Breast cancer (non-metastatic)

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ABSTRACT

INTRODUCTION: Breast cancer affects at least 1 in 10 women in the UK, but most present with primary operable disease, which has an 80% 5-year survival rate overall. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions after breast-conserving surgery for ductal carcinoma in situ? What are the effects of treatments for primary operable breast cancer? What are the effects of interventions in locally advanced breast cancer (stage 3B)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 83 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding chemotherapy (cyclophosphamide/methotrexate/fluorouracil and/or anthracycline and/or taxane-based regimens), or hormonal treatment to radiotherapy; adjuvant treatments (aromatase inhibitors, adjuvant anthracycline regimens, tamoxifen); axillary clearance; axillary dissection plus sentinel node dissection; axillary radiotherapy; axillary sampling; combined chemotherapy plus tamoxifen; chemotherapy plus monoclonal antibody (trastuzumab); extensive surgery; high-dose chemotherapy; hormonal treatment; less extensive mastectomy; less than whole-breast radiotherapy plus breast-conserving surgery; multimodal treatment; ovarian ablation; primary chemotherapy; prolonged adjuvant combination chemotherapy; radiotherapy (after breast-conserving surgery, after mastectomy, plus tamoxifen after breast-conserving surgery, to the internal mammary chain, and to the ipsilateral supraclavicular fossa, and total nodal radiotherapy); sentinel node biopsy; and standard chemotherapy regimens.

QUESTIONS

INTERVENTIONS

Key points

- Breast cancer affects at least 1 in 10 women in the UK, but most present with primary operable disease, which has an 80% 5-year survival rate overall.
- In women with ductal carcinoma in situ (DCIS), radiotherapy reduces local recurrence and invasive carcinoma after breast-conserving surgery. The role of tamoxifen added to radiotherapy for DCIS remains unclear because of conflicting results.
- In women with primary operable breast cancer, survival may be increased by full surgical excision, tamoxifen, chemotherapy, radiotherapy, ovarian ablation, or trastuzumab (in women who over-express *HER2/neu* oncogene).

  Incomplete excision may increase the risk of local recurrence, but less-extensive mastectomy that excises all local disease is as effective as radical mastectomy at prolonging survival, with better cosmetic results.

  Axillary clearance (removal of all axillary lymph nodes) achieves local disease control, but has not been shown to increase survival, and can cause arm lymphoedema.

  Sentinel lymph node biopsy or 4-node sampling may adequately stage the axilla with less morbidity compared with axillary clearance.

  Adjuvant tamoxifen reduces the risk of recurrence and death in women with oestrogen-positive tumours.

  Primary chemotherapy may facilitate successful breast-conserving surgery instead of mastectomy. Adjuvant combination chemotherapy improves survival compared with no chemotherapy, with greatest benefit likely with anthracycline-based regimens at standard doses for 4 to 6 months.

  Radiotherapy decreases recurrence and mortality after breast-conserving surgery. Post-mastectomy radiotherapy for women who are node-positive or at high risk of recurrence decreases recurrence and mortality.

  Adjuvant aromatase inhibitors improve disease-free survival compared with tamoxifen, but their effect on overall survival is unclear. Adjuvant taxane-based regimens may improve disease-free survival over standard anthracycline-based therapy.
- In women with locally advanced breast cancer, radiotherapy may be as effective as surgery or tamoxifen at increasing survival and local disease control.

  Adding tamoxifen or ovarian ablation to radiotherapy increases survival compared with radiotherapy alone, but adding chemotherapy may not reduce recurrence or mortality compared with radiotherapy alone.

  We don't know if chemotherapy alone improves survival in women with locally advanced breast cancer as we found few trials.

Clinical context

DEFINITION

This review examines the effects of treatment for non-metastatic, primary breast cancer. **Ductal carcinoma in situ** is a non-invasive tumour characterised by the presence of malignant cells in the breast ducts, but with no evidence that they breach the basement membrane and invade into periductal connective tissues. **Invasive breast cancer** occurs when cancer cells spread beyond the basement membrane, which covers the underlying connective tissue in the breast. This tissue is rich in blood vessels and lymphatic channels capable of carrying cancer cells beyond the breast. Invasive breast cancer can be separated into three main groups: early invasive breast cancer, locally advanced breast cancer, and metastatic breast cancer (see review on breast cancer [metastatic]). **Operable breast cancer** is disease apparently restricted to the breast and/or local lymph nodes in the absence of metastatic disease, and can be removed surgically. Although women do not have overt metastases at the time of staging, they remain at risk of local recurrence, and of metastatic spread. They can be divided into those with tumours greater than 4 to 5 cm, or multifocal cancers, or widespread malignant micro-calcifications that are usually treated by mastectomy, and those with tumours less than 4 to 5 cm that can be treated by breast-conserving surgery. **Locally advanced breast cancer** is defined according to the TNM staging system of the UICC [1] as stage 3B (includes T4 a–d; N2 disease, but absence of metastases [see table 1, p 51]). It is a disease presentation with clinical or histopathological evidence of skin and/or chest-wall involvement, and/or axillary nodes matted together by tumour extension. **Metastatic breast cancer** is presented in a separate review (see review on breast cancer [metastatic]).

INCIDENCE/ PREVALENCE

Breast cancer affects 1/10 to 1/11 women in the UK and causes about 21,000 deaths a year. Prevalence is about 5 times higher, with over 100,000 women in the UK living with breast cancer at any one time. Of the 36,000 new cases of breast cancer each year in England and Wales, most will present with primary operable disease. [2]

AETIOLOGY/ RISK FACTORS

The risk of breast cancer increases with age. Risk factors include an early age at menarche, nulliparity, older age at menopause, older age at birth of first child, family history, atypical hyperplasia, excess alcohol intake, radiation exposure to developing breast tissue, oral contraceptive use, postmenopausal HRT, and postmenopausal obesity. Risk in different countries varies fivefold. The cause of breast cancer in most women is unknown. About 5% of breast cancers can be attributed to mutations in the genes *BRCA1* and *BRCA2,* [3] but the contribution to inherited breast cancer of other genes, including *Chk2*, *ATM*, *p53*, and *PTEN* and other lower risk alleles, is currently less well established.

PROGNOSIS

Non-metastatic carcinoma of the breast is potentially curable. The risk of relapse depends on various clinicopathological features, including axillary node involvement, tumour grade, and tumour size, with biological markers including oestrogen receptor and HER2 receptor status prognostically important in the first 5 years following diagnosis. For women with operable disease, survival is stage and treatment dependent with 80% alive 5 years after diagnosis and treatment (adjuvant treatment is given to most women after surgery). The risk of recurrence is highest during the first 3 years, but the risk remains even 15 to 20 years after surgery. Recurrence at 10 years, according to one large systematic review, [4] is 60% to 70% in node-positive women, and 25% to 30% in node-negative women. The prognosis for disease-free survival at 5 years is worse for stage 3B (33%) than that for stage 3A (71%). Overall survival at 5 years is 44% for stage 3B and 84% for stage 3A. [5] Poor survival and high rates of local recurrence characterise locally advanced breast cancer.

AIMS OF INTERVENTION

To improve survival; to prevent local or regional node recurrence; to obtain prognostic information on the type and extent of tumour and the status of the axillary lymph nodes; to optimise cosmetic results and minimise psychosocial impact; to minimise adverse effects of treatment; and to maximise quality of life.

OUTCOMES

Mortality: overall survival. **Treatment success**: rates of local and regional recurrence, rates of mastectomy after breast-conserving treatment, rates of development of metastases, cosmetic outcomes, and quality of life. **Adverse effects** of treatment, including upper-limb lymphoedema.

METHODS

Clinical Evidence search and appraisal April 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2009, Embase 1980 to April 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2009, Issue 1 (1966 to date of issue). An additional search within the NHS Centre for Reviews and Dissemination (CRD) was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed

by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including unblinded studies and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US FDA and the UK MHRA, which are added to the reviews as required. Note: The authors also identified data by personal communication with experts in the field and through hand searches. Abstracts of studies that were considered to be fundamental to clinical practice and new developments were included in the comments sections. Phase 3 randomised published data are included. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 52). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions after breast-conserving surgery for ductal carcinoma in situ?

OPTION RADIOTHERAPY (AFTER BREAST-CONSERVING SURGERY FOR DUCTAL CARCINOMA IN SITU)

Treatment success

Compared with no radiotherapy Radiotherapy after breast-conserving surgery for ductal carcinoma in situ is more effective at reducing recurrence at up to 10.5 years of follow-up (high-quality evidence).

