cancer suggested that 'positive or close' versus 'negative' margin status has a prognostic effect in all women treated for invasive breast cancer. Increasing threshold distance for negative margins was weakly associated with reduced odds of local recurrence; however, this was not significant after adjustment for covariates (adjuvant therapy). A study[13] investigating the relationship between microscopic margins and outcome of breast conserving surgery indicated no significant difference in treatment results between close and free	A systematic review[18] of 5 studies (1 RCT; 4 cohort studies) found significant reductions in involved surgical margin status, re-operation rates and operative time with radioactive seed localisation for non-palpable invasive breast cancers compared with wire-guided localisation. Volume of specimens excised was not significantly different. A systematic review[19] of 6 studies (n=1611) of the available evidence on the accuracy of radioactive seed localisation in patients undergoing breast-conserving surgery showed that overall complete resection rates ranged from 73% to 97%. 3 studies included over 300 patients, and complete resection rates in these studies varied between 89.5% and 96.7%. The risk of	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. This area was not considered to need updating at the 3-year time point. Wider margins, relative to narrower widths, for declaring negative margins was unlikely to a have substantial additional benefit for long-term local control in breast-conserving therapy, which is in keeping with current recommendations. 4 studies supported wide margin excision when compared with narrow margin. However, dimensions were defined in the abstract of only 1 study suggesting margins of at least >2mm, which is in line with current recommendations. 1 study showed no significant difference between close and the free margins. No further evidence on the optimum tumour-free tissue margin

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margins. A study[14] retrospectively evaluating the outcome of patients with multifocal and multicentric breast cancer demonstrated that wide conservative surgery is a safe therapy in selected patients with multicentric or multifocal breast cancer. A study[15] evaluating 3 methods of breast-conserving surgery for non-palpable invasive breast cancer found that ultrasound-guided breast-conserving surgery for non-palpable invasive breast cancer was more accurate than wire localisation and radio-guided occult lesion localisation. Excision volumes were large in all groups, especially for radio-guided occult lesion localisation. A study[16] looked at the safe margin for breast-conserving surgery in early stage invasive breast cancer and DCIS. The study showed that a positive margin was associated with increased risk of local recurrence after breast-conserving surgery for invasive breast cancer and DCIS. There was no cut-off for margin width although the risk of local recurrence was accepted to be low if the margin was >10 mm whereas margins of <2 mm were considered inadequate. A study[17] comparing reoperation rates, volume of breast excised, and number of pathology slides examined in 2 groups of patients who underwent breast-conserving surgery with or without 4 or 5 additional margins suggested that resection of 4 to 5 additional margins	seed migration was 0–0.6% and failure of seed placement was 0–7.2%. A systematic review[20] of 37 studies of margin assessment techniques noted that after primary breast conservation surgery, re-excision rates were higher with permanent histopathological section (35%) than with imprint cytology (11%) or with frozen section analysis (10%). Imprint cytology had sensitivity of 72% and specificity of 97%. Frozen section analysis had sensitivity of 83% and specificity of 95%.		was identified at 6-year surveillance. However, at 6-year surveillance, studies were identified showing improved efficacy of radioactive seed localisation over wire-guided localisation and providing estimates of the rates of complete resection. Additional evidence highlighted the efficacy of imprint cytology and frozen section analysis in measuring margins. These techniques may improve evaluation of margin status but do not provide new evidence about the optimum size of margins. CG80 recommends radial margins of at least 2 mm. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

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during BCS for early-stage invasive breast cancer resulted in a higher rate of negative microscopic margins, lower volume of breast excised, and subsequently, a lower reoperation rate.			
80 – 5 What is the role of mastectomy in patients with localised Pagets disease of the nipple? (1.3.4)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Surgery to the axilla			
80 – 6 What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis? (1.4.7, 1.4.8)			
3-year surveillance (2011) A meta-analysis[21] comparing the effectiveness and safety of sentinel lymph node biopsy (SLNB) with axillary lymph node dissection (ALND) noted that SLNB was more effective for node-negative patients and selected patients with micro-metastasis. ALND remains standard management for macro-metastasis.	**Surgical procedures for ALND** A systematic review[22] of 6 RCTs (n=585) demonstrated that insertion of a suction drain in the axilla after breast cancer surgery resulted in significant reductions in the rate of seroma formation, and volume and frequency of seroma aspiration; however, hospital stay was longer. A Cochrane review[23] of 7 RCTs (n=960) of wound drainage after axillary dissection for breast carcinoma found a significant reduction in the incidence of seroma formation in participants with drains inserted. Infection rates did not	**SLNB versus ALND** In 3 reports from 2 RCTs (IBCSG 23-01[25] and ACSOG Z0011[26,27]) identified by topic expert feedback and 1 systematic review and meta-analysis,[28] identified by search SLNB was non-inferior to ALND in people with micro-metastasis (defined in 1 trial as ≤2 mm) or 1–2 lymph nodes positive for metastasis. SLNB was non-inferior across outcomes such as 5-year disease-free survival, overall survival at 6.3 years' follow-up, local or regional recurrence. SLNB avoided adverse effects associated with ALND including sensory and motor neuropathy and	**SLNB versus ALND** New evidence was identified that may change current recommendations. ALND remains standard management for macro-metastasis in the lymph nodes. Evidence at 3-year surveillance suggested that SLNB may be effective in selected patients with micro-metastases. Further evidence suggests that SLNB alone may be suitable if small metastases affecting 1 or 2 sentinel nodes are detected. This may have an impact on the guideline, which currently recommends ALND as the preferred option for micro- and macro-metastases.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	differ between groups. However hospital stay was 1.47 days longer when drains were used. No significant difference in the incidence of lymphoedema was noted. In a meta-analysis[24] of 4 studies (n= 352), electrosurgical bipolar vessel sealing systems significantly increased the number of retrieved axillary lymph nodes compared with traditional suture ligation. Intraoperative times and the volume or duration of postoperative axillary drainage were not significantly different. Bipolar systems may be associated with an increased risk of postoperative seroma formation.	lymphoedema. Topic expert feedback suggested that there may be issues with the populations in the studies such as differences in the number of metastases between groups. Additionally, Galimberti et al. (2013) included people with isolated tumour cells, and this population would not undergo treatment according to current guidance. These issues do not affect the need to update this section of the guideline but should be considered during development of any update.	Furthermore, the RCTs providing this new evidence were highlighted by several external commentators, indicating that this subject has high clinical relevance in the UK. The issues identified in topic expert feedback do not affect the need to update this section of the guideline but should be considered during development of any update. ***Surveillance decision*** The topic experts agreed that clinical practice had changed as a result of this evidence. This review question should be updated. **Surgical procedures for ALND** New evidence is unlikely to impact on guideline recommendations. For the studies investigating the use of suction drainage and bipolar vessel sealing systems during ALND, it is unclear whether any variation in practice around these interventions exists in the UK, and the current guidance does not specify techniques to be used during ALND.
80 – 7 In patients with invasive breast cancer or DCIS, when is sentinel lymph node biopsy justified as a staging procedure? (1.4.1–1.4.6)			
3-year surveillance (2011) A study[29] comparing negative sentinel lymph node dissection alone (SLND) with negative sentinel node dissection and negative axillary lymph node dissection (ALND) showed lower post-	A meta-analysis[35] of SLNB in people with breast cancer with previous surgery to the primary breast tumour compared with no surgery suggested that surgical biopsy of the primary breast malignant lesions does not affect the detection rate	None identified relevant to this question.	New evidence is consistent with guideline recommendations. At 3-year surveillance, the studies showed effectiveness of SLNB compared with ALND for people with sentinel-node negative disease and

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surgical morbidity in the SLND group over 3 years' follow-up. 2 studies[30,31] suggested that SLNB was not inferior to ALND. 1 study found that overall survival, disease-free survival, and regional control were equivalent between groups. When the SLN was negative, SLN surgery alone with no further ALND was an appropriate, safe, and effective therapy for people with breast cancer patients and clinically negative lymph nodes. A study[32] comparing ALND with no ALND after negative sentinel node testing noted that preservation of healthy lymph nodes may be beneficial. A meta-analysis[33] of the incidence of SLN metastasis in patients with DCIS concluded that patients with a preoperative diagnosis of DCIS should be considered for SLN biopsy. A systematic review[34] suggested that position emission tomography (PET), with or without CT, for assessment of axillary nodes in early breast cancer had lower sensitivity and specificity than sentinel lymph node biopsy SLNB.	of SLNB. However, the false negative rate was slightly higher. A meta-analysis[36] found that sentinel node detection in both deep and superficial lymphatics was associated with higher detection rates and lower false-negative rates than either superficial or deep node detection alone. A meta-analysis[37] of 15 studies suggested that SLNB after neoadjuvant chemotherapy in node-positive breast cancer patients had a pooled identification rate of 89%, and a false-negative rate of 14%. The false-negative rate was lower when immunohistochemistry plus haematoxylin and eosin staining was used (8.7%) compared with haematoxylin and eosin staining alone (16.0%). A systematic review[38] of 10 studies of SLNB in people having neoadjuvant chemotherapy showed identification rates from 97% to 100%, sensitivity of 100%, and a 0% false-negative rate. Using an isotope combined with blue dye was associated with slightly higher probability of identification of metastasis (99.5%) than using an isotope or blue dye alone (98.5%). SLNB before neoadjuvant chemotherapy testing before had a lower false negative rate (0% vs 15.8%) and higher success rate (100% vs 81%) than after neoadjuvant chemotherapy. A meta-analysis[39] of 24 studies of SLNB in people with micro-invasive breast		DCIS. These findings were in line with current recommendations. The study of PET had no effect on recommendations because of poor performance compared with SLNB. In addition, new evidence identified at 6-year surveillance focused on SLNB in subgroups of patients, such as those having neoadjuvant treatment or those with micro-invasive breast cancer. SLNB may be effective in people who have had neoadjuvant chemotherapy or primary surgery. However, there is some evidence to suggest that SLNB may be more accurate if performed before neoadjuvant treatment. Rates of positive lymph nodes in micro-invasive disease are low but may still be clinically significant. The false-negative rate of SLNB remains a concern, but improvements may be seen if both deep and superficial nodes are tested; if immunohistochemistry testing plus haematoxylin and eosin staining is used; or if an isotope plus blue dye is used. The study of ultrasonography plus fine-needle aspiration cytology did not provide evidence to suggest that this strategy is better than SLNB in staging the axilla. CG80 recommends SLNB for staging using the dual technique with isotope and blue dye. **Surveillance decision**

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	cancer found sentinel-node positivity rates of 3.2% for macro-metastasis, 4.0% for micro-metastasis, and 2.9% for isolated tumour cells. A meta-analysis[40] of 20 studies of ultrasonography plus fine-needle aspiration cytology had moderate sensitivity and high specificity for staging of axillary lymph nodes in people with breast cancer. The positive likelihood ratio was 22.7 and the negative likelihood ratio was 0.32.		Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 8 What is the prognostic significance of small metastatic deposits in sentinel nodes? (1.4.7, 1.4.8)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Breast reconstruction			
80 – 9 When is it appropriate to perform immediate breast reconstructive surgery?			
No relevant evidence identified.	A systematic review[41] of 12 studies (n=1853) assessed the outcome of adjuvant radiotherapy after an immediate 2-stage prosthetic breast reconstruction, either following tissue expansion or after removal of the tissue expander and insertion of a final breast implant. Outcomes were compared with those of patients who had reconstruction without	None identified relevant to this question.	The new evidence is unlikely to impact on guideline recommendations. New evidence suggests that immediate breast reconstruction may be associated with poorer outcomes in terms of failure rate, severe capsular contractures, cosmesis and fat necrosis if adjuvant radiotherapy is then administered.