Compared with tamoxifen plus radiotherapy Radiotherapy alone and radiotherapy plus tamoxifen seem to be equally effective at a median follow-up of 52 months at reducing invasive or ductal carcinoma in situ events in women undergoing local excision (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Radiotherapy versus no radiotherapy:

We found one systematic review (search date 2008, 4 RCTs, 3925 women, follow-up 4.4–10.5 years). [6] Three of the RCTs identified by the systematic review compared radiotherapy versus no radiotherapy after local excision surgery for ductal carcinoma in situ (DCIS). The fourth RCT identified by the systematic review was a 2 x 2 factorial design comparing the use of radiotherapy and tamoxifen, which included randomisation to tamoxifen or no tamoxifen, along with randomisation to radiotherapy or no radiotherapy. The review found that, compared with no radiotherapy, radiotherapy significantly reduced all ipsilateral breast recurrence (4 RCTs, 3925 women; 153/1976 [8%] with radiotherapy *v* 393/1949 [20%] with no radiotherapy; HR 0.49, 95% CI 0.41 to 0.59). It found no significant difference in ipsilateral breast DCIS between radiotherapy and no radiotherapy, although this approached significance (2 RCTs, 1848 women; 39/935 [4%] with radiotherapy *v* 77/913 [8%] with no radiotherapy; HR 0.64, 95% CI 0.41 to 1.01; P = 0.05). It also found that radiotherapy reduced ipsilateral breast invasive recurrence compared with no radiotherapy, although this did not reach significance (2 RCTs, 1848 women; 30/933 [3%] with radiotherapy *v* 71/913 [8%] with no radiotherapy; HR 0.64, 95% CI 0.38 to 1.06; P = 0.08). The review did not pool data for mortality, but reported that mortality owing to any cause was low in both arms of all RCTs and was similar between trials. [6]

Radiotherapy versus radiotherapy plus tamoxifen:

See benefits of tamoxifen plus radiotherapy, p 5 .

Harms:

Radiotherapy versus no radiotherapy:

The systematic review reported that there was no information about short-term adverse effects in the 4 identified RCTs and that long-term adverse effects were not well reported. [6] From the information that was available, it found that mortality caused by vascular disease, pulmonary toxicity, or second malignancies was similar between radiotherapy and no radiotherapy (absolute numbers

and significance not reported). The review commented that longer follow-up may be required to assess long-term toxicity owing to radiotherapy. [6]

One RCT included in the review found an increase in contralateral breast cancer associated with radiotherapy at 4 years (3% with surgery plus radiotherapy *v* 1% with surgery alone; HR 2.57, 95% CI 1.24 to 5.33). [7] However, the update at 10-years' follow-up found that there was no longer a statistically significant increase between groups in the risk of contralateral breast cancer (8% with surgery plus radiotherapy *v* 4% with surgery alone; HR 1.41, 95% CI 0.87 to 2.30). [8]

Radiotherapy versus radiotherapy plus tamoxifen:
See harms of tamoxifen plus radiotherapy, p 5 .

Comment:

Clinical guide: One RCT has reported a subgroup analysis to assess what impact radiotherapy has after breast-conserving surgery for various pathological subgroups. [9] The study found that relative risk reduction of radiotherapy was homogeneous across all groups (i.e., that there was a similar hazard reduction for all pathological subgroups, which is statistically significantly different). However, for some subgroups the overall risk of local recurrence at 4 years' follow-up was low (clinging or micropapillary pattern: 3% recurrence with surgery plus radiotherapy *v* 8% with surgery alone; well-differentiated lesions: 7% recurrence with surgery plus radiotherapy *v* 13% with surgery alone). [9] There were similar findings in the systematic review. [6] One of the RCTs attempted to identify a subgroup of patients with good prognostic features, but found that all of the prognostic strata examined were of sufficient risk to warrant discussion with the patient regarding radiotherapy. [10] All estimates of cumulative incidence proportions in the control arms defined by good prognostic characteristics (tumour size <10 mm, unifocality, complete excision, screen detection) had recurrence rates of >15% at 8 years' follow-up. An attempt at identifying patients with a group of good prognostic features still yielded an 8-year recurrence rate of >10%, and radiotherapy was found to be significantly protective in this group. In good prognosis subgroups, a case can be made to omit radiotherapy when the overall local control benefit for radiotherapy is low, although this should be done in consultation with the patient, explaining the pros and cons of treatment and the risk of recurrence. Patients undergoing breast-conserving surgery should be referred for discussion on the pros and cons of whole-breast radiotherapy, unless in the context of a clinical trial.

OPTION TAMOXIFEN PLUS RADIOTHERAPY (AFTER BREAST-CONSERVING SURGERY FOR DUCTAL CARCINOMA IN SITU)

Treatment success
Compared with radiotherapy plus placebo We don't know whether adding tamoxifen to radiotherapy confers additional benefits for reducing invasive ipsilateral or contralateral breast cancers and breast cancer events in women who have been treated with wide excision and radiotherapy because trials have given conflicting results (low-quality evidence).

Mortality
Compared with radiotherapy plus placebo or radiotherapy alone Adjuvant treatment with tamoxifen in women with oestrogen receptor-positive tumours may be no more effective at 6 years at reducing overall survival in women who have been treated with wide excision and radiotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Tamoxifen plus radiotherapy versus radiotherapy plus placebo or versus radiotherapy alone: We found no systematic review but found two RCTs, one reported in two publications. [11] [12] [13]

The first RCT (1804 women with ductal carcinoma in situ [DCIS] treated with wide excision and radiotherapy) compared adjuvant treatment with tamoxifen 20 mg daily versus placebo for 5 years. [11] At a median follow-up of 74 months, there were significantly fewer breast cancer events with tamoxifen than with placebo, and significantly fewer invasive ipsilateral or contralateral breast cancers (breast cancer events: OR 0.63, 95% CI 0.47 to 0.83; invasive ipsilateral or contralateral breast cancers: OR 0.57, 95% CI 0.38 to 0.85). However, there was no significant difference in overall survival (RR 0.88, 95% CI 0.33 to 2.28). A subsequent subgroup analysis found that only women with oestrogen receptor-positive DCIS derived a benefit from tamoxifen. [12]

The second RCT (1694 women having local excision) compared 4 treatments in a factorial design: no adjuvant treatment, tamoxifen alone, radiotherapy alone, and tamoxifen plus radiotherapy (see comment on radiotherapy, p 4). [13] It found no significant difference between tamoxifen plus radiotherapy and radiotherapy alone in ipsilateral invasive disease, ipsilateral DCIS, and invasive or DCIS events after a median follow-up of 52 months (523 women in comparison; ipsilateral invasive disease: HR 1.25, 95% CI 0.43 to 3.61; ipsilateral DCIS: HR 0.75, 95% CI 0.28 to 2.02; invasive or DCIS: 3% in both groups; HR 0.95, 95% CI 0.51 to 1.77). [13]

Harms:

Tamoxifen plus radiotherapy versus radiotherapy plus placebo or versus radiotherapy alone: The first RCT found a higher, but non-significant rate of endometrial cancers associated with tamoxifen (RR 3.4, 95% CI 0.6 to 33.4). [11] The second RCT reported that 11% of the patients randomised to take tamoxifen ceased taking the drug before the prescribed 5 years because of toxicity. [13]

The second RCT did not report results comparing harms of tamoxifen plus radiotherapy versus radiotherapy alone. [13] The risks of congenital malformations, or late teratogenic manifestations in adulthood are unknown, and women should be offered choices in all cases concerning continuing with pregnancy or termination. Women are conventionally advised to stop tamoxifen before attempting pregnancy.

Comment:

Clinical guide: With conflicting results from the two published RCTs, it is difficult to recommend the addition of tamoxifen to breast-conserving surgery and radiotherapy in the management of DCIS. Tamoxifen might be considered appropriate if the patient has other risk factors for recurrence — such as if they choose to omit radiotherapy, or if they have a family history. Tamoxifen does not seem to improve survival if given with radiotherapy for breast conservation, but may reduce local disease recurrence in oestrogen receptor-positive DCIS.

QUESTION What are the effects of treatments for primary operable breast cancer?

OPTION ADJUVANT AROMATASE INHIBITORS (ANASTROZOLE, LETROZOLE, EXEMESTANE) FOR PRIMARY OPERABLE BREAST CANCER

Treatment success

Compared with placebo Letrozole seems more effective at 5 years at improving estimated disease-free survival rates in postmenopausal women who have completed 5 years of postoperative tamoxifen therapy (moderate-quality evidence).

Compared with tamoxifen Adjuvant aromatase inhibitors (anastrozole and exemestane) are more effective at reducing breast cancer events and at improving disease-free survival in postmenopausal women with early breast cancer (moderate-quality evidence).