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	radiotherapy. No RCTs were identified and only 1 prospective, non-randomised study was found. Adjuvant radiotherapy resulted in a significantly higher reconstruction failure rate in immediate 2-stage prosthetic breast reconstruction compared with controls (18.6% versus 3.1%). Radiotherapy increased the failure rate when given after tissue expansion but also after implant insertion. Severe capsular contractures and inferior cosmetic results were also seen with radiotherapy. A meta-analysis[42] of 25 observational studies (n=1247) of immediate autologous breast reconstruction with postoperative radiotherapy compared with no radiotherapy found no significant differences in total prevalence of complications or revision surgery but a summary measure for fat necrosis favoured the group without radiotherapy. Results from 12 studies (n=1633) comparing immediate reconstruction and radiotherapy with delayed reconstruction after radiotherapy reported no significant difference in overall incidence of complications and fat necrosis, but delayed reconstruction was associated with a significant reduction in the need for revision surgery.		However, there are inconsistencies in findings for different comparisons – analysis of immediate reconstruction plus radiotherapy versus immediate reconstruction alone showed no effects on complications or revision surgeries. In contrast, analysis of immediate versus delayed reconstruction with both groups receiving radiotherapy indicated better results with delayed reconstruction. The guideline acknowledged that immediate reconstruction may be associated with increased complications that could lead to a delay in adjuvant treatment, but noted that knowledge of the pros and cons of the techniques available was necessary. The evidence is consistent with current recommendations to discuss and offer all appropriate breast reconstruction options with patients. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

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Postoperative assessment and adjuvant therapy planning			
80 – 10 Does progesterone receptor status add further, useful information to that of oestrogen receptor status in patients with invasive breast cancer? (1.6.1–1.6.4)			
No relevant evidence identified.	No relevant evidence identified.	Topic expert feedback highlighted a population cohort[43] study of 1074 patients presenting to a single cancer centre found that PR-negative tumours had significantly poorer prognosis for overall survival, breast cancer-specific survival and disease-free survival, even in the ER-positive, LN-negative group and was not influenced by endocrine therapy.	The new evidence is unlikely to impact on guideline recommendations. The evidence on poorer prognosis with PR-negative tumours adds to the inconsistent evidence base considered in developing the recommendation to not routinely assess progesterone receptor status. However, this study does not provide evidence that would affect treatment options for people with PR-negative tumours. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 11 What is the best method of adjuvant treatment planning? (1.6.5–1.6.7)			
No relevant evidence identified.	No relevant evidence identified.	The 'predict' tool was highlighted by topic experts. This tool aims to help patients and clinicians decide what adjuvant treatments are appropriate for the person.	New evidence was identified that may change current recommendations. The guideline noted that 'Researchers were unable to define this question specifically enough to enable it to be appraised. The Guideline Development Group commissioned an expert position paper to assess the validity of Adjuvant! Online as a tool to assist with clinical decisions, about adjuvant therapy in patients with early invasive breast

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			cancer'. It is not clear how current the information in Adjuvant! Online remains. There are no indications that updates to the website have been made since 2011; however, this is difficult to prove by simply browsing the website. 'Predict' is under active maintenance with the most recent update to the model in November 2014. For this reason, and the fact that the Predict model is based on UK data mean that the recommendation to use Adjuvant! Online may no longer be appropriate. **Surveillance decision** The topic experts agreed that Adjuvant Online was no longer appropriate to recommend because a range of tools were available. They thought that new recommendations should focus on guiding people about how to choose a good tool, rather than specifying the tool to use. This review question should be updated.
80 – 12 What is the optimal time interval from completion of definitive surgery to commencement of adjuvant therapy? (1.6.8)			
No relevant evidence identified.	**Effect of time to treatment** A meta-analysis[44] of 7 studies (n=34,097) suggested that a 4-week increase in time to adjuvant chemotherapy was associated with a significant decrease in both overall survival and disease-free survival. The	None identified relevant to this question.	New evidence is consistent with guideline recommendations. The evidence that delay to adjuvant chemotherapy is associated with poorer outcomes is consistent with CG80, which recommends that adjuvant treatments are started as soon as possible within 31

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	most common adjuvant chemotherapy regimens were cyclophosphamide, methotrexate, and fluorouracil (CMF) or anthracycline-based. **Sequence of adjuvant treatment** A Cochrane review[45] of 3 RCTs (n=1166) of various methods of sequencing of adjuvant chemotherapy and radiotherapy in women with early breast cancer found no significant differences for local recurrence-free survival, overall survival, relapse-free survival and metastasis-free survival. However, concurrent chemoradiation increased anaemia, telangiectasia and pigmentation.		days of completing surgery. The guideline notes 'Whether these treatments should be given concurrently or sequentially and if sequentially in what order, is unclear.' It also recognised the increased risk of increased toxicity with concurrent chemoradiation. The new evidence does not provide further evidence to change this position. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Endocrine therapy			
80 – 13 In premenopausal breast cancer patients, what are the benefits of ovarian suppression versus tamoxifen? (1.7.1, 1.7.2)			
No relevant evidence identified.	No relevant evidence identified.	Topic expert feedback identified the SOFT trial,[46] in which premenopausal women with hormone-receptor positive breast cancer (n=3066) were randomly assigned to receive 1 of 3 treatments stratified by whether or not patients had previously received chemotherapy. The treatment groups were 5 years of tamoxifen or tamoxifen plus ovarian suppression or exemestane plus ovarian suppression. The analysis focused on only the tamoxifen only and tamoxifen plus ovarian suppression groups. After 67 months of follow-up, disease-free survival was 86.6% in the tamoxifen plus ovarian suppression group versus 84.7% in the tamoxifen only group. However,	New evidence is unlikely to impact on guideline recommendations. The SOFT trial showed no significant benefit of adding ovarian suppression to tamoxifen treatment in premenopausal women with early breast cancer. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

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		this difference was not significant. In a sub-analysis of only people who had chemotherapy, the rate of freedom from breast cancer was 82.5% in the tamoxifen plus ovarian suppression group and 78.0% in the tamoxifen-only group; again this difference was not significantly different.	
80 – 14 What is the best timing/sequencing of aromatase inhibitors and the duration of treatment as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer? (1.7.3–1.7.7)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 15 What are the indications for hormonal treatments for the adjuvant treatment of early oestrogen-positive breast cancer? (1.7.3–1.7.7)			
3-year surveillance (2011) **Extended tamoxifen or aromatase inhibitors** A cost-effectiveness analysis[47] of anastrozole versus tamoxifen from the perspective of the German public health insurance suggested that adjuvant treatment with anastrozole for postmenopausal women with hormone receptor-positive early breast cancer was a cost-effective alternative to tamoxifen.	***Extended hormonal treatments*** This question incorporated Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer (NICE TA112), which recommends endocrine therapy with anastrozole, letrozole or exemestane alone or after tamoxifen for up to 5 years. A meta-analysis[48] of 8 randomised trials (n=29,138) comparing the efficacy of 5 years of hormonal therapy with more than 5 years of hormonal therapy, in	***Extended hormonal treatments*** Topic expert feedback highlighted the ATLAS trial,[54] in which women with early breast cancer (n=12,894) who had completed 5 years of treatment with tamoxifen were randomly allocated to continue tamoxifen to 10 years or stop at 5 years. In ER positive breast cancer, continuing tamoxifen to 10 years was associated with lower risk of breast cancer recurrence, breast cancer mortality, and overall mortality. The reductions in adverse breast cancer outcomes were greatest after year 10.	**Extended tamoxifen or aromatase inhibitors** This question incorporated Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer (NICE TA112). Additional analysis of aromatase inhibitors was done for CG80. The finding from 3-year surveillance that anastrozole was cost effective in postmenopausal women with hormone receptor positive breast cancer compared with tamoxifen, was in line

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	patients with early breast cancer was identified. Overall, in oestrogen receptor positive breast cancer, extended endocrine therapy beyond 5 years of tamoxifen significantly improved overall survival, breast-cancer specific survival and relapse-free survival compared with only 5 years of hormonal therapy. Loco-regional and distant relapses were reduced by 36 and 13%, respectively. Compared with 5 years of tamoxifen, additional adjuvant endocrine therapy reduced risk of death by about 10% and risk of relapse of oestrogen-receptor positive breast cancer by 30%. ***Tamoxifen versus aromatase inhibitors*** An individual patient data meta-analysis[49] included 31,920 postmenopausal women with ER positive early breast cancer. It looked at data from randomised trials of 5 years of treatment with tamoxifen or aromatase inhibitors or sequential use of tamoxifen then aromatase inhibitors for a total of 5 years. When 5 years of aromatase inhibitors was compared with 5 years of tamoxifen, aromatase inhibitors were associated with lower recurrence rates in the first year of treatment. In years 2–4 the difference remained but was smaller and after 5 years there was no significant difference between treatments. 10-year breast cancer mortality was significantly lower with aromatase inhibitors (12.1%) compared with tamoxifen (14.2%).	Mortality from causes other than breast cancer was not significantly affected. Ischaemic heart disease was less common in the group continuing tamoxifen but pulmonary embolus and endometrial cancer were more common in the group continuing tamoxifen. The cumulative risk of endometrial cancer during years 5–14 was 3.1% (mortality 0.4%) for women allocated to continue tamoxifen versus 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%).	with current guideline recommendations. ***Extended hormonal treatments*** New evidence may impact on current recommendations. At 6-year surveillance, results from 1 meta-analysis and 1 RCT suggest that longer duration of treatment with endocrine treatments, specifically tamoxifen, is associated with better outcomes. The guideline noted that 5 years of treatment with tamoxifen was standard practice for low-risk patients with aromatase inhibitors offered to specific subgroups of postmenopausal women as adjunctive or alternative to treatment with tamoxifen. No evidence on efficacy of tamoxifen was analysed. Evaluation of efficacy and adverse events associated with standard versus extended treatment with tamoxifen may be warranted. Reconsideration of tamoxifen may also affect the selection and duration of aromatase inhibitor treatment, which may be outside the current marketing authorisation for these drugs. Because the aromatase inhibitors are covered by NICE TA112 (Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer November 2006), which is currently on the static list, this information has been passed to the TA team for consideration. ***Tamoxifen versus aromatase inhibitors*** New evidence may impact on current

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	When 5 years of aromatase inhibitors was compared with 2–3 years of tamoxifen then aromatase inhibitors to 5 years, recurrence was significantly lower in year 1 of taking aromatase inhibitors. In years 2–4 or year 5, when both groups were receiving aromatase inhibitors, recurrence did not differ significantly between groups. Overall recurrence was lower in people who had taken aromatase inhibitors for the full 5 years, but the difference in breast cancer mortality reduction was not significant. 10 year breast cancer mortality was significantly lower in people who switched to aromatase inhibitors (8.7%) than in those who had 5 years of tamoxifen (10.1%). There were fewer endometrial cancers with aromatase inhibitors than tamoxifen (10-year incidence 0·4% vs 1·2) but more bone fractures (5-year risk 8·2% versus 5·5); non-breast-cancer mortality was similar. Overall the authors concluded that 5 years of aromatase inhibitors was associated with a reduction in 10-year breast cancer mortality of about 15% compared with 5 years of tamoxifen. **Safety of aromatase inhibitors versus tamoxifen** A meta-analysis[50] of 7 trials (n=30,023) suggested that longer duration of aromatase inhibitor use was associated with significantly increased odds of developing cardiovascular disease and		recommendations. Evidence suggests that in postmenopausal women, 5 years of aromatase inhibitors is associated with lower breast cancer mortality than 5 years of tamoxifen. 5 years of aromatase inhibitors may also be more effective than using tamoxifen first then switching to aromatase inhibitors after 2–3 years. Because the aromatase inhibitors are covered by NICE TA112 (Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer November 2006), which is currently on the static list, this information has been passed to the TA team for consideration. However, not all aromatase inhibitors are licensed for use as a first endocrine treatment: exemestane is licensed for use only after tamoxifen. The new evidence does not consider each aromatase inhibitor separately according to its licensed indication, so may not be appropriate for consideration in a technology appraisal. ***Overall impact of extended tamoxifen or aromatase inhibitors*** The new evidence may impact on the length of time that tamoxifen should be offered to women with early breast cancer. Currently there is no recommendation stating that tamoxifen should be offered, and therefore no recommendation about the duration of treatment. A recommendation about use

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	bone fractures, but a decreased odds of venous thrombosis and endometrial cancer. 5 years of treatment with aromatase inhibitors was not associated with a significant increase in death without recurrence compared with 5 years of tamoxifen alone or tamoxifen for 2–3 years followed by an aromatase inhibitor for 2–3 years. **Endocrine therapy versus surgery** A Cochrane review[51] of 7 studies (n=1571) assessed surgery (with or without adjuvant endocrine therapy) compared with primary endocrine therapy for operable breast cancer in women aged 70 years and over who were fit for surgery. In all studies the endocrine therapy was tamoxifen. Surgery alone did not significantly affect overall survival but progression-free survival was significantly greater compared with primary endocrine therapy. Surgery plus endocrine therapy did not significantly affect overall survival, but progression-free survival was significantly greater compared with primary endocrine therapy. **Toremifene versus tamoxifen** A meta-analysis[52] of 23 RCTs (n=7242) showed that in early breast cancer, toremifene was associated with significantly higher 5-year survival rates, more vaginal discharge, a greater decrease in serum triglyceride levels, a smaller decrease in LDL cholesterol levels and in bone mineral density in Ward's triangle, and a greater increase in HDL cholesterol levels than tamoxifen.		of tamoxifen may need consideration of the populations who most benefit from tamoxifen, for example by menopausal status. Aromatase inhibitors may be more effective than tamoxifen overall, but can only be used in postmenopausal women. Tamoxifen is the only one of these endocrine therapies that may be used in premenopausal women. Current recommendations on aromatase inhibitors already outline different approaches to treatment depending on whether a woman has previously had treatment with tamoxifen or not. These recommendations may be impacted by any change to the duration of use of tamoxifen. The evidence also raises a question about whether 10 years of treatment with tamoxifen would be better than 5 years of treatment with aromatase inhibitors, but this question cannot be answered using only the evidence identified in this surveillance review. An update of this question will need to address these issues. **Surveillance decision** The topic experts agreed that there were several issues about duration and switching of tamoxifen and aromatase inhibitors that needed to be addressed. This review question should be updated. **Safety of aromatase inhibitors versus tamoxifen** New evidence is unlikely to impact on

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	However, the methodological quality of the included studies was low. **Tamoxifen-induced endometrial lesions** A meta-analysis[53] of 3 RCTs (n=359) of the levonorgestrel-releasing intrauterine system for treating tamoxifen-induced endometrial lesions in breast cancer patients demonstrated that the levonorgestrel-releasing intrauterine system prevented formation of new polyps. However, the levonorgestrel-releasing intrauterine system did not show clear effects on maintaining endometrial proliferation or secretory status, difference in atrophic or inactive changes, or endometrial hyperplasia without atypia. It did not significantly increase breast cancer recurrence or cancer-induced death. Bleeding was more frequent in the treatment group than in the control group.		guideline recommendations. The evidence suggests that aromatase inhibitors are generally safe for up to 5 years of use compared with tamoxifen. Both treatments are associated with adverse effects but they differ between treatments. **Endocrine therapy versus surgery** New evidence is consistent with guideline recommendations. The evidence comparing surgery with primary endocrine therapy indicates poorer performance of primary systemic therapy for progression-free survival despite showing no differences in overall survival. The adverse effects of aromatase inhibitors reported in the new evidence are consistent with those identified in the guideline. **Torimefene versus tamoxifen** New evidence is unlikely to impact on guideline recommendations. Toremifene is licensed only for metastatic breast cancer and no application for marketing authorisation in this indication is expected. This drug was not covered in the guideline and, although a meta-analysis was identified through the 6 year surveillance, the quality of the evidence identified in the meta-analysis was rated as low. Further research on the risks and benefits of toremifene compared with endocrine therapy is warranted before considering for inclusion in the guideline.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			Tamoxifen-induced endometrial lesions New evidence is unlikely to impact on guideline recommendations. Evidence suggests that the levonorgestrel-releasing intrauterine system may reduce the formation of new polyps without increasing risk of recurrence. However, there is no clear clinical need for recommendations for treating tamoxifen-induced endometrial lesions and the levonorgestrel-releasing intrauterine system is not licensed for this indication.
80 – 16 Is there an indication for the use of tamoxifen after excision of pure DCIS? (1.7.8)			
No relevant evidence identified.	A Cochrane review[55] of 2 RCTs (n=3375) evaluated the effects of postoperative tamoxifen in women having local surgical resection of DCIS. Tamoxifen after surgery for DCIS significantly reduced the recurrence of both ipsilateral DCIS and contralateral DCIS. The number needed to treat in order for tamoxifen to have a protective effect against all breast events was 15. There was no evidence of a difference detected in all-cause mortality.	None identified relevant to this question.	The new evidence is unlikely to impact on guideline recommendations. The results of a Cochrane review suggest that tamoxifen may reduce recurrence in people with DCIS, but may not reduce overall mortality. The guideline assessed 2 RCTs, which may be the same trials assessed in the Cochrane review; although this information is not available from the abstract. The reduction in local recurrence noted in the Cochrane review is about the same as that noted in the guideline so this evidence is unlikely to add much to what is already known. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			guideline update means that this question may be updated.
Chemotherapy			
80 – 17 What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer? (1.8.1, 1.8.2)			
3-year surveillance (2011) **Lapatinib** A meta-analysis[56] evaluated the clinical efficacy of lapatinib in HER2-positive and HER2-negative patients. Clinical benefit from treatment with lapatinib was limited to patients with HER2-positive breast cancer. The study concluded that lapatinib should not be administered to women with HER2-negative disease outside of the clinical trial setting, because it causes increased toxicity without improving disease outcome. **Inositol hexaphosphate** A pilot study[57] evaluated the beneficial effects of inositol hexaphosphate plus inositol in breast cancer patients treated with adjuvant therapy. Inositol hexaphosphate plus inositol as an adjunctive therapy was valuable help in ameliorating the side effects and preserving quality of life among the patients treated with chemotherapy. **Combination chemotherapy** A study[58] determined the effect of adding gefitinib to neoadjuvant epirubicin and cyclophosphamide on tumour response rates. A significantly higher pathological complete response rate was observed post hoc in triple negative breast cancer	**Combination chemotherapy** ***Anthracyclines versus CMF*** An individual patient data meta-analysis[59] included 5 randomised trials that compared adjuvant anthracycline-based regimens with CMF regimens. In people with HER2 overexpression, anthracycline-based treatment was associated with significantly lower event free survival and overall survival than CMF regimens. In people without HER2 overexpression, anthracycline-based treatment was not associated with lower event free survival or overall survival than CMF regimens. In people with normal TOP2A status, TOP2A overexpression or TOP2A deletion, anthracycline-based treatment was associated with lower event free survival and overall survival than CMF regimens. The authors noted that their findings do not support the use of anthracyclines only in patients with HER2-overexpressing or TOP2A-aberrated tumours. ***Adding taxanes to chemotherapy*** This question incorporated Paclitaxel for the adjuvant treatment of early node-positive breast cancer (NICE TA108) and Docetaxel for the adjuvant treatment of	**Managing adverse effects of chemotherapy** A UK-based retrospective audit[67] of amendments to chemotherapy regimens because of adverse events was highlighted at the consultation on the 3-year surveillance decision. It showed that in 1 hospital in Scotland, nearly a third of patients with node-positive breast cancer who had chemotherapy with fluorouracil plus epirubicin plus cyclophosphamide plus docetaxel needed to interrupt their treatment schedule for more than a week and a similar proportion needed dose reductions because of adverse events. This study was cited as an example of the need to inform patients about the adverse effects of taxanes. Although this cohort study is not the correct type for assessing effectiveness of chemotherapy it provides real-world information about adverse events.	**Lapatinib** New evidence is unlikely to impact on guideline recommendations. The benefit of lapatinib is not clear because no results were reported in the study abstract for the population with locally-advanced disease separate from those with advanced and metastatic disease. Lapatinib is not licensed for locally advanced breast cancer and no application for marketing authorisation is expected. **Inositol hexaphosphate** New evidence is unlikely to impact on guideline recommendations. Inositol hexaphosphate plus inositol is a dietary supplement that is not licensed for reducing side-effects of chemotherapy, and is not covered in CG80. **Combination chemotherapy** New evidence identified that may change current recommendations. At 3-year surveillance, evidence on adding gefitinib to combination chemotherapy was not expected to affect recommendations because gefitinib did not have a license for use in early breast

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
versus non-triple negative breast cancer independent of treatment. More patients in the gefitinib group discontinued treatment because of adverse events.	early node-positive breast cancer (NICE TA109), which recommend docetaxel but not paclitaxel. An individual-patient-data meta-analysis[60] of RCTs was identified comparing: any taxane-plus-anthracycline-based regimen versus the same, or more, non-taxane chemotherapy (n=44,000); one anthracycline-based regimen versus another (n=7000) or versus CMF (n=18,000); and polychemotherapy versus no chemotherapy (n=32,000). In trials adding 4 separate cycles of a taxane to a fixed anthracycline-based control regimen, extending treatment duration, breast cancer mortality was reduced. In trials with 4 such extra cycles of a taxane counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling non-taxane dosage, there was no significant difference. Trials with CMF-treated controls showed that standard 4AC and standard CMF were equivalent, but that anthracycline-based regimens with substantially higher cumulative dosage than standard 4AC (eg, CAF or CEF) were superior to standard CMF. Trials versus no chemotherapy also suggested greater mortality reductions with CAF than with standard 4AC or standard CMF. A meta-analysis[61] of 14 randomised adjuvant trials (n=25,067) comparing docetaxel-containing versus non-taxane-containing regimens was identified. The		cancer and the license status has not changed. At 6-year surveillance an individual patient data meta-analysis suggested that anthracycline-based chemotherapy is associated with a poorer response than cyclophosphamide, methotrexate, and fluorouracil (CMF) in people with HER2 positive breast cancer or abberations in TOPA2 expression. Another individual patient data meta-analysis looking at more than 100,000 women found that adding a taxane to anthracycline-based treatment was associated with lower breast cancer mortality, and this approach was as effective as using double the dose of anthracyclines alone. A further meta-analysis noted differences in the side-effects profiles of anthracycline-based chemotherapy depending on whether taxane-based treatment is added. The study showing benefits of docetaxel is consistent with the recommendation to offer docetaxel as part of adjuvant chemotherapy for breast cancer. In the original guideline anthracycline-based chemotherapy was noted to be used routinely, and only the benefit of adding taxanes was assessed. Evidence indicates a need to review the benefits, adverse effects, and costs of chemotherapy regimens, particularly in identifying regimens with better efficacy in types of breast cancer with the poorest

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	results favoured docetaxel for disease-free survival and overall survival. However, these outcomes were not significantly improved in people with node-negative breast cancer. A meta-analysis[62] of 10 RCTs (n=18,198) suggested that anthracycline-based chemotherapy plus taxane showed lower risks of incident leukaemia, venous thrombus and severe cardiotoxicity, but higher risks of incident severe neurotoxicity and non-recurrent death compared with anthracyclines alone. **Capecitabine** A meta-analysis[63] to evaluate the efficacy of the addition of capecitabine to anthracycline plus taxane-based adjuvant chemotherapy in people with high-risk early breast cancer found significant improvement in the additional capecitabine arm versus control in disease-free survival, overall survival, distant recurrence and death from breast cancer only. Meanwhile, subgroup analysis revealed that capecitabine significantly improved disease-free survival in triple negative, hormone receptor negative and HER2 negative patients. **Lapatanib** A meta-analysis[64] of 4 trials (n=073) in patients with HER-2+ locally advanced or metastatic breast cancer found a significantly higher overall response rate in patients who received the combination of lapatinib plus chemotherapy or		prognosis. Because this question incorporated Paclitaxel for the adjuvant treatment of early node-positive breast cancer (NICE TA108) and (Docetaxel for the adjuvant treatment of early node-positive breast cancer (NICE TA109), which recommend docetaxel but not paclitaxel, the information relating to these drugs will be passed to the TA team for consideration. **Capecitabine** New evidence identified that may change current recommendations. Capecitabine is currently licensed in locally advanced or metastatic breast cancer only after failure of previous anthracycline-based chemotherapy. No application for marketing authorisation is expected for capecitabine in early breast cancer. However, the evidence suggests that capecitabine may have a role in treating high-risk early breast cancer. Evaluation of this treatment in the guideline may be warranted. **Managing adverse effects of chemotherapy** New evidence is unlikely to impact on guideline recommendations. An audit suggested that patients need frequent amendments to chemotherapy regimens because of adverse events. The evidence that obese people tolerate chemotherapy better than people with lower body mass is interesting but does