Adjuvant aromatase inhibitors plus tamoxifen versus tamoxifen alone Anastrozole plus tamoxifen seems no more effective than tamoxifen alone at improving breast cancer outcomes (moderate-quality evidence)

Mortality

Compared with placebo Letrozole seems no more effective at 5 years at prolonging estimated overall survival in postmenopausal women who have completed 5 years of postoperative tamoxifen therapy (moderate-quality evidence).

Compared with tamoxifen Exemestane seems modestly more effective at improving overall survival in women with oestrogen receptor-positive breast cancer (moderate-quality evidence).

Adverse effects

Adjuvant aromatase inhibitors (letrozole, anastrozole, and exemestane) are more likely to increase the incidence of arthralgia and fractures compared with placebo or tamoxifen, but are less likely to cause thromboembolic and endometrial events compared with tamoxifen.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Adjuvant aromatase inhibitors versus placebo:
We found no systematic review but found one RCT. [14] The RCT (5187 postmenopausal women who had completed 5 years of postoperative tamoxifen treatment; see comment below) compared letrozole (2.5 mg orally daily) versus placebo. It found that the estimated disease-free survival rate at 4 years was greater with letrozole compared with placebo, although there was no significant difference in estimated overall survival at 4 years (disease-free survival: 93% with letrozole *v* 87% with placebo; ARR 6.0, 95% CI 2.0 to 10.1; overall survival: 96.0% with letrozole *v* 93.6% with placebo; ARR 2.4, 95% CI –0.9 to +5.6). [14] In two follow-ups to this trial, HER2 status was found to be irrelevant to the benefit of letrozole, [15] and efficacy results for subpopulations defined by age were similar to the overall trial results. [16]

Adjuvant aromatase inhibitors versus tamoxifen:
We found no systematic review but found two RCTs (5 publications), which compared adjuvant aromatase inhibitors versus tamoxifen. [17] [18] [19] [20] [21] The first RCT (4 publications, 9366 postmenopausal women with operable, invasive, non-metastatic breast cancer, who had completed primary surgery and chemotherapy; see comment below) compared anastrozole versus tamoxifen versus a combination of anastrozole and tamoxifen. [17] [18] [19] [20] It found that anastrozole

significantly increased disease-free survival at all follow-up points compared with tamoxifen alone (HR at 3 years: 0.83, 95% CI 0.71 to 0.96; P = 0.013; [18] HR at 4 years: 0.86, 95% CI 0.76 to 0.99; P = 0.03; [17] HR at 5 years: 0.87, 95% CI 0.78 to 0.97; P = 0.01; [19] HR at 8.5 years: 0.90, 95% CI 0.82 to 0.99; P = 0.025 [20]). Anastrozole also significantly reduced recurrence and distant metastases at 5 years (recurrence: 402 events with anastrozole *v* 498 events with tamoxifen; HR 0.87, 95% CI 0.78 to 0.97; P = 0.01; distant metastases: 324 events with anastrozole *v* 375 events with tamoxifen; HR 0.79, 95% CI 0.70 to 0.90; P = 0.0005) [19] and significantly reduced recurrence and distant recurrence at 8.5 years (recurrence: 538 events with anastrozole *v* 645 events with tamoxifen; HR 0.81, 95% CI 0.73 to 0.91; distant recurrence: 424 events with anastrozole *v* 487 events with tamoxifen; HR 0.86, 95% CI 0.75 to 0.98). [20] Contralateral breast cancer was significantly reduced with anastrozole compared with tamoxifen at 5 years (35 events with anastrozole *v* 59 events with tamoxifen; P = 0.01) [19] and at 8.5 years (61 events with anastrozole *v* 87 events with tamoxifen; HR 0.68, 95% CI 0.49 to 0.94). [20]

The second RCT (4742 recurrence-free postmenopausal women, who had completed 2 to 3 years of tamoxifen treatment following surgery for primary, oestrogen receptor-positive breast cancer) compared exemestane versus continuing tamoxifen treatment for the recommended 5 years. [21] It found that exemestane significantly improved disease-free and breast cancer-free survival, and reduced risk of contralateral breast cancer at a median follow-up of 31 months compared with tamoxifen (disease-free survival: HR 0.68, 95% CI 0.56 to 0.82; P <0.001, see comment below; breast cancer-free survival: HR 0.63, 95% CI 0.51 to 0.77; P = 0.00001; reduced risk of contralateral breast cancer: HR 0.44, 95% CI 0.20 to 0.98; P = 0.04). [21] It found no significant difference in overall survival between treatments at the time of analysis (HR 0.88, 95% CI 0.67 to 1.16; P = 0.41). [21] However, subsequent follow-up of this RCT has confirmed a survival advantage for women with oestrogen receptor-positive tumours (HR 0.83, 95% CI 0.69 to 1.00; P = 0.05). [22]

Adjuvant aromatase inhibitors plus tamoxifen versus tamoxifen alone:
We found no systematic review but found one RCT (2 publications), which compared adjuvant aromatase inhibitors plus tamoxifen versus tamoxifen alone. [17] [18] The first RCT (2 publications, 9366 postmenopausal women with operable, invasive, non-metastatic breast cancer, who had completed primary surgery and chemotherapy; see comment below) compared anastrozole versus tamoxifen versus a combination of anastrozole and tamoxifen. [17] [18] It found that anastrozole plus tamoxifen did not significantly improve outcomes compared with tamoxifen alone at 3 or 4 years (3 years: HR 1.02, 95% CI 0.89 to 1.18; P = 0.8; [18] 4 years: HR 1.08, 95% CI 0.98 to 1.24; P = 0.3 [17]).

Harms:

Adjuvant aromatase inhibitors versus placebo:
The RCT comparing letrozole versus placebo found that hot flushes, arthritis, arthralgia, and myalgia were more common with letrozole (P <0.05 for each). Vaginal bleeding was more common with placebo (P = 0.01). [14] The RCT found non-significant increases in osteoporosis and fracture rates with letrozole versus placebo (osteoporosis: 5.8% with letrozole *v* 4.5% with placebo; P = 0.07; fracture rate: 3.6% with letrozole *v* 2.9% with placebo; P = 0.24). [14] In women aged 75 years and over, letrozole had a significantly higher incidence of any grade 3 to 5 protocol-specified non-fracture adverse effects compared with tamoxifen (P = 0.002; absolute numbers not reported), although there was no significant difference in cardiac adverse effects (P = 0.10; absolute numbers not reported) and thromboembolic adverse effects (time to first thromboembolic event: P = 0.54; absolute numbers not reported) between letrozole and tamoxifen. [16]

Adjuvant aromatase inhibitors versus tamoxifen:
Treatment with anastrozole reduced the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes, and vaginal discharge compared with tamoxifen, but increased fracture rate and arthralgia (endometrial cancer: OR 0.29, 95% CI 0.11 to 0.80; P = 0.02; thromboembolic events: OR 0.61, 95% CI 0.47 to 0.80; P = 0.0004; ischaemic cerebrovascular events: OR 0.70, 95% CI 0.50 to 0.97; P = 0.03; vaginal bleeding: OR 0.50, 95% CI 0.41 to 0.61; P <0.0001; hot flushes: OR 0.80, 95% CI 0.73 to 0.89; P <0.0001; vaginal discharge: OR 0.24, 95% CI 0.19 to 0.30; P <0.0001; fracture rate: OR 1.49, 95% CI 1.25 to 1.77; P <0.0001; arthralgia: OR 1.32, 95% CI 1.19 to 1.47; P <0.001). [19] Increases in adverse musculoskeletal events are probably best explained as being because of a "second menopause" induced by lower levels of oestrogen, and seem to be similar to the aches and pains associated with the normal menopause. In a subset of 308 women, there was a median bone mineral loss over 2 years of 4.1% in the lumbar spine and 3.9% in the hip with anastrozole, compared with small increases in bone mineral density with tamoxifen. With a median follow-up of 68 months, this has translated into an increase of fractures from 7.7% to 11.0%, or a 50% relative increase. [23]

Similarly, exemestane reduced thromboembolic events, vaginal bleeding, and muscle cramps compared with tamoxifen, but was associated with a higher incidence of arthralgia and diarrhoea (thromboembolic events: 1.0% with exemestane *v* 1.9% with tamoxifen; P = 0.003; vaginal bleeding:

4.0% with exemestane *v* 5.5% with tamoxifen; P = 0.05; muscle cramps: 2.8% with exemestane *v* 4.4% with tamoxifen; P <0.001; arthralgia: 5.4% with exemestane *v* 3.6% with tamoxifen; P = 0.01; diarrhoea: 4.3% with exemestane *v* 2.3% with tamoxifen; P <0.001). [21] In this RCT, a further report found that the increase in survival by the switch therapy was achieved at the expense of some detriment to skeletal health, as bone mineral density was significantly lowered in the exemestane group compared with the tamoxifen group (bone mineral density lowered at the lumbar spine: 2.7%, 95% CI 2% to 3.4%; P <0.0001). [24]

Comment:

Adjuvant aromatase inhibitors versus placebo:
The RCT comparing letrozole versus placebo was terminated after a median follow-up of 2.4 years owing to the efficacy of the aromatase inhibitor. [14] Some have criticised this early unblinding but compared with tamoxifen, adjuvant treatment with letrozole has increased disease-free survival in all groups. [16]

Adjuvant aromatase inhibitors versus tamoxifen:
Assessment of hormone receptor status was not routinely performed in some countries, so some women included in the RCT comparing anastrozole versus tamoxifen were hormone receptor-negative. [17] [18] [19] In the RCT comparing continuing tamoxifen treatment with exemestane, adjusting for oestrogen receptor status, nodal status, chemotherapy, and use of HRT did not affect the results, [21] although a significant survival benefit was observed with switching in the oestrogen receptor-positive group, [22] at the expense of some loss in bone mineral density. [24] Anastrozole, letrozole, and exemestane, all third-generation aromatase inhibitors, seem to have greater specificity compared with tamoxifen, with a more favourable adverse-effect profile. One small RCT (426 people, 30 months' follow-up) suggests that anastrozole is superior to tamoxifen in women already receiving adjuvant tamoxifen. [25]

Clinical guide: Aromatase inhibitors have an increased disease-free (but not overall) survival for oestrogen receptor-positive cancers in postmenopausal women compared with tamoxifen, and have a different safety profile. Aromatase inhibitors may be advantageous for women with a higher risk of disease recurrence, but caution regarding bone density and cardiovascular events remains. The randomised data suggest that there are now three possible strategies that may be better than 5 years of tamoxifen in postmenopausal women with oestrogen receptor-positive breast cancer: first, tamoxifen for 5 years followed by letrozole for 5 years; second, anastrozole for 5 years; third, tamoxifen for 2 to 3 years followed by exemestane for 2 to 3 years.

OPTION ADJUVANT COMBINATION CHEMOTHERAPY

Treatment success
Compared with no chemotherapy Adjuvant combination chemotherapy is more effective at reducing recurrence and is independent of nodal or menopausal status (moderate-quality evidence).

Different treatment durations compared with each other Longer regimens and shorter regimens are equally effective at reducing recurrence rates (high-quality evidence).

Different doses compared with each other Enhanced and standard-dose chemotherapy regimens seem to be equally effective at improving disease-free survival (moderate-quality evidence).

Mortality
Compared with no chemotherapy Adjuvant combination chemotherapy is more effective at reducing all-cause death and is independent of nodal or menopausal status (moderate-quality evidence).

Different treatment durations compared with each other Longer regimens and shorter regimens are equally effective at prolonging survival (high-quality evidence).

Different doses compared with each other Enhanced and standard-dose chemotherapy regimens seem to be equally effective at prolonging survival (moderate-quality evidence).

Adverse effects
Chemotherapy has been associated with fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Adjuvant combination chemotherapy versus no chemotherapy:
We found one systematic review (search date not reported, 47 RCTs, 18,000 women), which compared prolonged combination chemotherapy versus no chemotherapy. [26] Chemotherapy was associated with significantly lower rates of any kind of recurrence and death from all causes (recur-

rence: women aged under 50 years; OR 0.65, 95% CI 0.61 to 0.69; women aged 50–69 years; OR 0.80, 95% 0.72 to 0.88; death from all causes: women aged under 50 years; OR 0.73, 95% CI 0.68 to 0.78; women aged 50–69 years; OR 0.89, 95% CI 0.86 to 0.92). Proportional benefits were similar for women with node-negative and node-positive disease. Survival at 10 years according to nodal and age group is summarised (see table 2, p 51). The same group published a subsequent systematic review (search date 2006) comparing combination chemotherapy versus no chemotherapy in oestrogen-receptor-poor breast cancer. [27] The review (46 RCTs, 6000 women with receptor-poor breast cancer [chemotherapy alone versus no adjuvant treatment: 3000 women; chemotherapy plus tamoxifen versus tamoxifen alone: 3000 women]) found that chemotherapy significantly reduced recurrence compared with no chemotherapy (1358/3311 [41%] with chemotherapy *v* 1317/2718 [48%] with no chemotherapy; treatment *v* control recurrence rate ratio 0.7; P <0.00001 [two sided]). [27]

Harms:

Acute adverse effects:
Adverse effects include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance.

Long-term adverse effects:
Fertility and ovarian function may be permanently affected by chemotherapy, especially in women aged over 40 years, although for some women with hormone-dependent cancer, reduced ovarian function may contribute to the benefit of adjuvant treatment. Other potential long-term risks include induction of second cancers (especially haematological malignancies, although the risk is low) and cardiac impairment with cumulative anthracycline dosages. Provided that the cumulative dose of doxorubicin (adriamycin) does not exceed 300 mg/m^2 to 350 mg/m^2, the risk of congestive heart failure is lower than 1%.

Comment:

The absolute benefits of these regimens need to be balanced against their toxicity for different women. New and highly active cytotoxic agents such as the taxanes are being examined with anthracyclines either in combination or in sequence. Alternating sequences of cytotoxic agents may prove an effective way of circumventing acquired drug resistance and thus enhancing the efficacy of a regimen, such as the Milan regimen of single-agent anthracycline followed by standard CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy. [28]

Clinical guide: Anthracycline-based chemotherapy should be used as adjuvant therapy, and these regimens may need to include a taxane (see adjuvant taxanes, p 15).

OPTION PROLONGED ADJUVANT COMBINATION CHEMOTHERAPY (8–12 MONTHS V 4–6 MONTHS)

Treatment success
Different treatment durations compared with each other Longer regimens (8–12 months) and shorter regimens (4–6 months) are equally effective at reducing recurrence rates (high-quality evidence).

Mortality
Different treatment durations compared with each other Longer regimens (8–12 months) and shorter regimens (4–6 months) are equally effective at prolonging survival (high-quality evidence).

Adverse effects
Chemotherapy has been associated with fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Duration of treatment:
We found one systematic review (search date not reported, 11 RCTs, 6104 women), which compared longer regimens (doubling duration of chemotherapy from between 4–6 months to 8–12 months) with shorter regimens. [26] It found no significant additional survival or recurrence benefit from longer treatment duration (recurrence: 754/1747 [43%] with longer duration *v* 778/1702 [46%] with shorter duration; P = 0.06; deaths: 541/1747 [31%] with longer duration *v* 526/1702 [31%] with shorter duration; reported as not significant). [26]

Harms:

Acute adverse effects:
Adverse effects include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Prolonged chemotherapy is more likely to be associated with lethargy and haematological toxicity (anaemia and neutropenia), and anthracycline regimens cause complete hair loss.

Long-term adverse effects:
Fertility and ovarian function may be permanently affected by chemotherapy, especially in women aged over 40 years, although for some women with hormone-dependent cancer, reduced ovarian function may contribute to the benefit of adjuvant treatment. Other potential long-term risks include induction of second cancers (especially haematological malignancies, although the risk is low) and cardiac impairment with cumulative anthracycline dosages. Provided that the cumulative dose of doxorubicin (adriamycin) does not exceed 300 mg/m^2 to 350 mg/m^2, the risk of congestive heart failure is lower than 1%.

Comment:

The absolute benefits of these regimens need to be balanced against their toxicity for different women. New and highly active cytotoxic agents such as the taxanes are being examined with anthracyclines either in combination or in sequence. Alternating sequences of cytotoxic agents may prove an effective way of circumventing acquired drug resistance and thus enhancing the efficacy of a regimen, such as the Milan regimen of single-agent anthracycline followed by standard CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy. [28]

OPTION ENHANCED-DOSE REGIMENS OF ADJUVANT COMBINATION CHEMOTHERAPY

Treatment success
Different doses compared with each other Enhanced and standard-dose chemotherapy regimens seem to be equally effective at improving disease-free survival (moderate-quality evidence).

Mortality
Different doses compared with each other Enhanced and standard-dose chemotherapy regimens seem to be equally effective at prolonging survival (moderate-quality evidence).