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	endocrine therapy compared with chemotherapy or endocrine therapy alone, but with significant heterogeneity. Progression-free survival and overall survival were significantly longer in patients who received chemotherapy or endocrine therapy plus lapatinib. The group receiving chemotherapy or endocrine therapy plus lapatinib had higher rates of neutropenia, diarrhoea, and rash. ***Managing adverse effects of chemotherapy*** A systematic review[65] of 10 studies of dose modification of chemotherapy in obese women with breast cancer noted low rates of adjustment for confounders such as prophylactic hematopoietic growth factor use and empirical dose reductions. 7 studies found reduced toxicity in obese compared with non-obese women. Of 4 studies, in which dose capping was precluded or statistically adjusted for, 3 found reduced toxicity in obese women. These outcomes included less febrile neutropenia, fewer hospital admissions and fewer neutropenic events. A meta-analysis[66] of 17 studies (n=807) of long-term cognitive deficits in patients treated with standard-dose chemotherapy for breast cancer more than 6 months previously was identified. Deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or pre-chemotherapy baseline in the domains of verbal ability and visuospatial ability.		not have a clear clinical application. Additionally the study finding deficits in verbal and visuospatial ability does not indicate any methods to reduce this adverse effect. **Surveillance decision** The topic experts thought that this question was not correct, and is answered by the question on the best method of adjuvant therapy planning (see review question 80-11). The topic experts thought that an update of the guideline should not attempt to recommend specific chemotherapy regimens because of the pace of change in this area. This review question should be updated.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Age, education, time since treatment, and use of endocrine therapy did not affect observed cognitive deficits in verbal ability or visuospatial ability.		
Biological therapy			
80 – 18 What are the indications for the use of adjuvant biological therapy for early stage HER2-positive breast cancer? (1.9.1–1.9.3)			
	Efficacy of trastuzumab This question incorporated Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (NICE TA107), which recommended this drug for up to a year. A Cochrane review[68] of 8 RCTs (n=11,991) assessed trastuzumab alone, or in combination with chemotherapy, compared with no treatment, or chemotherapy alone, in women with HER2-positive early or locally advanced breast cancer. The combined HRs for overall survival and disease-free survival significantly favoured trastuzumab treatment. Trastuzumab significantly increased the risk of congestive heart failure and left ventricular ejection fraction decline. A meta-analysis[69] of 8 studies in people with small (<1cm pT1a-bN0M0) breast cancer tumours demonstrated a deleterious effect of HER2+ phenotype on disease-free survival and distant disease-free survival compared with the HR+/HER2- subgroup. A significant improvement in disease-free survival was observed with the addition of	None identified relevant to this question.	**Efficacy of trastuzumab** New evidence is unlikely to impact on guideline recommendations. The evidence suggests that trastuzumab is associated with better outcomes in people with HER2 positive breast cancer, even if they have very small tumours at presentation. The adverse events noted are consistent with previous knowledge. These findings are in line with the guideline recommendation to offer trastuzumab to people with HER2 positive early breast cancer. A related research recommendation about trastuzumab was included in the guideline (see below), but it is not likely to be answered by the new evidence. Because this question incorporated Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (NICE TA107), which recommended this drug for up to a year, the new evidence will be passed to the TA team for consideration. **Adverse effects of anti -HER2 treatments**

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	trastuzumab for HER2-positive pT1a-bN0M0 patients. **Adverse effects of anti-HER2 treatments** A meta-analysis[70] of 7 studies evaluating anti-HER2 monotherapy (lapatinib or trastuzumab or pertuzumab) versus anti-HER2 combination therapy was identified. The overall incidence results for severe diarrhoea for combined anti-HER2 therapy was 3.48% (95% CI: 11.60 to 15.37%) and for anti-HER2 monotherapy was 8.68% (95% CI: 7.33 to 10.03%). A meta-analysis[71] of 6 randomised trials investigating cardiac adverse events with combination anti-HER2 therapy compared to anti-HER2 monotherapy was identified. Congestive heart failure occurred in 0.88% (95% CI: 0.47 to 1.64%) of the combined anti-HER2 therapy group and 1.49% (95% CI: 0.98 to 2.23%) of the anti-HER2 monotherapy group. **Colony stimulating factors** A Cochrane review[72] of 8 RCTs (n=2156) assessed prophylactic colony-stimulating factors during chemotherapy in patients with breast cancer. In most trials, the chemotherapy regimens had a risk of febrile neutropenia that was below the threshold at which current guidelines recommend routine primary prophylaxis with colony-stimulating factors. Colony-stimulating factors significantly reduced the proportion of patients with febrile neutropenia. Colony-stimulating factors		New evidence is unlikely to impact on guideline recommendations. The studies on risk of severe diarrhoea and congestive heart failure with anti-HER2 treatment provide information that may be useful for doctors when discussing treatment options with patients. But the summary of product characteristics for trastuzumab already lists diarrhoea as a very common adverse event and congestive heart failure as a common adverse event. Furthermore, lapatinib and pertuzumab are not licensed for early breast cancer. Because this question incorporated Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (NICE TA107), which recommended this drug for up to a year, the new evidence will be passed to the TA team for consideration. **Colony stimulating factors** The new evidence is unlikely to impact on guideline recommendations. New evidence suggests that colony stimulating factors may improve some outcomes such as the proportion of patients with febrile neutropenia. However; adverse effects are common. Neutropenic sepsis (NICE CG151) contains a 'do not do' recommendation in this area, which this evidence is unlikely to overturn. 'Do not routinely offer G-CSF (granulocyte-colony stimulating factor)for the prevention of neutropenic sepsis in

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	also reduced early mortality, risk for hospitalisation and use of intravenous antibiotics. No significant difference in infection-related mortality was seen. The risks of severe neutropenia, infection or not maintaining the scheduled dose of chemotherapy did not differ between colony-stimulating factor-treated and control groups. Colony-stimulating factors frequently led to bone pain and injection-site reactions. **Chemotherapy-induced alopecia** A meta-analysis[73] of 8 RCTs and 9 controlled trials (n=1098) assessed interventions to prevent chemotherapy-induced alopecia. Participants were mainly breast cancer patients receiving chemotherapy containing doxorubicin or epirubicin. Scalp cooling, significantly reduced the risk of chemotherapy-induced alopecia, whereas topical 2% minoxidil and other interventions did not. No serious adverse effects associated with scalp cooling were reported.		adults receiving chemotherapy, unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity'. **Chemotherapy-induced alopecia** New evidence is unlikely to impact on guideline recommendations. Scalp cooling appears to be the only intervention to reduce the risk of alopecia associated with chemotherapy. This intervention is already common in clinical practice. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Assessment and treatment of bone loss			
80 – 19 What are the indications for the measurement of bone mineral density in patients with invasive breast cancer who are on adjuvant endocrine therapy? (1.10.1, 1.10.2)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	The new evidence is unlikely to impact on guideline recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			question may be updated.
80 – 20 What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer? (1.10.3)			
No relevant evidence identified.	A systematic review[74] of 11 RCTs suggested that postmenopausal women receiving endocrine therapy for breast cancer may have fracture rates ranging from 0.9% to 11%. Aromatase inhibitors have a risk about 1.5 times that of tamoxifen or placebo. 5 meta-analyses[75-79] of zoledronic acid as adjuvant treatment in breast cancer were identified, but the number of studies informing each meta-analysis varied. Overall survival was not affected by zoledronic acid in 4 meta-analyses, and was significantly in favour of zoledronic acid in 1 analysis. For disease-free survival, zoledronic acid had no significant effect in 4 analyses, and was not reported in 1 analysis. 2 meta-analyses noted no beneficial effect on bone metastases. Zoledronic acid was associated with fewer fracture events in 2 meta-analyses.	The AZURE study was identified from topic expert feedback. In an open-label, parallel-group RCT (AZURE)[80,81] in women aged ≥ 18 years (n=3360) with stage II or III breast cancer were randomly assigned to receive standard adjuvant systemic treatment alone (control group) or with zoledronic acid for 5 years. At the final analysis there was no significant difference between groups for the outcomes of disease-free survival, overall survival or distant recurrence. However, zoledronic acid was associated with lower development of bone metastases. Osteonecrosis of the jaw was confirmed in 26 people, all of which occurred in the zoledronic acid group (1.7%). These results were consistent with previously reported interim results from the AZURE study. Topic experts additionally identified an individual patient data meta-analysis[82] including 18,766 women who had participated in trials of bisphosphonates in early breast cancer. The aim of this study was to determine the benefits and risks of adjuvant bisphosphonate treatment. A significant reduction in recurrence in breast cancer in the bone was seen with bisphosphonates treatment, whereas reductions in recurrence, distant recurrence and	New evidence identified that may change current recommendations. The guideline referred to a position statement on management of breast cancer treatment induced bone loss, which remains valid. The evidence suggests that postmenopausal women with breast cancer receiving aromatase inhibitors may have a greater risk of fracture than those on tamoxifen or placebo, which is in line with recommendations in CG80. Evidence for survival benefit and reductions in bone metastasis with zoledronic acid has been inconsistent, although evidence supports a reduction in fracture risk, which is in line with current recommendations in CG80. The individual patient data meta-analysis aimed to resolve the inconsistencies seen in results from individual trials. It suggested that adjuvant bisphosphonates significantly improve recurrence rates and breast-cancer related mortality in postmenopausal women. Current guidance recommends bisphosphonates only for treatment of bone loss associated with treatments. The new evidence indicates that bisphosphonate treatment may have benefits in a wider population of postmenopausal women with early

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		breast cancer mortality were reported to be of borderline significance. No outcome was significant in premenopausal women, but in postmenopausal women, recurrence, distant recurrence, bone recurrence and breast cancer mortality were significantly lower with bisphosphonates. Bone fractures were significantly reduced but non-breast cancer mortality was not.	breast cancer. However, the benefits of bisphosphonate treatment must be weighed against the risks, particularly of osteonecrosis of the jaw. The 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.' **Surveillance decision** The topic experts agreed that bisphosphonates showed benefits in postmenopausal women, but the dosage and duration of treatment need to be established. This review question should be updated.
Radiotherapy			
80 – 21 What are the indications for radiotherapy after breast conserving surgery? (1.11.1, 1.11.2)			
3-year surveillance (2011) A study[83] concluded that high-dose-rate brachytherapy was feasible, reproducible and associated with very low perioperative and acute toxicity in selected patients with early-stage breast cancer. A study[84] suggested that letrozole can be safely delivered shortly after surgery and	**Adjuvant radiotherapy after breast-conserving surgery** A meta-analysis[90] of individual patient data (n=10,801) for women in 17 randomised trials of radiotherapy versus no radiotherapy after breast-conserving surgery found that radiotherapy significantly reduced the 10-year risk of any first recurrence from 35.0% to 19.3%	**Adjuvant radiotherapy after breast-conserving surgery** Topic expert feedback identified an RCT (PRIME II)[97] of 1326 women aged 65 years or older with early breast cancer judged low-risk who had had breast-conserving surgery and were receiving adjuvant endocrine treatment, showed that whole-breast radiotherapy was	**Adjuvant radiotherapy after breast-conserving surgery** New evidence is unlikely to impact on guideline recommendations. The evidence suggests that radiotherapy after breast-conserving surgery is associated with better outcomes on recurrence and breast-cancer related deaths compared with no radiotherapy.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
concomitantly with radiotherapy. However, the authors concluded that long-term follow-up is needed to investigate cardiac side-effects and cancer-specific outcomes. A systematic review[85] suggested that if immediate reconstruction is undertaken with the necessity of postmastectomy radiation therapy, an autologous flap results in less morbidity compared with implant-based reconstruction. A study[86] of long-term data concluded that breast conserving surgery in eligible patients was as effective as mastectomy for local tumour control, recurrence-free survival and overall survival. A study[87] comparing adjuvant radiotherapy with no radiotherapy following breast-conserving surgery for DCIS showed no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality after 10 years of follow-up. A study[88] suggested that trastuzumab administered concurrently with radiotherapy after breast-conserving surgery or mastectomy was not associated with increased acute adverse events. A study[89] found no effect on long-term outcomes when comparing 2 different radiotherapy and chemotherapy sequences in conservatively treated patients with breast cancer. This trial suggested that radiation therapy may be	and the 15-year risk of breast cancer death from 25.2% to 21.4%. The risk reductions remained significant when the population was stratified into node-negative or node-positive groups. The absolute benefits from radiotherapy varied substantially according to characteristics of the patient that can be predicted at the time when treatment decisions need to be made (age, grade, oestrogen-receptor status, tamoxifen use, and extent of surgery). A Cochrane review[91] of 4 RCTs (n=3925) of breast conserving surgery with and without radiotherapy in women at first diagnosis of pure DCIS noted a statistically significant benefit from the addition of radiotherapy on all ipsilateral breast events, ipsilateral invasive recurrence and ipsilateral DCIS recurrence. All subgroups analysed benefited from addition of radiotherapy. There were insufficient data to pool for long-term toxicity from radiotherapy. No information about short-term toxicity from radiotherapy or quality of life data were reported. A systematic review[92] of adjuvant radiotherapy after breast conserving surgery for invasive breast cancer and DCIS was identified. Overall, adjuvant radiotherapy had 15.7% lower local recurrence, 3.8% lower 15-year risk of breast cancer death and a 60% risk reduction in local recurrence in DCIS with no impact on distal metastases or overall survival.	associated with lower 5-year ipsilateral breast tumour recurrence than no radiotherapy. Compared with women allocated to whole-breast radiotherapy, the univariate hazard ratio for ipsilateral breast tumour recurrence in women assigned to no radiotherapy was 5.19 (95% CI 1.99 to 13.52). No differences in regional recurrence, distant metastases, contralateral breast cancers, or new breast cancers were noted between groups. 5-year overall survival was 93.9% in both groups.	This finding applies to the population with DCIS, which is in line with recommendations in CG80 to offer radiotherapy to this group of patients. Evidence suggests that radiotherapy is also beneficial after breast conserving surgery in people with invasive and node-positive disease. This evidence does not suggest that breast-conserving surgery is an appropriate treatment for invasive or node-positive cancer; merely that radiotherapy retains its benefits in this population. **Partial and accelerated partial breast irradiation** New evidence is unlikely to impact on guideline recommendations. The evidence on use of partial or accelerated partial breast radiotherapy do not seem to differ significantly from whole breast radiotherapy for many outcomes; however, systematic reviews have found inconsistent results for overall survival, recurrence-free survival and toxicity. The guideline does not make recommendations about partial or accelerated radiotherapy. **Radiation-associated angiosarcoma** New evidence is unlikely to impact on guideline recommendations. Evidence suggests that angiosarcoma associated with previous radiotherapy for breast cancer may be associated with poor survival, but treatment including re-irradiation may be effective. However, no evidence was identified on methods to