Adverse effects
Chemotherapy has been associated with fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Different doses:
We found no systematic review, but found three RCTs, which compared enhanced versus standard-dose chemotherapy regimens. The first RCT (2305 women with primary breast cancer) compared 4 courses of standard doxorubicin–cyclophosphamide versus the same dose of cyclophosphamide delivered in two courses versus double the dose of cyclophosphamide. It found no significant difference between treatments in disease-free survival or overall survival rates (P = 0.30 and P = 0.95). [29]

The second RCT (1572 women with node-positive, stage 2 breast cancer) compared three arms: cyclophosphamide (400 mg/m^2 of body-surface area) plus doxorubicin (40 mg/m^2 once every 28 days) plus fluorouracil (400 mg/m^2 twice every 28 days) for 6 cycles (moderate intensity) versus 50% higher doses of the three drugs (cyclophosphamide 600 mg, doxorubicin 60 mg, and fluorouracil 600 mg) for only 4 cycles (high intensity) versus half the total dose used in the other two groups, and at half the dose intensity used in the second group (low intensity). [30] It found that although moderate- or high-dose intensity significantly increased disease-free survival and overall survival compared with low-dose intensity, there was no significant difference in survival between moderate and high doses (proportion of women with relapse: 132/513 [26%] with moderate-dose intensity *v* 144/507 [28%] with high-dose intensity *v* 190/509 [37%] with low-dose intensity; P <0.001 for moderate-dose intensity *v* low-dose intensity; P = 0.28 for moderate-dose intensity *v* high-dose intensity). [30]

The third RCT (777 women with primary node-positive breast cancer) randomised women to three arms: epirubicin plus cyclophosphamide (EC) for 8 cycles (267 women; epirubicin 60 mg/m^2 intravenously [iv] and cyclophosphamide 500 mg/m^2 iv on day 1 every 21 days), higher-dose epirubicin plus cyclophosphamide (HEC) for 8 cycles (255 women; epirubicin 100 mg/m^2 iv and cyclophosphamide 830 mg/m^2 iv on day 1 every 21 days), or cyclophosphamide plus methotrexate plus fluorouracil (CMF) for 6 cycles (255 women; oral cyclophosphamide 100 mg/m^2 on days 1 to 14, methotrexate 40 mg/m^2 iv, and fluorouracil 600 mg/m^2 iv on days 1 and 8 every 28 days). [31] At 15 years, it found that higher-dose epirubicin significantly improved event-free survival compared with standard-dose epirubicin (proportion of women with event-free survival at 15 years: 50% with HEC *v* 39% with EC; HR 0.77, 95% CI 0.60 to 0.98 for HEC *v* EC; absolute numbers not reported). There was no significant difference in overall survival between higher-dose epirubicin and standard-dose epirubicin (59% with HEC *v* 56% with EC; HR 0.85, 95% CI 0.64 to 1.13 for HEC *v* EC). [31]
For full details of comparisons with CMF, see adjuvant anthracycline regimens, p 11 .

Harms:

Acute adverse effects:
Adverse effects include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance.

Long-term adverse effects:
Fertility and ovarian function may be permanently affected by chemotherapy, especially in women aged over 40 years, although for some women with hormone-dependent cancer, reduced ovarian function may contribute to the benefit of adjuvant treatment. Other potential long-term risks include induction of second cancers (especially haematological malignancies, although the risk is low) and cardiac impairment with cumulative anthracycline dosages. Provided that the cumulative dose of doxorubicin (adriamycin) does not exceed 300 mg/m^2 to 350 mg/m^2, the risk of congestive heart failure is lower than 1%. In the third RCT the authors could not recommend HEC over the standard-dose regimen (EC) because of increased cardiotoxicity seen with HEC, although the difference was not significant (proportion of women with congestive heart failure: 11/255 [4%] with HEC *v* 5/267 [2%] with EC; P = 0.21). [31]

Comment:

The absolute benefits of these regimens need to be balanced against their toxicity for different women. New and highly active cytotoxic agents such as the taxanes are being examined with anthracyclines either in combination or in sequence. Alternating sequences of cytotoxic agents may prove an effective way of circumventing acquired drug resistance and thus enhancing the efficacy of a regimen, such as the Milan regimen of single-agent anthracycline followed by standard CMF chemotherapy. [28]

OPTION ADJUVANT ANTHRACYCLINE CHEMOTHERAPY

Treatment success
Compared with standard CMF regimens Adjuvant regimens containing an anthracycline seem more effective than a standard multidrug chemotherapy regimen (cyclophosphamide, methotrexate, fluorouracil) at reducing recurrence (moderate-quality evidence).

Mortality
Compared with standard CMF regimens Adjuvant regimens containing an anthracycline are modestly more effective than a standard multidrug chemotherapy regimen (cyclophosphamide, methotrexate, fluorouracil) at improving 5-year survival (moderate-quality evidence).

Adverse effects
Chemotherapy has been associated with nausea and vomiting, hair loss, bone marrow suppression, fatigue, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Anthracycline regimens versus standard CMF (cyclophosphamide, methotrexate, fluorouracil) regimen:
We found one systematic review (search date not reported) [26] and one subsequent RCT. [31] The review (11 RCTs, 5942 women) compared regimens containing anthracycline (including the drugs doxorubicin [adriamycin] or epirubicin) versus standard CMF regimens. [26] It found a significant reduction in recurrence rates in those on anthracycline regimens (P = 0.006), and a modest but significant improvement in 5-year survival (72% with anthracycline *v* 69% with CMF; P = 0.02). The RCT (777 women with primary node-positive breast cancer) randomised women to three arms: epirubicin plus cyclophosphamide (EC) for 8 cycles (267 women; epirubicin 60 mg/m^2 intravenously [iv] and cyclophosphamide 500 mg/m^2 iv on day 1 every 21 days), higher-dose epirubicin plus cyclophosphamide (HEC) for 8 cycles (255 women; epirubicin 100 mg/m^2 iv and cyclophosphamide 830 mg/m^2 iv on day 1 every 21 days), or CMF for 6 cycles (255 women; oral cyclophosphamide 100 mg/m^2 on days 1 to 14, methotrexate 40 mg/m^2 iv and fluorouracil 600 mg/m^2 iv on days 1 and 8 every 28 days). [31] At 15 years' follow-up, the RCT found no significant difference in disease-free survival or overall survival between CMF and EC (proportion of women with event-free survival at 15 years: 39% with EC *v* 45% with CMF; P = 0.21 for EC *v* CMF; overall survival: 56% with EC *v* 57% with CMF; P = 0.70 for EC *v* CMF; absolute numbers not reported). There was also no significant difference in disease-free survival and overall survival between CMF and the chemotherapy regimen containing higher-dose epirubicin (disease-free survival: 50% with HEC *v* 45% with CMF; P = 0.39 for HEC *v* CMF; overall survival: 59% with HEC *v* 57% with CMF; P = 0.45 for HEC *v* CMF; absolute numbers not reported). [31]

Harms:

Acute adverse effects:
Adverse effects include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Anthracycline regimens cause complete hair loss.

Long-term adverse effects:
Fertility and ovarian function may be permanently affected by chemotherapy, especially in women aged over 40 years, although for some women with hormone-dependent cancer, reduced ovarian function may contribute to the benefit of adjuvant treatment. Other potential long-term risks include induction of second cancers (especially haematological malignancies, although the risk is low) and cardiac impairment with cumulative anthracycline dosages. Provided that the cumulative dose of doxorubicin (adriamycin) does not exceed 300 mg/m^2 to 350 mg/m^2, the risk of congestive heart failure is lower than 1%.

Comment:

The absolute benefits of these regimens need to be balanced against their toxicity for different women. New and highly active cytotoxic agents such as the taxanes are being examined with anthracyclines either in combination or in sequence. Alternating sequences of cytotoxic agents may prove an effective way of circumventing acquired drug resistance and thus enhancing the efficacy of a regimen, such as the Milan regimen of single-agent anthracycline followed by standard CMF chemotherapy. [28] There seems to be a particular benefit of adjuvant therapy with anthracyclines in women with HER2-overexpressed or HER2-amplified primary breast tumours. [32]

Clinical guide:
Anthracycline-based chemotherapy should be used as adjuvant therapy.

OPTION ADJUVANT TAMOXIFEN

Treatment success
Compared with placebo Adjuvant tamoxifen taken for up to 5 years is more effective at reducing the risk of recurrence in women with oestrogen receptor-positive tumours, irrespective of age, menopausal status, nodal involvement, or the addition of chemotherapy (moderate-quality evidence).

Compared with adjuvant aromatase inhibitors (anastrozole and exemestane) Tamoxifen is less effective at reducing breast cancer events and at improving disease-free survival in postmenopausal women with early breast cancer (moderate-quality evidence).