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
delayed until after anthracycline-based chemotherapy to avoid an increased risk of distant recurrence or excessive toxicity. For radiotherapy and breast conserving surgery, the evidence suggested that radiotherapy and breast conserving-surgery were effective and some studies showed that combining the treatments with trastuzumab and letrozole may also be effective but further evaluation was needed. The evidence at the 3 year surveillance review was considered to be in line with recommendations in the guideline.	A meta-analysis[93] of 5 RCTs (n=3190) to evaluate outcomes of radiotherapy after breast-conserving surgery in older patients (39% over 70 years) was identified. Most people had hormone receptor-positive T1 tumours without node involvement and all received adjuvant systemic therapy. Patients who received radiotherapy had a significantly lower relative risk of locoregional recurrence. The 5-year absolute risk was 2.2% among patients who received radiotherapy versus 6.5% among patients who did not. The absolute risk difference was 4.3 %, corresponding with a number needed to treat of 24. No differences were observed for distant recurrence or overall survival. **Partial and accelerated partial breast irradiation** A Cochrane review[94] of 4 RCTs (n=2253) determined that partial breast irradiation or accelerated partial breast irradiation was associated with significantly worse local recurrence-free survival compared with whole breast irradiation. Cosmesis was improved with partial breast irradiation or accelerated partial breast irradiation, but late toxicity (telangiectasia) and subcutaneous fibrosis appeared to increase. There was no clear evidence of a difference for the comparison of partial breast irradiation or accelerated breast irradiation versus whole-breast radiotherapy for overall survival, cause-specific survival, distant metastasis-free survival, subsequent mastectomy rate and relapse-free		reduce incidence of this late effect of radiotherapy. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	survival. A meta-analysis[95] of 4 RCTs (n=919) comparing accelerated partial breast irradiation with whole-breast radiotherapy in patients with early-stage breast cancer who had breast-conserving surgery was identified. Accelerated partial breast irradiation was associated with better cosmetic results. Overall survival at 5 or 8 years did not differ significantly but 10-year overall survival was significantly worse. There were no differences in 5-year local recurrence-free survival, cancer-specific, disease-free survival, local recurrence, the rate of contralateral breast cancer, and distant metastasis. **Radiation-associated angiosarcoma** A systematic review[96] of 74 studies (n=222) of treatment and prognosis of radiation-associated angiosarcoma of the breast was identified. The 5-year overall survival was 43% and 5-year local recurrence-free interval was 32%. Tumour size and age were significant prognostic factors on local recurrence-free interval and overall survival. Of all patients, 68% received surgery alone, 17% surgery and re-irradiation and 6% surgery with chemotherapy. The remaining 9% received primary treatments without surgery. Surgery with radiotherapy had a better 5-year local recurrence-free interval of 57% compared with 34% for surgery alone.		

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
80 – 22 When should patients with DCIS who have undergone complete excision or wide local excision be given radiotherapy? (1.11.2)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 23 Which groups of patients should receive chest wall radiotherapy after mastectomy? (1.11.3–1.11.4)			
No relevant evidence identified.	A meta-analysis[98] of 10 studies (n=3432) of adjuvant radiotherapy in people with T1–2, N1–3 breast cancer was identified. Adjuvant radiotherapy was associated with lower risk of locoregional recurrence in people with T1–2, N1–3 breast cancer. Overall survival was not significantly different between the adjuvant radiotherapy and no-adjuvant radiotherapy groups.	None identified relevant to this question.	New evidence identified that may change current recommendations. It is not clear from the study abstract whether the target of this radiotherapy is the chest wall, however the evidence suggests that radiotherapy after mastectomy may be associated with lower recurrence than no radiotherapy, although there may be no benefit on overall survival. The population studied equates to people at intermediate risk of local recurrence noted in the guidance. The full text of this study was reviewed as part of the evidence prioritisation for the surveillance report and all included studies targeted the chest wall plus between 1 and 3 nodal sites. It may be difficult to assess nodal radiotherapy without also addressing chest wall radiotherapy. The full text of this study was reviewed as part of the evidence prioritisation for the surveillance report and all included

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			studies targeted the chest wall plus between 1 and 3 nodal sites. It may be difficult to assess nodal radiotherapy without also addressing chest wall radiotherapy. Additional evidence on radiotherapy in this population comes from an individual patient data meta-analysis included in the section on nodal radiotherapy below. However the abstract states the target of radiotherapy to be 'chest wall and regional lymph nodes' so it is unclear which target the results are most applicable to. The study found improved outcomes of recurrence and breast cancer mortality in the intermediate risk group. Additionally, the outcome of the in-development technology appraisal on the Intrabeam radiation system may affect the groups of patients who would receive chest wall radiotherapy. The recommendation for the intermediate risk population is to consider entering the person into a trial such as SUPREMO to assess the value of radiotherapy. SUPREMO should have completed in November 2014 so this recommendation needs to be refreshed to remove this cross-reference. No results from SUPREMO are available. **Surveillance decision** The topic experts noted that the chest wall is the most common site of recurrence, thus an update should look at this clinical area.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			This review question should be updated.
80 – 24 What is the most effective radiotherapy dose fractionation regimen for patients undergoing external beam radiotherapy after surgical excision of breast cancer? (1.11.6)			
No relevant evidence identified.	No relevant evidence identified.	The topic expert feedback identified the FAST RCT[99], which included women aged 50 years or younger (n=915) with node-negative early breast cancer. The results indicated that after 3 years of median follow-up, 28.5 Gy in 5 fractions was comparable to 50 Gy in 25 fractions, and significantly milder than 30 Gy in 5 fractions, in terms of adverse effects in the breast.	New evidence is unlikely to impact on guideline recommendations. The evidence suggests that hypofractionation may be associated with fewer adverse events than standard-dose radiotherapy. However, data for outcomes such as recurrence and survival are not yet available. As such, it may be premature to consider hypofractionation for inclusion in the guideline at this time. Currently the guideline recommends giving 40 Gy in 15 fractions. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 25 What are the indications for an external beam radiotherapy boost to the site of local excision after breast conserving surgery? (1.11.7, 1.11.8)			
3-year surveillance (2011) A review and meta-analysis[100] showed that external beam radiation therapy was associated with a significantly lower axillary recurrence rate after negative SLNB.	No relevant evidence identified.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. At the 3 year surveillance review the evidence showed external beam radiation therapy to be effective which is in line with the current guideline recommendation to offer this treatment to people with a high risk of local

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			recurrence. No new evidence was identified in the 6 year surveillance review to change this conclusion. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 26 What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla? (1.11.9–1.11.14)			
No relevant evidence identified.	**Internal mammary node radiotherapy** A meta-analysis[101] suggested that radiotherapy to the internal mammary lymph node and medial supraclavicular lymph node in people with node-positive breast cancer, node-negative disease at high risk of recurrence or medial/central tumour resulted in a significant improvement in overall survival. Regional radiotherapy of the medial supraclavicular lymph node and the internal mammary lymph node was associated with a significant improvement in disease-free survival and distant metastasis-free survival. The effect sizes were not significantly different between trials for any end point. **Radiotherapy after ALND** An individual patient data meta-analysis[102] (n=8135) was identified. Women were randomly assigned to treatment groups during 1964-86 in 22 trials of radiotherapy to the chest wall and regional lymph nodes	Trials relevant to this question were identified through topic expert feedback. **Internal mammary node radiotherapy** The MA.20 study[103] randomly assigned 1832 women with node-positive or high-risk node-negative breast cancer to either whole breast radiotherapy or whole breast plus regional node radiotherapy (internal mammary, supraclavicular and axilla). All participants had breast-conserving surgery and adjuvant chemotherapy. At 10 year follow-up, survival did not significantly differ, but disease-free survival was higher in the group who had regional nodal radiation. People who had nodal radiotherapy also had significantly higher rates of grade 2 or worse acute pneumonitis and lymphoedema. In the EORTC 22922/10925 trial[104] 4004 women were randomly assigned to either radiotherapy of the whole breast and chest wall or radiotherapy of the whole breast, chest wall, and regional nodes.	**Internal mammary node radiotherapy** New evidence identified that may change current recommendations. The new evidence suggests that radiotherapy to the internal mammary lymph node may be associated with improved disease-free and distant metastasis-free survival, but may not affect overall survival. A meta-analysis showed that radiation to the internal mammary and supraclavicular lymph nodes may be associated with improved overall survival, but the effect attributable to internal mammary radiotherapy is not clear, and an additional RCT showed no benefit on overall survival. The studies indicate possible benefit of nodal radiotherapy for some outcomes in groups of patients for whom CG80 includes 'do not do' recommendations including: • adjuvant radiotherapy to the supraclavicular fossa for patients

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	(supraclavicular or axillary fossa or both, and internal mammary chain) after mastectomy and axillary surgery versus the same surgery but no radiotherapy. Follow-up lasted 10 years for recurrence and to 1 January 2009, for mortality. Axillary dissection was performed to at least level II in 3786 women and had 0, 1–3, or 4 or more positive nodes. For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on locoregional recurrence, overall recurrence or breast cancer mortality. For 1314 women with axillary dissection and 1–3 positive nodes, radiotherapy reduced locoregional recurrence, overall recurrence and breast cancer mortality. 1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and, for them, radiotherapy again reduced locoregional recurrence, overall recurrence, and breast cancer mortality. For 1772 women with axillary dissection and 4 or more positive nodes, radiotherapy reduced locoregional recurrence, overall recurrence, and breast cancer mortality.	Participants had central or medial breast tumours or external tumours with axillary involvement. At 10 years, overall survival did not differ significantly. People in the nodal radiotherapy group had significantly higher disease-free survival, distant disease-free survival and lower breast cancer mortality. A study[105] of patients with stage II–III breast cancer (n=396) treated with post-mastectomy radiation therapy with (n=197) or without (n=199) internal mammary node irradiation was identified. The 10-year disease-free survival with and without internal mammary node irradiation was 65% and 57%, respectively (p=0.05). Multivariate analysis demonstrated that internal mammary node irradiation was an independent, positive predictor of disease-free survival. Benefits on disease-free survival were most apparent in N2 patients (and inner/central tumours. The 10-year overall survival with internal mammary node irradiation was 72% and 66% without (p=0.62). A multicentre trial[106] (the French trial) enrolled patients (n=1334) with positive axillary nodes (pN+) or central/medial tumours with or without pN+. All patients had mastectomy and radiotherapy to the chest wall and supraclavicular nodes. Randomisation was to receive internal mammary node irradiation or not. No benefit of internal mammary node radiotherapy was seen on overall survival: the 10-year overall survival was	with node-negative early breast cancer • adjuvant radiotherapy to the internal mammary chain in patients with early breast cancer who have had breast surgery. Reassessment of the benefits and harms of radiotherapy in these populations may be warranted to check whether evidence still supports these do-not-do recommendations **ALND versus axillary radiotherapy** New evidence identified that may change current recommendations. Evidence from 1 RCT (AMAROS) suggests that either axillary radiotherapy or ALND are associated with low rates of 5-year axillary recurrence in people with positive sentinel nodes. However, the trial was unable to determine non-inferiority of axillary radiotherapy because of the lower than expected recurrence in both groups. Currently radiotherapy to the axilla is recommended after SLNB if ALND cannot be performed. This evidence is consistent with this recommendation. However, evidence identified in question 80-6 suggests that SLNB is preferable to ANLD for people with micrometastases, which would in turn affect the recommendation about radiotherapy after these procedures. A related research recommendation about entry into trials on axillary