Mortality
Compared with placebo Adjuvant tamoxifen taken for up to 5 years is more effective at reducing mortality in women with oestrogen receptor-positive tumours, irrespective of age, menopausal status, nodal involvement, or the addition of chemotherapy (moderate-quality evidence).

Different treatment durations compared with each other Treatment with tamoxifen for 5 years seems more effective than shorter durations (2 years) at improving event-free and overall survival, but there does not seem to be any additional benefit at prolonging treatment beyond 5 years (moderate-quality evidence).

Compared with exemestane Tamoxifen seems less effective at improving overall survival in women with oestrogen receptor-positive breast cancer (moderate-quality evidence).

Adverse effects
Tamoxifen has been associated with a higher incidence of endometrial cancer and thrombotic complications compared with placebo or adjuvant aromatase inhibitors (letrozole, anastrozole, and exemestane), but is less likely to cause arthralgia and fractures.

Note
We found no clinically important results from RCTs about adjuvant tamoxifen compared with radiotherapy in the treatment of women with primary operable breast cancer.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Adjuvant tamoxifen versus placebo:
We found one systematic review (search date not reported, 55 RCTs, 37,000 women), which compared adjuvant tamoxifen with placebo. [33] The review found that taking tamoxifen for a median of 5 years significantly reduced recurrence and mortality compared with placebo (RR for recurrence 0.58; RR for mortality 0.78; CI presented graphically; for both comparisons P <0.00001). [33] These benefits seemed to be largely irrespective of age, menopausal status, daily tamoxifen dose (generally 20–40 mg), and of whether chemotherapy had been given to both groups.

Oestrogen receptor and lymph node status:
Subgroup analysis in the systematic review (search date not reported, 55 RCTs, 37,000 women) [33] found that tamoxifen was associated with a greater reduction in the recurrence rate for women with oestrogen receptor-positive versus those with receptor-negative tumours after 5 years (RR for recurrence: 0.5 with oestrogen receptor-positive tumours *v* 0.94 with oestrogen receptor-negative

tumours), and with a slightly greater reduction in the absolute risk of 10-year recurrence in women with node-positive compared with node-negative disease (ARR: 15.2% with node-positive disease *v* 14.9% with node-negative disease). Tamoxifen treatment for 5 years was also associated with a greater absolute improvement in 10-year survival in node-positive than node-negative women (see table 3, p 51). [33]

The same group published a subsequent systematic review (search date 2006) comparing tamoxifen versus no tamoxifen in oestrogen-receptor-poor breast cancer. [27] The review (50 RCTs, 14,000 women with receptor-poor disease; most RCTs comparing chemotherapy plus tamoxifen *v* chemotherapy alone) found no significant difference in recurrence or mortality between tamoxifen and no tamoxifen (absolute numbers and significance not reported).

Duration of treatment:
The review found significantly greater reductions in the risk of recurrence with increasing duration of adjuvant tamoxifen (RR for recurrence: 0.74 with 5 years of tamoxifen use *v* 0.88 with 1 year of tamoxifen use; P <0.0001). [33] One RCT included in the review (3887 women) compared 2 years and 5 years of treatment and found similar results. [34] The RCT found that 5 years of adjuvant tamoxifen treatment improved event-free and overall survival rates compared with 2 years of treatment (event-free survival: HR 0.82, 95% CI 0.71 to 0.96; overall survival: 0.82, 95% CI 0.69 to 0.99). The effects of prolonged treatment beyond 5 years are unclear. The largest RCT included in the systematic review (1153 women who had completed 5 years of tamoxifen therapy) compared placebo versus 5 more years of tamoxifen. [35] It found that placebo increased disease-free survival compared with continued tamoxifen after a further 4-year follow-up (86% with continued tamoxifen *v* 92% with placebo; P = 0.003), although there was no significant difference in overall survival. Another RCT included in the review found no difference between placebo and continuing tamoxifen beyond 5 years. [36]

Adjuvant tamoxifen versus radiotherapy:
We found no systematic review or RCTs comparing adjuvant tamoxifen versus radiotherapy in women with primary operable breast cancer.

Adjuvant aromatase inhibitors versus tamoxifen:
See benefits of adjuvant aromatase inhibitors, p 6 .

Harms:

One systematic review found an increased risk of endometrial cancer with tamoxifen (average HR 2.58, 95% CI 2.23 to 2.93). [33] For 5 years of tamoxifen treatment, this resulted in a cumulative risk over 10 years of 2 deaths per 1000 women (95% CI 0 deaths per 1000 women to 4 deaths per 1000 women). There was no evidence of an increased incidence of other cancers, or of non-breast cancer related deaths (i.e., cardiac or vascular), although one extra death per 5000 women-years of tamoxifen was attributed to pulmonary embolus. Bone loss was found in premenopausal women (1.4% bone loss a year) but not in postmenopausal women, because of the partial agonist effects of tamoxifen. [37] There were mixed effects on cardiovascular risk, with significant reductions in low-density lipoprotein cholesterol associated with a reduced incidence of myocardial infarction in some studies, but an increased risk of thrombosis. Overall, no effect has been found on non-breast cancer mortality (HR 0.99, 95% CI 0.88 to 1.16). [33] The second systematic review did not report adverse effects. [27]

Adjuvant tamoxifen versus radiotherapy:
See harms of tamoxifen plus radiotherapy, p 5 . The risks of congenital malformations or late teratogenic manifestations in adulthood are unknown, and women should be offered choices in all cases concerning continuing with pregnancy or termination. Women are conventionally advised to stop tamoxifen before attempting pregnancy.

Adjuvant aromatase inhibitors versus tamoxifen:
See harms of adjuvant aromatase inhibitors, p 6 .

Comment:

The risk:benefit ratio may vary between women, with oestrogen receptor-negative women deriving little benefit. Current clinical practice has been to recommend tamoxifen for only 5 years, [38] though we are awaiting results of longer studies using tamoxifen for 10 years.

Adjuvant aromatase inhibitors versus tamoxifen:
See comments of adjuvant aromatase inhibitors, p 6 .

Clinical guide: Tamoxifen for 5 years' adjuvant use has clinical benefits in improved survival for oestrogen receptor-positive breast cancer, but endometrial cancer and thrombotic events may cause significant morbidity or mortality.

OPTION CHEMOTHERAPY PLUS MONOCLONAL ANTIBODY (TRASTUZUMAB) IN WOMEN WITH OVEREXPRESSED HER2/NEU ONCOGENE

Treatment success
Compared with observation (during or after chemotherapy) Trastuzumab, started after or during chemotherapy, is more effective at 1 year at increasing disease-free survival in HER2-positive women compared with 2 years of observation (moderate-quality evidence).

Mortality
Compared with observation (during or after chemotherapy) Trastuzumab, started after chemotherapy but not during chemotherapy, is more effective at 1 year at increasing overall survival in HER2-positive women compared with 2 years of observation (moderate-quality evidence).

Adverse effects
Trastuzumab has been associated with cardiac dysfunction.

Benefits:

Trastuzumab versus placebo:
We found no systematic review or RCTs.

Trastuzumab versus observation, after chemotherapy:
We found one RCT comparing three treatments: trastuzumab every 3 weeks for 1 year; trastuzumab every 3 weeks for 2 years; or observation. [39] Women completed locoregional therapy and at least 4 cycles of primary or adjuvant chemotherapy before randomisation. The RCT found that 1 year of trastuzumab increased disease-free survival (absence of recurrence, contralateral breast cancer, second non-breast malignant disease, or death without prior recurrence) compared with observation at 2 years (5081 women with HER2-positive and either node-positive or node-negative breast cancer; AR of recurrence, secondary primary event, or death without prior recurrence: 127/1694 [7%] with 1 year of trastuzumab *v* 220/1693 [13%] with observation; HR 0.54, 95% CI 0.43 to 0.67). [39] It found no significant difference in overall survival between 1 year of trastuzumab and observation at 2 years (AR of death: 29/1694 [1.7%] with trastuzumab *v* 37/1693 [2.2%] with observation; HR 0.76, 95% CI 0.47 to 1.23). [39] Outcomes with 2 years of trastuzumab were not reported. A later subgroup analysis of these data defined populations by nodal status (4 groups: nodal status not assessed, node negative, 1–3 positive nodes, or 4 or more positive nodes) and by steroid hormone receptor status (4 groups: oestrogen-receptor negative plus progesterone-receptor negative, oestrogen-receptor negative plus progesterone-receptor positive, oestrogen-receptor positive plus progesterone-receptor negative, or oestrogen-receptor positive plus progesterone-receptor positive). [40] The analyses found that trastuzumab improved disease-free survival across subgroups compared with observation, with estimated difference in 3-year disease-free survival ranging from +11.3% in women with both hormone receptor-positive, node-negative disease to +0.6% for women with hormone receptor-negative, node-negative disease.