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		62.6% in people who had internal mammary node radiotherapy versus 59.3% in those who did not. **ALND versus axillary radiotherapy** In a non-inferiority RCT[107] (AMAROS), patients (n=4806) with T1–2 primary breast cancer, no palpable lymphadenopathy, and positive sentinel lymph node were randomly assigned to receive either ALND (n=2402) or axillary radiotherapy (n=2404). The primary end point was non-inferiority of 5-year axillary recurrence, of not more than 4% for axillary radiotherapy compared with 2% expected for ALND. 5-year axillary recurrence was 0.43% after ALND versus 1.19% after axillary radiotherapy. The planned non-inferiority test was underpowered because of the low number of events. Lymphoedema was significantly more common after ALND than after axillary radiotherapy.	radiotherapy versus completion ALND refers to the AMAROS trial. This trial is no longer recruiting and results of 5-year follow-up were identified. The new evidence may address this research recommendation. **Radiotherapy after ALND** New evidence is consistent with current recommendations. Evidence from an individual patient data meta-analysis suggests no benefit of radiotherapy after ALND in people with node-negative disease. The trials included in this analysis started about 30–50 years ago and, this treatment is not in line with current practice, which would no longer use ALND for node-negative disease. However, this lack of benefit supports current practice. CG80 says 'do not offer' adjuvant nodal radiotherapy to patients with early breast cancer who have been shown to be histologically lymph node-negative. Benefits of radiotherapy after mastectomy and ALND were seen for node-positive disease, irrespective of whether or not adjuvant chemotherapy was used, but the effectiveness on specific nodal targets is not clear. The guideline notes that after ALND, radiotherapy to the axilla does not improve outcomes, but adjuvant radiotherapy to the supraclavicular fossa is recommended in people at higher risk of recurrence. The new evidence is consistent with current guidance.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			Surveillance decision The topic experts agreed that clinical practice had changed in terms of what to do if in the axilla for people with positive SLNB results. Additionally the topic experts advised that the UK is out of step with Europe in radiotherapy of the internal mammary nodes. This review question should be updated.
Primary systemic therapy			
80 – 27 What is the role of primary systemic treatment in patients with early, invasive breast cancer? (1.12.1, 1.12.2)			
No relevant evidence identified.	**Capecitabine** A meta-analysis[108] of 5 RCTs comparing neoadjuvant chemotherapy with or without capecitabine in early or operable breast cancer without distant metastasis showed that neoadjuvant capecitabine with anthracycline and/or taxane based therapy was not associated with significant improvement in clinical outcomes including: pathological complete response in breast, pathological complete response in breast tumour and nodes, overall response rate, or breast-conserving surgery. **Platinum agents** A meta-analysis[109] of 28 randomised studies (n=1598) assessed the activity of platinum agents in patients with triple negative breast cancer treated with neoadjuvant chemotherapy. Overall, pathological complete response in patients treated with platinum-based neoadjuvant chemotherapy was 45%.	None identified relevant to this question.	**Capecitabine** New evidence is unlikely to impact on guideline recommendations. Evidence suggests that adding capecitabine to anthracycline or taxane-based primary systemic therapy does not improve clinical outcomes. Capecitabine is currently not licensed for early breast cancer and was not considered in the guideline. **Platinum agents** New evidence is unlikely to impact on guideline recommendations. Platinum-based primary systemic therapy may be associated with improved clinical and pathological response rates in triple-negative breast cancer, but progression-free survival at 1 and 2 years does not seem to be affected. CG80 did not have any recommendations about the use of

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Neoadjuvant chemotherapy containing cisplatin or carboplatin significantly increased the rate of pathological complete response compared with non-platinum agents. Compared with non-triple-negative breast cancers, triple negative breast cancers were associated with a threefold increase in the pathological complete response rate when treated with platinum-based neoadjuvant chemotherapy. Another meta-analysis[110] of 7 studies (n= 717), in which 225 had triple-negative breast cancer (31%) and 492 did not (69%) showed that with platinum-based neoadjuvant chemotherapy, the clinical and pathological complete response rates were significantly higher for the triple-negative group. The 6-month progression-free survival rate for the triple-negative group was higher however, the 1- and 2-year progression-free survival rates were not significantly different. **Pathological complete response** A meta-analysis[111] of 17 studies assessed the pathological complete response rate and breast conserving surgery in patients after neoadjuvant chemotherapy in infiltrating lobular carcinoma (n=1764) compared with infiltrating ductal carcinoma (n=12,645). Infiltrating ductal carcinoma of the breast was associated with better pathological complete response and rate of breast-conserving surgery compared with infiltrating lobular carcinoma.		platinum agents. **Pathological complete response** New evidence is unlikely to impact on guideline recommendations. Pathological complete response after primary systemic therapy may be better in infiltrating ductal carcinoma than in infiltrating lobular carcinoma. However, these findings are unlikely to impact on recommendations in CG80 which does not make recommendations specifically for each subtype of breast cancer. **Trastuzumab** New evidence is unlikely to impact on guideline recommendations. The study on trastuzumab is unlikely to impact on guidance because use of trastuzumab is already recommended for people with HER2 positive breast cancer. Although this study shows that it may be given with primary systemic therapy, it does not provide evidence on whether this strategy is better than administration after surgery, chemotherapy or radiotherapy. A further study indicated that for add-on treatment in primary systemic therapy, trastuzumab plus lapatinib was more effective than trastuzumab alone, which in turn was more effective than lapatinib alone. This is unlikely to impact on guidance because lapatinib is not licensed for early breast cancer and no application for marketing authorisation is expected.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	Trastuzumab A meta-analysis[112] of 5 studies of trastuzumab (n=515) combined with neoadjuvant chemotherapy in HER2-positive breast cancer was identified. The probability of pathological complete response was significantly higher for the trastuzumab plus chemotherapy arm. No significant difference in terms of breast-conserving surgery between the two treatment arms was observed. There was no increase in incidence of neutropenia, neutropenic fever, and cardiac adverse events. A meta-analysis[113] of 6 studies (n=1494) in HER2-positive breast cancer showed that the probability of pathological complete response was significantly higher for the trastuzumab plus chemotherapy arm versus lapatinib plus chemotherapy. Probability of pathological complete response was significantly higher in the group receiving lapatinib and trastuzumab than in the group with trastuzumab alone. Grade II–IV diarrhoea and dermatological toxicities were statistically more frequent in patients receiving lapatinib. No differences in cardiac adverse events were seen between groups.		Because Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (NICE TA107), recommends trastuzumab for up to a year, the new evidence will be passed to the TA team for consideration. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 28 For patients treated with primary systemic therapy for breast cancer, including inflammatory or locally advanced disease, what is the role of surgery and/or radiotherapy? (1.12.3)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision**

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Complications of local treatment and menopausal symptoms			
80 – 29 In patients with breast cancer which strategies are effective in preventing arm lymphoedema? (1.13.1–1.13.3)			
3-year surveillance (2011) One study[114] compared a preventive protocol with control. The preventive protocol included preoperative upper limb lymphscintigraphy, principles for lymphoedema risk minimisation, and early management. Assessments were made preoperatively and at 1, 3, 6, 12 and 24 months postoperatively. These prophylactic strategies appeared to reduce the development of secondary lymphoedema and alter its progression compared with control. One study[115] investigated the effectiveness of early physiotherapy in reducing the risk of secondary lymphoedema after surgery for breast cancer. The results suggested early physiotherapy could be an effective intervention in the prevention of secondary lymphoedema in women for at least 1 year after surgery for breast cancer involving dissection of axillary lymph nodes.	A meta-analysis[116] of 10 RCTs (n=566) to assess whether manual lymphatic drainage could prevent or manage limb oedema in women after breast-cancer surgery was identified. 2 studies evaluating the preventive outcome of manual lymphatic drainage found no significant difference in the incidence of lymphoedema or reduction of arm volume between the manual lymphatic drainage and standard treatment groups. A meta-analysis[117] of 72 studies of unilateral arm lymphoedema after breast cancer found an overall occurrence of 16.6% which increased to 21.4% when only data from prospective cohort studies were assessed. The incidence of arm lymphoedema seemed to increase up to 2 years after diagnosis or surgery of breast cancer, was highest when assessed by more than one diagnostic method, and was about 4 times higher in women who had ALND (19.9%, 13.5 to 28.2) than it was in those who had sentinel-node biopsy (5.6%, 6.1 to 7.9). Risk factors that had a strong level of evidence were extensive surgery (ie, ALND, greater number of lymph nodes	None identified relevant to this question.	New evidence is consistent with recommendations. At 3-year surveillance, studies showed a programme of preventive interventions and early physiotherapy as beneficial for preventing lymphoedema, which is currently recommended in the guideline. Evidence identified at 6-year surveillance suggests that lymphoedema remains a substantial problem, especially for people who have had ALND. Manual lymphatic drainage does not seem to effectively prevent or treat lymphoedema **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	dissected, mastectomy) and overweight or obesity.		
80 – 30 What strategies are effective in reducing arm and shoulder mobility problems after breast cancer surgery? (1.13.4–1.13.7)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
80 – 31 What treatments are effective and safe for use to treat patients with menopausal symptoms and invasive breast cancer or DCIS? (1.13.8–1.13.14)			
No relevant evidence identified.	A systematic review[118] assessed efficacy of flax for menopausal symptoms in women living with breast cancer and effects on risk of recurrence included 10 studies. Flax ingestion of 7.5 g/day was not significantly associated with decreases in menopausal symptoms. Observational data suggested lower mortality in people with breast cancer. A systematic review[119] of black cohosh use in women with or at risk of breast cancer included 26 studies. The evidence on efficacy on menopausal symptoms was inconsistent, with some benefits seen compared with baseline, but not compared with placebo. Evidence supporting the use of black cohosh for menopausal symptoms in	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The evidence suggests that neither flax nor black cohosh significantly reduce menopausal symptoms. These results are in line with the evidence presented in the guideline which found that the evidence for interventions such as black cohosh was limited and conflicting. The finding that flax is associated with lower mortality is based on observational data, however, this study type was not used in the guideline. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	breast cancer patients is lacking.		question may be updated.
Follow-up			
80 – 32 What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer or DCIS? (1.14.1–1.14.4)			
No relevant evidence identified.	**Fluorodeoxyglucose PET** A meta-analysis[120] of 13 studies of the use of tumour markers to detect recurrence in patients with breast cancer as a guide for fluorodeoxyglucose PET imaging. Sensitivity was 0.878, specificity was 0.693, and accuracy was 0.828. **Comparison of surveillance techniques** A Health Technology Assessment[121] assessed strategies for surveillance and follow-up of women after treatment for primary breast cancer in the UK. The 8 studies included in the effectiveness review suggested that mammography has a survival benefit compared with a surveillance without mammography. In 9 studies of test performance. For routine ipsilateral recurrence detection, mammography sensitivity ranged from 64% to 67% and specificity ranged from 85% to 97%. For MRI, sensitivity ranged from 86% to 100% and specificity was 93%. For non-routine ipsilateral recurrence detection, sensitivity and specificity for surveillance mammography ranged from 50% to 83% and from 57% to 75%, respectively, and for MRI from 93% to 100% and from	None identified relevant to this question.	**Fluorodeoxyglucose PET** New evidence is unlikely to impact on guideline recommendations. The evidence suggests that fluorodeoxyglucose PET has fairly high specificity for detecting recurrence using tumour markers, but specificity may not be high enough. CG80 did not consider the use of fluorodeoxyglucose PET in follow-up of people who have had treatment for early breast cancer. **Comparison of surveillance techniques** New evidence is consistent with current recommendations. The Health Technology Assessment indicates that mammography has higher sensitivity and specificity than was noted in the guideline. The sensitivity and specificity of MRI was much the same as noted in the guideline. Overall these results are consistent with the recommendation to offer annual mammography. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	88% to 96%, respectively. In the base-case analysis, the strategy with the highest net benefit, and most likely to be considered cost-effective, was surveillance mammography alone, every 12 months. Few studies met the review inclusion criteria and none of the studies was an RCT. The limited and variable nature of the data available precluded any quantitative analysis. There was no useable evidence contained in the Breast Cancer Registry database to assess the effectiveness of surveillance mammography directly. The results of the economic model were considered exploratory given the paucity of data available to inform the economic model.		question may be updated.
80 – 33 What is the best setting for clinical follow up of patients treated for breast cancer? (1.14.5, 1.14.6)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** Although the new evidence does not indicate a need to update this review question, the decision to do a full guideline update means that this question may be updated.
Research recommendations			
RR – 01 What is the effectiveness of cognitive behavioural therapy compared with other psychological interventions for breast cancer patients?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			Surveillance decision The decision was a full update of the guideline therefore this research recommendation will be considered as part of that process.
RR – 02	**How effective is trastuzumab in patients with invasive breast cancer: (a) as adjuvant therapy without chemotherapy, (b) in terms of scheduling and duration of treatment in patients who are also receiving or who have completed chemotherapy, and (c) as primary systemic treatment in terms of quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?**		
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** The decision was a full update of the guideline therefore this research recommendation will be considered as part of that process.
RR – 03	**In the absence of good data about differences in clinical outcome between axillary radiotherapy and completion ALND, entry into appropriate clinical trials, e.g. AMAROS, is recommended for early breast cancer patients when the axilla has been found by SLNB to contain metastasis.**		
No relevant evidence identified.	See 80-26 above	None identified relevant to this question.	See 80-26 above **Surveillance decision** The decision was a full update of the guideline therefore this research recommendation will be considered as part of that process.
RR – 04	**What is the effectiveness in patients with early invasive breast cancer of: (a) different hypofractionation radiotherapy regimens (b) partial breast radiotherapy and (c) newer radiotherapy techniques (including intensity modulated radiotherapy), in terms of long term outcomes such as, quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?**		
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** The decision was a full update of the