Trastuzumab versus observation, starting during chemotherapy:
We found a pooled analysis of two RCTs, which compared doxorubicin plus cyclophosphamide followed by paclitaxel versus doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab (for 1 year). [41] One of the RCTs also included a group with doxorubicin plus cyclophosphamide followed by paclitaxel followed by trastuzumab, which was excluded from joint analysis. The RCTs found that 1 year of trastuzumab significantly increased disease-free survival and overall survival compared with observation at a median follow-up of 2 years (3351 women with HER2-positive and either node-positive or node-negative breast cancer; AR for disease-free survival events: 133/1672 [8%] with trastuzumab *v* 261/1679 [16%] with observation; HR 0.48, 95% CI 0.39 to 0.59; AR for death: 62/1672 [4%] with trastuzumab *v* 92/1679 [6%] with observation; HR 0.67, 95% CI 0.48 to 0.93). [41]

Harms:

In women with previous exposure to anthracycline, there is concern about cardiac toxicity associated with trastuzumab therapy. Therefore, the RCTs only included women with normal left ventricular ejection fraction. The RCTs monitored cardiac function (symptoms and left ventricular ejection fraction) during the trials, with specific stopping criteria for cardiotoxicity.

Trastuzumab versus observation, after chemotherapy:
The RCT found that 1 year of trastuzumab significantly increased grade 3 or 4 toxicity and severe congestive heart failure compared with observation (at least one grade 3 or 4 event: 132/1677 [8%] with 1 year of trastuzumab *v* 75/1710 [4%] with observation; P <0.001; severe congestive heart failure: 9/1677 [0.5%] with 1 year of trastuzumab *v* 0/1710 [0%] with observation; P = 0.002). [39]

It found that left ventricular ejection fraction decreased in a significantly higher proportion of women with trastuzumab than with observation (113/1677 [7%] with trastuzumab *v* 34/1710 [2%] with observation; P <0.001).

Trastuzumab versus observation, starting during chemotherapy:
The RCT found that 1 year of trastuzumab increased cardiac toxicity compared with observation (New York Heart Association class III or IV congestive heart failure or death from cardiac causes; in the first RCT: 4% with trastuzumab *v* 1% with observation; second RCT: 3% with trastuzumab *v* 0% with observation; significance not reported). [41] The RCT found no differences in any other common toxicity criteria (data not reported). [41]

Comment:

In two of the RCTs, enrolment was closed after the first interim analysis by the data safety monitoring boards of each trial. [39] [41] Trastuzumab, a monoclonal antibody, led to decreases in the initial peak of recurrences during the first 2 to 3 years, with a projected absolute benefit of 18% at 5 years. [42] The optimal schedule of trastuzumab is unclear with regard to it being given simultaneously with or sequentially after chemotherapy. The nature and reversibility of cardiac dysfunction is unclear, and even with its large therapeutic benefits, avoiding unnecessary toxic effects is important. There was a trend towards an increase in brain metastases in the trastuzumab groups in the pooled analysis of two RCTs, [41] although this was offset by a decrease in other second malignancies.

Clinical guide: There is no consensus in HER2-positive (either 3+ or FISH-positive) women about whether to start trastuzumab during or after chemotherapy, and current expert opinion seems to favour continuing trastuzumab for 1 year with 3-monthly echocardiograms to assess cardiac function. Patients with HER2+ tumours by immunohistochemistry should have the appropriate HER2 status assessment by FISH.

OPTION ADJUVANT TAXANES

Treatment success
Taxane-based regimens compared with anthracycline-based regimens Adjuvant taxane-based regimens are more effective at increasing disease-free survival (moderate-quality evidence).

Different taxane-based chemotherapy regimens compared with each other Docetaxel-based and paclitaxel-based regimens seem equally effective at increasing disease-free survival (moderate-quality evidence).

Mortality
Taxane-based regimens compared with anthracycline based regimens Adjuvant taxane-based regimens are more effective at improving 5-year overall survival (moderate-quality evidence).

Different taxane-based chemotherapy regimens compared with each other Docetaxel-based and paclitaxel-based regimens seem equally effective at increasing overall survival (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Taxane-based chemotherapy regimens versus anthracycline-based regimens:
We found one systematic review (search date 2006) [43] and two subsequent phase III trials. [44] [45]

The systematic review (13 RCTs, 22,903 women) compared taxane-anthracycline-based regimens versus anthracycline-based regimens alone. [43] It found taxane plus anthracycline combination chemotherapy significantly improved disease-free survival and overall survival compared with anthracycline combination chemotherapy (disease-free survival: 13 RCTs, 22,903 women; HR 0.83, 95% CI 0.79 to 0.89; absolute numbers not reported; overall survival: 12 RCTs, 22,379 women; HR 0.85, 95% CI 0.79 to 0.91; absolute numbers not reported). Risk reduction was not influenced by the type of taxane, oestrogen receptor expression, number of axillary metastases, or by age or menopausal status. The systematic review performed sensitivity analyses for taxanes given in combination with anthracyclines and for taxanes given in sequence with anthracyclines. It found that taxanes given in sequence with anthracyclines significantly improved disease-free survival and overall survival compared with anthracycline-based regimens alone (disease-free survival: 9 RCTs, 15,363 women; HR 0.83, 95% CI 0.78 to 0.88; overall survival: 9 RCTs, 14,839 women; HR 0.86, 95% CI 0.79 to 0.93; absolute numbers not reported). Taxanes given in combination with anthracyclines also significantly improved disease-free survival compared with anthracycline-based regimens alone (5 RCTs, 7540 women; HR 0.84, 95% CI 0.76 to 0.93; absolute numbers not reported), but there was no significant difference in overall survival (5 RCTs, 7540 women; HR 0.89, 95% CI 0.79 to 1.02). [43]

The first subsequent RCT (1016 women) compared taxanes versus anthracyclines, namely 4 cycles of standard-dose doxorubicin plus cyclophosphamide (AC; 60/600 mg/m^2) versus 4 cycles of docetaxel plus cyclophosphamide (TC; 75/600 mg/m^2). [44] At a median follow-up of 7 years, it found that docetaxel plus cyclophosphamide significantly improved disease-free survival events (relapse or recurrence, second cancer, and death without relapse or recurrence) compared with doxorubicin plus cyclophosphamide (88/506 [17%] with TC *v* 118/510 [23%] with AC; HR 0.74, 95% CI 0.56 to 0.98). Docetaxel plus cyclophosphamide also significantly improved overall survival compared with doxorubicin plus cyclophosphamide (deaths from all causes: 58/506 [11%] with TC *v* 84/510 [16%] with AC; HR 0.69, 95% CI 0.5 to 0.97). [44]

However, a further subsequent RCT (2882 oestrogen receptor-positive women with 1–3 positive nodes) did not show a benefit comparing a very similar combination. [45] It found no significant difference in overall survival at 5 years between doxorubicin 60/600 mg/m^2 plus cyclophosphamide 75/600 mg/m^2 (AC) and doxorubicin 60/600 mg/m^2 plus docetaxel 60/600 mg/m^2 (AT) (91% with AC *v* 92% with AT; HR 1.06, 95% CI 0.85 to 1.31; P = 0.62; absolute numbers not reported). It also found no significant difference between groups in progression-free survival at 5 years (85% with either treatment; HR for AC *v* AT 1.02, 95% CI 0.86 to 1.22; P = 0.78, absolute numbers not reported). [45]

Different taxane-based chemotherapy regimens versus each other:
We found one RCT (4950 women with axillary lymph node-positive or high-risk, lymph-node-negative breast cancer) comparing two different taxanes, docetaxel and paclitaxel, given at either 3-week intervals for 4 cycles or 1-week intervals for 12 cycles. [46] All women first received 4 cycles of doxorubicin plus cyclophosphamide. The RCT found no significant difference in overall survival between paclitaxel and docetaxel after a median follow-up of 63.8 months (OR 1.03, 95% CI 0.91 to 1.17; absolute numbers not reported). Three-weekly docetaxel significantly improved disease-free survival compared with 3-weekly paclitaxel, although there was no significant difference between weekly docetaxel and 3-weekly paclitaxel (5-year survival rates: 77% with 3-weekly paclitaxel *v* 81% with weekly paclitaxel *v* 81% with 3-weekly docetaxel *v* 78% with weekly docetaxel; P = 0.02 for 3-weekly docetaxel *v* 3-weekly paclitaxel; P = 0.29 for weekly docetaxel *v* 3-weekly paclitaxel). There was no significant difference in overall survival between 3-weekly paclitaxel and 3-weekly docetaxel, or between 3-weekly paclitaxel and weekly docetaxel (5-year overall survival rates: 86% with 3-weekly paclitaxel *v* 87% with 3-weekly docetaxel *v* 86% with weekly docetaxel; P = 0.25 for 3-weekly docetaxel *v* 3-weekly paclitaxel; P = 0.8 for weekly docetaxel *v* 3-weekly paclitaxel). [46]