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			guideline therefore this research recommendation will be considered as part of that process.
RR – 05 For patients who have been treated for early invasive breast cancer or DCIS, what is the optimal frequency and length of surveillance of follow-up mammography?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** The decision was a full update of the guideline therefore this research recommendation will be considered as part of that process.
Areas not currently covered in the guideline			
NQ – 01 What is the role of imaging modalities in the diagnosis of breast cancer in people with suspicious breast lesions?			
No relevant evidence identified.	A meta-analysis[122] of 8 studies (n=873) of the diagnostic performance of fluorodeoxyglucose positron emission mammography in women with breast lesions showed sensitivity of 85% and specificity of 79%. An individual patient data meta-analysis[123] of 5 studies (n=1412) compared the diagnostic performance of ultrasound elastography versus B-mode ultrasound across size ranges of breast lesions. Ultrasound elastography had higher specificity and lower sensitivity compared with B-mode ultrasound in characterising breast masses. Test performance did not vary significantly by lesion size.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The identified new evidence suggests that imaging may accurately detect breast cancer; however, the studies do not provide any evidence of benefit over standard triple test diagnostic procedures. Currently there are no recommendations about triple testing; but the full version of the guidance refers to this strategy (page 44, section 2.2). **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
NQ – 02 What is the best biopsy method for women suspected of having breast cancer?			
3-year surveillance (2011) 1 study[124] suggested that stereotactic- and ultrasonography-guided core-needle biopsy procedures were almost as accurate as open surgical biopsy, with lower complication rates in average-risk women suspected of having breast cancer.	No relevant evidence identified.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. This area was not considered to need updating at the 3-year time point. No new evidence since the 3-year surveillance review has been identified relating to biopsy methods. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.
NQ – 03 What are the best procedures and techniques for surgical treatment of breast cancer?			
No relevant evidence identified.	**Mastectomy** A meta-analysis[125] of 6 trials (n=287) of ultrasonic dissection versus electrocautery for mastectomy showed no effect on total postoperative drainage or seroma development. Intra-operative bleeding was slightly less with ultrasonic dissection. There were no differences between groups for the outcomes operative time and wound complications. A systematic review and pooled analysis[126] of 48 studies (n=6615) of breast reconstruction after nipple-sparing mastectomy showed an overall complication rate of 22%, nipple necrosis rate of 7%, locoregional recurrence rate of 1.8%, and distant metastasis rate of 2.2%.	None identified relevant to this question.	**Mastectomy** New evidence is unlikely to impact on guideline recommendations. The evidence for ultrasonic dissection and electrocautery suggest that these surgical techniques are equally effective. There is no clear need to make a recommendation about these techniques, which are well established for other types of surgery. Nipple-sparing mastectomy seems to be associated with low rates of complications and cancer recurrence, but the data are limited by the lack of comparison with standard mastectomy for the outcomes reported. Although contralateral prophylactic mastectomy was associated with

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	A meta-analysis[127] of 14 studies of contralateral prophylactic mastectomy found that this procedure was associated with significantly higher rates of overall survival and significantly lower rates of breast cancer-specific mortality compared with no contralateral prophylactic mastectomy. The absolute risk of metachronous contralateral breast cancer was not reduced. **Other surgical techniques** A meta-analysis[128] of 13 studies evaluated the incidence of flap-related complications, donor-site morbidity, and operative times for preoperative computed tomographic (CT) angiography compared with Doppler ultrasonography. Preoperative CT angiography was associated with significantly fewer flap-related complications, reduced donor-site morbidity, and shorter reconstruction operative time by 87.7 minutes. A Cochrane review[129] of 18 RCTs (n=1252) assessed the effectiveness of fibrin glue in breast and axillary surgery. Most trials were of poor quality and heterogeneity was significant. Fibrin glue under skin flaps following breast and axillary surgery did not significantly reduce postoperative seroma, mean volume of seroma, wound infection, postoperative complications or length of hospital stay. Fibrin glue was associated with reduced total volume of drained seroma and duration of persistent seroma needing frequent aspiration.		improved survival in people with breast cancer, it did not affect the likelihood of developing cancer in the contralateral breast. Further evidence on the benefits and harms of this procedure is needed before considering for inclusion in the guideline. **Other surgical techniques** New evidence is unlikely to impact on guideline recommendations. Although evidence suggests that preoperative CT angiography may be better than Doppler ultrasonography, the clinical need for guidance in this area is not clear. Fibrin glue does not appear to be associated with improvements in many outcomes after breast and axillary surgery. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
NQ – 04 What is the best method to determine the characteristics of breast tumours for adjuvant treatment planning?			
3-year surveillance (2011) ***Gene profiling*** One study[130] systematically reviewed and analysed clinical and analytic validity and clinical utility for HER2 testing (immunohistochemistry - IHC and fluorescent in situ hybridisation - FISH) for the appropriate selection of breast cancer patients who were suitable for trastuzumab therapy. The findings have shown high concordance rates between IHC and FISH in tumours IHC0 and IHC1+, and discordance rates among cases with IHC2+ and IHC3+. In this study, FISH was considered gold standard for confirming or excluding HER2 amplification.	**Index tumour biopsy** A meta-analysis[131] of 21 studies noted good concordance between core needle biopsy and excisional biopsy for hormone receptor status. Core needle biopsy and excisional biopsy had good concordance for both ER and PR, but negative hormone receptor testing results should be interpreted with caution or repeated on excisional biopsy. **Intraoperative tests** After publication of NICE CG80, Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer (NICE DG8) was issued. RD-100i OSNA is recommended but Metasin is not recommended. A meta-analysis[132] of 12 studies (n=2192, 5057 lymph nodes) of OSNA showed a similar overall proportion of breast cancer macrometastases detected by OSNA compared with standard histology. Analysis of concordance showed that the positive predictive value for detecting macrometastases was 0.79, suggesting that up to 21% of patients with macrometastases determined by OSNA would have axillary clearance when histology would not have classified them as macrometastases. **Gene profiling** After publication of NICE CG80, Gene expression profiling and expanded	Studies relating to characteristics of multicentric or multifocal breast tumours were identified through topic expert feedback. **Multifocal tumours** A single-centre retrospective analysis[135] of 51 patients with multifocal or multicentric breast cancer, found differences between morphology (6 cases) and grade (7 cases) in different tumour foci. Of the 7 cases with differing grades of tumour differences in ER and PR status (3 cases) and HER2 status (1 case) were also seen between foci. A retrospective study[136] (n=155) evaluating differences in molecular subtype, morphology, and tumour grade between separate tumour foci of multiple breast carcinoma found that assessment of all tumour foci would have changed treatment choice in 19 people (12%) compared with assessing only the largest primary tumour. A prospective study[137] of 113 cases of invasive multifocal or multicentric breast cancer were prospectively tested. Mismatches in ER status were present in 5 cases (4.4%) and PR in 18 cases (15.9%). Mismatches in tumour grading were present in 21 cases (18.6%), proliferative index (Ki-67) in 17 cases (15%) and HER2 status in 11 (9.7%) cases. These findings led to a change in treatment in 14 (12.4%) or patients. Further information from topic experts	**Multifocal tumours** New evidence is unlikely to impact on current recommendations. Evidence suggests that multifocal tumours may have differing characteristics in different foci. However, the studies are small and it is unclear whether there is variation in practice in the UK for assessing these tumours. Topic expert feedback suggested that clinicians would often test multiple foci suggesting that guidance in this area is not a priority. **Intraoperative tests** New evidence is consistent with current guidance. Evidence suggests that OSNA is better for detecting lymph node macro-metastases than histology. OSNA is recommended in NICE DG8. **Gene profiling** New evidence is unlikely to impact on current recommendations. At 3-year surveillance, 1 study showed effectiveness of immunohistochemistry for HER2 testing. Since then new guidance has been issued on specific gene profiling tests. At 6-year surveillance new evidence suggested that Oncotype Dx test results could change the recommended treatment regimens for people with early breast cancer. Oncotype Dx is recommended in NICE

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (NICE DG10) was issued. Oncotype DX is recommended but MammaPrint, IHC4 and Mammostrat are not recommended. A meta-analysis[133] included 23 studies of Oncotype Dx in patients who had ER positive, node negative, early-stage breast cancer and that reported using Oncotype Dx results to inform adjuvant chemotherapy decisions. Recurrence score was low in 49% of patients, intermediate in 39% and high in 12% (21 studies, n=4156). Adjuvant chemotherapy was used in 28% of patients overall, 6% of those with low recurrence score, 37% with intermediate recurrence score, and 83% with high recurrence score. Oncotype Dx changed the adjuvant chemotherapy recommendation in 33% of patients (8 studies, 1,437 patients). **Circulating tumour cells** A meta-analysis[134] of 24 studies suggested that detection of circulating tumour cells was significantly associated with poor overall survival, recurrence-free survival, high histological grade, tumour size greater than 2 cm and more than 1 positive node. Cytokeratin-19 mRNA-positive circulating tumour cells were not associated with these clinicopathological parameters of breast cancer. The presence of circulating tumour cells was not associated with ER	indicated that testing for heterogeneity in multifocal tumours, is often done anyway at the discretion of the pathologist.	DG10. The new evidence identified through the 6 year surveillance review is consistent with current guidance. **Circulating tumour cells** New evidence is unlikely to impact on guideline recommendations. Evidence suggests that circulating tumour cells may be associated with poorer prognosis, but no evidence was found to guide treatment decisions if circulating tumour cells are detected. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	or PR negative status, or HER2 overexpression.		
NQ – 05 What is the role of imaging or other methods for assessing response to treatments for breast cancer?			
3-year surveillance (2011) ***Imaging for assessing response to primary systemic therapy*** One study[138] found that predictions of response and residual tumour size after neoadjuvant chemotherapy for locally advanced or inflammatory breast cancer made on MRI were better correlated with the assessments made with pathology than with predictions made with clinical examination, mammography or sonography.	**Imaging for assessing response to primary systemic therapy** A meta-analysis[139] of 17 studies (n=781) determined the diagnostic performance of fluorodeoxyglucose PET or computed tomography for evaluating response to neoadjuvant chemotherapy in patients with breast cancer. Overall sensitivity was 0.840 and specificity was 0.713. Another meta-analysis[140] of 15 studies (n=745) found that the sensitivity was 80.5% and specificity was 78.8%. A meta-analysis[141] of 4 studies of fluorothymidine positron emission tomography or computed tomography in assessing response to chemotherapy showed sensitivity of 0.773 and specificity of 0.685. A systematic review[142] of 35 studies of MRI in evaluating residual disease extent and the ability to detect pathological complete response after neoadjuvant chemotherapy for invasive breast cancer was identified. Median correlation coefficient was 0.698 for residual tumour size assessed by MRI and pathology and across studies, reported sensitivity was 25–100%, specificity was 50–97%. **Pathological complete response** A meta-analysis[143] of 12 trials (n=11,955) assessed 3 definitions of pathological	None identified relevant to this question.	**Imaging for assessing response to primary systemic therapy** New evidence is unlikely to impact on guideline recommendations. At 3-year surveillance evidence suggested that MRI may predict tumour response better than clinical examination, mammography or sonography, but no impact on guidance was expected because further research was needed. Evidence from 6-year surveillance suggests that fluorodeoxyglucose PET or computed tomography may have reasonable sensitivity but inadequate specificity for assessing response to primary systemic therapy, and fluorothymidine PETor computed tomography has poorer sensitivity and specificity. The reported performance of MRI in detecting response to primary systemic therapy varied to a large extent across trials. **Pathological complete response** New evidence is unlikely to impact on guideline recommendations. Defining pathological complete response as eradication of tumour from both the breast and lymph nodes rather than from the breast alone may result in better outcomes of event-free and overall

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	complete response in people with breast cancer who had primary systemic therapy were assessed as surrogate end points to predict long-term clinical outcomes. Eradication of tumour from both breast and lymph nodes was better associated with improved event-free survival and overall survival (than tumour eradication from the breast alone. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer and in those with HER2-positive, hormone-receptor-negative tumours who received trastuzumab. Trial-level analysis showed little association between increases in frequency of pathological complete response and event-free survival and overall survival which the authors noted could not validate pathological complete response as a surrogate endpoint for improved event-free survival and overall survival. **Circulating tumour cells** A meta-analysis[144] noted that change in circulating tumour cell number (decrease or increase) during neoadjuvant chemotherapy was not correlated with pathological complete response.		survival. However, increased frequency of pathological complete response was not associated with increases in event-free survival. **Circulating tumour cells** New evidence is unlikely to impact on guideline recommendations. Change in circulating tumour cell count was not associated with pathological complete response. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.
NQ – 06 Fertility after treatment for breast cancer			
3-year surveillance (2011) No relevant evidence identified.	A meta-analysis[145] of RCTs compared the levonorgestrel-releasing intrauterine system with placebo or endometrial surveillance in preventing endometrial	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The study of the levonorgestrel-releasing

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	pathology in women treated with tamoxifen. The levonorgestrel-releasing intrauterine system was associated with a significant reduction in the incidence of endometrial hyperplasia (OR=0.13, 95% CI 0.03 to 0.58, p=0.007) and endometrial polyps (OR=0.22, 95% CI 0.13 to 0.37, p<0.00001). Chemotherapy with concurrent gonadotrophin releasing hormone (GnRH) analogues compared with chemotherapy alone in premenopausal women with breast cancer was evaluated in 3 meta-analyses. The first meta-analysis[146] included 7 RCTs (n=677) and noted higher resumption of menstruation in the GnRH analogue group (OR=2.83, 95% CI 1.52 to 5.25). The second meta-analysis[147] included 5 RCTs (n=528) and found no significant differences between groups for resumed menstruation (RR=1.31, 95% CI 0.93 to 1.85) or spontaneous pregnancy (RR=0.96, 95% CI 0.20 to 4.56). Significantly fewer women in the GnRH agonist group had premature ovarian failure 1 year after chemotherapy (RR 0.40, 95% CI 0.21 to 0.75). The third meta-analysis[148] included 4 randomised trials (n=252) in women with breast cancer who did not receive tamoxifen. The rate of return of menstruation after 1 year was not significantly different between groups (OR=1.47, 95% CI 0.60 to 3.62). A meta-analysis[149] of 5 studies		intrauterine system is unlikely to have an impact on guidance because the relation of the outcomes studied to fertility (that is, the ability to conceive) is not clear. The 2 meta-analyses of GnRH agonists show conflicting results on the outcome of menstruation, and the relation of this outcome to fertility is not clear. The third meta-analysis looking at GnRH agonists only in women not treated with tamoxifen also showed no significant effect on menstruation. The study showing improved survival in women who become pregnant after surgical treatment for breast cancer is clinically reassuring. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	suggested that pregnancy after surgical treatment for breast cancer significantly increased overall survival compared with controls. Disease-free survival was not affected by pregnancy.		
NQ – 07 What are the effects of diet on outcomes of breast cancer?			
No relevant evidence identified.	A meta-analysis[150] of 10 studies (n=17,696) of dietary vitamin C intake and breast cancer survival included 2791 total deaths, and 1558 breast cancer-specific deaths. Total mortality was significantly lower in people who took vitamin C supplements after diagnosis of breast cancer (RR=0.81, 95% CI 0.72 to 0.91) and a similar result was seen for breast cancer-specific mortality (RR=0.85, 95% CI 0.74 to 0.99). A meta-analysis[151] of 8 observational studies (n=5691) assessed the association of vitamin D with breast cancer outcomes. The definition of vitamin D deficiency varied across studies; a median of 36.8% of patients were classified as deficient. Low levels vitamin D were associated worse recurrence (HR= 2.13, 95% CI 1.64 to 2.78) and mortality (HR=1.76, 95 % CI 1.35 to 2.30), with no evidence of significant heterogeneity across studies. A meta-analysis[152] of 2 RCTs and 1 large multicentre prospective cohort study (n=9966) of post-diagnosis low-fat diet found a reduced risk of recurrence of breast cancer (HR=0.77, 95%CI 0.63 to 094, p=0.009) and all-cause mortality of breast cancer (HR=0.83, 95%CI 0.69 to	None identified relevant to this question.	The new evidence is unlikely to impact on guideline recommendations. Evidence suggests that higher intake of vitamin C, greater vitamin D levels, and low-fat diets may have beneficial effects on survival. For the studies on vitamin C and vitamin D it is not clear whether adjustment for known inequities in health and mortality such as socioeconomic status were adjusted for in these analyses. Finally, the study of low-fat diet does not clearly define ‘low fat’. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	1.00, p=0.05).		
NQ – 08 What is the diagnostic accuracy of specific investigations to recognise lymphoedema early in patients with early and locally advanced breast cancer?			
3-year surveillance (2011) ***Focused searching*** One study[153] investigated if bioimpedance spectroscopy (BIS) could detect localised lymphoedema of the arm and to compare BIS measurements with equivalent measures of limb volume by perometry. The study suggested that BIS can be used for localised measurement of lymphoedema and because it is specific to extracellular fluid, BIS is more sensitive to localised lymphoedema than perometry. One study[154] evaluated circumference measurement (CM) and water displacement (WD) for volume measurements (VM) of the breast cancer-related lymphedema (BCRL) arm and the contralateral arm, comparing the results with regional dual energy X-ray absorptiometry (DXA). The study showed that DXA was superior in repeatability when compared to CM and WD for VM, especially for the BCRL arm but also the contra lateral arm. One study[155] compared diagnostic accuracy of different measures of breast cancer-related lymphoedema (BCRL). The study findings supported the use of bioimpedance spectroscopy in the assessment of existing BCRL. The authors concluded that refining	No relevant evidence identified.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. At 3-year surveillance, 2 studies showed bioimpedance spectroscopy to be accurate in detecting breast cancer-related lymphoedema but warrant further validation and investigation. One study showed circumference measurement and water displacement were not as accurate compared with X-ray absorptiometry. This evidence was not considered to invalidate current recommendations. No new evidence was identified in the 6 year surveillance review. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
diagnostic cut-off values may improve accuracy of diagnosis and warrant further investigation.			
NQ – 09 What is the best management strategy for lymphoedema?			
<u>3-year surveillance (2011)</u> **Complex decongestive therapy** A systematic review[156] indicated that beneficial treatments for secondary lymphoedema following breast cancer include complex decongestive therapy, physiotherapy and exercise. An additional systematic review[157] concluded that complex decongestive therapy (referred to as combined physical therapy) is effective for breast cancer-related lymphoedema. A systematic review.[158] concluded that evidence on physiotherapeutic methods used in complex decongestive therapy for treating lymphoedema was limited although compression bandages seemed to be beneficial in reducing lymphoedema. A systematic review[159] of physiotherapeutic treatments for breast cancer-related lymphoedema concluded that better results were obtained with combined treatments. Complex decongestive therapy plus pneumatic compression was effective. However a subsequent RCT[160] assessing complex decongestive therapy alone or in combination with intermittent pneumatic compression for breast cancer related lymphoedema indicated that complex	No relevant evidence identified.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. Overall, no significant new literature was identified at 3-year surveillance that would invalidate current recommendations. No new evidence was identified in the 6 year surveillance review. Treatment of lymphoedema is covered extensively in advanced breast cancer (CG81), and a partial update of this area was published in 2014. New evidence about treatment of lymphoedema will be covered in surveillance of CG81. **Complex decongestive therapy** At 3-year surveillance, complex decongestive therapy seemed to be beneficial as did physiotherapy and exercise. The benefits of adding pneumatic compression to complex decongestive therapy are not clear. Kinesio tape may be an acceptable alternative to standard compression bandages. This evidence is consistent with current guidance: the full version of the guideline directs readers to recommendations on management of lymphoedema in '<u>Advanced breast cancer</u>' (NICE CG81). Complex decongestive therapy is recommended as the first-line treatment.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
decongestive therapy alone produced better results. An RCT[161] of decongestive lymphatic therapy plus pneumatic compression in which participants used either a standard compression bandage or Kinesio tape for found no significant differences between groups for any breast cancer-related lymphoedema outcomes. ***Compression therapy*** A randomised study[162] compared low pressure (20–30 mmHg) compression bandages with high pressure bandaging (44–58 mmHg) in reducing the volume of breast cancer-related arm lymphoedema. No significant changes in volume were observed between groups in the first 24 hours after application although the low-pressure bandages were better tolerated. An RCT[163] comparing alginate semi-rigid bandaging with conventional bandaging concluded that alginate bandages are a good alternative to conventional bandaging for minimising increases in lymphoedema in periods when the person does not have manual lymphatic drainage such as weekends. An RCT[164] suggested that methods of intermittent pneumatic compression effectively reduced lymphoedema volume irrespective of the protocol used (for example, cycle time and number of sleeve chambers). However, a systematic review[165] found no evidence to suggest that treatment with an			***Compression therapy*** Compression bandaging is a standard component of complex decongestive therapy. Studies aim to show improvements on the effects of standard bandages; however, evidence does not show clear benefit of novel compression strategies. ***Therapeutic exercise*** Exercise is a standard component of complex decompressive therapy and evidence supports this practice with no evidence that any exercise method such as weightlifting leads to worsening of lymphoedema ***Other therapies*** For the other methods of treating arm lymphoedema related to breast cancer treatments, laser therapy shows promise but further research is needed. Similarly further research is needed to clarify the role of stem cell transplantation, because current evidence is conflicting. Evidence suggests that aqua lymphatic therapy and hyperbaric oxygen therapy are not effective. **Surveillance decision** Although the new evidence does not indicate a need to add this review question, the decision to do a full guideline update means that this question may be added.

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
intermittent compression pump was more beneficial than education about arm care and hygiene. ***Therapeutic exercise*** An RCT[166] evaluating a mixed exercise programme among women who had completed treatment for breast cancer concluded that exercise did not exacerbate the lymphoedema. An RCT[167] of complex decongestive physiotherapy alone or in combination with active resistive exercise for treatment of breast cancer-related lymphoedema indicated that combination therapy did not cause additional swelling, reduced arm volume and improved quality of life. A systematic review[168] concluded resistance exercise can be done without an increased risk of lymphoedema in breast cancer patients. An RCT[169] indicated that twice-weekly weight lifting had no significant effect on breast cancer-related lymphoedema limb swelling but resulted in decreased incidence of exacerbations of lymphoedema. A further analysis of results from this RCT[170] assessed the rates of lymphoedema when assessed by 4 different diagnostic methods. Results suggested that diagnosis of lymphoedema in their cohort would vary from 22% to 52% depending on the diagnostic criteria used. ***Laser therapy*** An RCT[171] comparing laser treatment			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
with placebo in women with breast cancer-related lymphoedema found that limb volume tended to decline in both groups but significantly greater reduction was observed in the active laser group at 8 and 12 weeks. An RCT[172] comparing low-level laser therapy with no laser for managing post-mastectomy lymphoedema concluded that low-level laser therapy was effective at 4 week follow-up. ***Autologous stem cell transplantation*** One small study[173] (n=15) found that autologous bone marrow stromal cell transplantation was effective and feasible for the treatment of breast cancer related lymphoedema compared with complex decongestive physiotherapy. Another small RCT[174] (n=20) compared autologous stem cells with decongestive compression sleeves in the treatment of post-mastectomy lymphoedema. The volume of lymphoedema reduced in both groups. ***Aqua lymphatic therapy*** An RCT[175] showed that, compared with self-management of breast cancer-related lymphoedema, aqua lymphatic therapy had significant short term effects but did not have significant long-term effects on limb volume. ***Hyperbaric oxygen therapy*** An RCT[176] showed no beneficial effect of hyperbaric oxygen therapy compared with best standard care for arm			

Summary of evidence from previous surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
lymphoedema after radiotherapy for breast cancer.			

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