Harms:

Taxane-based chemotherapy regimens versus anthracycline-based regimens:
The systematic review did not report adverse effects. [43]

The first subsequent RCT reported increased febrile neutropenia (fever 38.5 °C with neutropenia) with taxane plus cyclophosphamide (TC) compared with doxorubicin plus cyclophosphamide (AC) (5% with TC *v* 2.5% with AC; significance not reported). [44] When this was reanalysed by age, the rates of febrile neutropenia were doubled in the older women: for TC, 8% for older and 4% for younger women compared with 4% in older and 2% in younger women for AC. Of note, these rates of febrile neutropenia reflect the widespread use of prophylactic antibiotics during haematological nadirs during the conduct of the RCT (1997 to 2000). Use of prophylactic granulocyte colony-stimulating factor to stimulate neutrophil production was not used in this trial. [44] This increase in febrile neutropenia with the taxane-based regimen was similar in the second subsequent RCT (grade 3/4 neutropenia: 54% with doxorubicin 60/600 mg/m^2 plus docetaxel 60/600 mg/m^2 [AT] *v* 38% with doxorubicin 60/600 mg/m^{2}plus cyclophosphamide 75/600 mg/m^2 [AC]; P <0.05). [45] There were 7 cases of myelodysplastic syndromes/acute myeloid leukemia in each group. Twelve women developed congestive heart failure during chemotherapy; 8 receiving AT (six grade 3, one grade 4, one grade 5), 4 receiving AC (all grade 3), and 19 women developed congestive heart failure more than 30 days after chemotherapy; 12 receiving AT (11 grade 3, one grade 4), 7 receiving AC (all grade 3). The RCT did not assess the significance of difference between groups for this outcome.

Different taxane-based chemotherapy regimens versus each other:
In the RCT, grade 2, 3, or 4 neuropathy was more frequent with weekly paclitaxel than with 3-weekly paclitaxel (27% with weekly paclitaxel *v* 20% with 3-weekly paclitaxel; significance and absolute numbers not reported).

Comment:

Clinical guide: Although the National Institute for Health and Clinical Excellence has approved TAC (docetaxel, doxorubicin, and cyclophosphamide) in England and Wales, many clinicians have indicated their preference to use docetaxel as part of the FEC-T (fluorouracil, epirubicin, and cyclophosphamide plus docetaxel) regimen as per the PACS 01 study. [47] The rationale for favouring FEC-T over TAC is based on cost, capacity issues, and data reported in the PACS 01 [47] and BCIRG 001 [48] studies, in particular the rate of haematological toxicities — specifically febrile

neutropenia and the need for 7 days of primary prophylactic granulocyte colony-stimulating factor (G-CSF) with the TAC regimen. In conclusion, sequential adjuvant chemotherapy with FEC followed by docetaxel significantly improves disease-free and overall survival in node-positive breast cancer patients and has a significantly more favourable safety profile. In other words, FEC followed by docetaxel buys efficacy with lower toxicity and costs (less G-CSF). A crucial issue is whether taxanes should be combined with anthracyclines or whether they should be administered sequentially after an anthracycline-based regimen. Both options have theoretical advantages and drawbacks: combination regimens require dose reduction for both compounds, but may, in theory, exploit drug synergism. In sequential regimens, both compounds can be administered at optimal doses. However, comparing these two approaches was not an aim of the included systematic review [43] and we still do not know the answer to this question.

OPTION LESS EXTENSIVE MASTECTOMY

Treatment success

Radical or total mastectomy compared with simple mastectomy with or without postoperative radiotherapy Extended radical mastectomy or simple mastectomy with or without postoperative radiotherapy seem equally effective at 25 years' follow-up at improving disease-free survival in women with operable breast cancer (moderate-quality evidence).

Mastectomy compared with breast conservation with or without radiotherapy Mastectomy seems no more effective than breast conservation surgery with or without radiotherapy at reducing local or overall recurrence rates (moderate-quality evidence).

Different extents of local excision compared with each other We don't know whether lumpectomy is more effective than quadrantectomy at reducing local recurrence (moderate-quality evidence).

Mortality

Supraradical, radical, and total mastectomy compared with each other Extensive surgery and less extensive surgery seem to be equally effective at improving the annual risk of death at 10 years in women with operable breast cancer, but extensive surgery has worse cosmetic outcomes (moderate-quality evidence).

Radical or total mastectomy compared with simple mastectomy with or without radiotherapy Radical and total mastectomy (with or without axillary radiotherapy) are equally effective at 25 years and 50 years at improving survival in women with operable breast cancer regardless of nodal status (moderate-quality evidence).

Mastectomy compared with breast conservation with or without radiotherapy Mastectomy and breast conservation surgery (with or without radiotherapy) seem to be equally effective at reducing the annual risk of death at 10 years (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Radical or total mastectomy versus simple mastectomy with or without radiotherapy:
We found one systematic review (search date not reported, 4 RCTs, 1296 women with operable breast cancer), which compared radical or total mastectomy versus simple mastectomy [49] and one subsequent RCT. [50]

The systematic review found no significant difference in the annual risk of death over a 10-year period (OR for more-extensive *v* less-extensive surgery 0.98, CI presented graphically; P = 0.8). [49]

Long-term follow-up of one RCT included in the review (1079 women), which compared radical mastectomy versus total mastectomy with or without axillary radiotherapy found no significant difference in survival between total and radical mastectomy, regardless of nodal status at 25-year follow-up (in women with negative nodes: HR for total mastectomy plus radiotherapy *v* radical mastectomy 1.08, 95% CI 0.91 to 1.28; HR for total mastectomy without radiotherapy *v* radical mastectomy 1.03, 95% CI 0.87 to 1.23; in women with positive nodes: HR for total mastectomy plus radiotherapy *v* radical mastectomy 1.06, 95% CI 0.89 to 1.27). [51]

The subsequent RCT (666 women randomised; 241 women subsequently excluded because of inoperability) compared extended radical mastectomy versus simple mastectomy plus postoperative radiotherapy to the chest wall, axilla, and supraclavicular fossa. [50] It found no significant difference in disease-free survival at 25 years and overall survival at 50 years between extended radical mastectomy and simple mastectomy plus radiotherapy (disease-free survival: P = 0.54; overall survival: P = 0.79; absolute results presented graphically for both outcomes). [50]

Supraradical, radical, and total mastectomy compared with each other:
We found one systematic review (search date not reported, 5 RCTs, 2090 women with operable breast cancer) comparing supraradical mastectomy versus radical mastectomy (2 RCTs), radical versus total mastectomy (2 RCTs), and supraradical versus total mastectomy (1 RCT). [49] It found no significant difference in the annual risk of death over a 10-year period (OR for more extensive *v* less extensive surgery 0.98, CI presented graphically; P = 0.7).

Mastectomy versus breast conservation with or without radiotherapy:
We found three systematic reviews. [49] [52] [53] The reviews included many but not all of the same RCTs and performed different analyses so we report all three here.

The first review (search date not reported, 9 RCTs, 5610 women potentially suitable for breast-conserving surgery) compared mastectomy versus breast-conserving surgery (with or without radiotherapy; the proportion of women receiving mastectomy who also received radiotherapy was unclear). [49] It found no significant difference in annual risk of death over 10 years between mastectomy and breast-conserving surgery either with or without radiotherapy (mastectomy *v* breast conservation alone: 1 RCT, 1432 women; OR 0.97, CI presented graphically; P = 0.4; mastectomy *v* breast conservation plus radiotherapy: 9 RCTs, 4891 women; OR 1.02, CI presented graphically; P = 0.7). It also found no significant difference in overall rates of recurrence or rates of local recurrence between mastectomy and breast-conserving surgery plus radiotherapy (6 RCTs, 3107 women; OR for overall recurrence mastectomy *v* breast conservation plus radiotherapy 0.96, 95% CI 0.88 to 1.04; AR for local recurrence: 6.2% with mastectomy *v* 5.9% with breast conservation plus radiotherapy; P value reported as not significant).

The second review (search date 1995, 6 RCTs) compared breast conservation with or without radiotherapy versus mastectomy and performed several subgroup analyses. [52] Overall, it found no significant difference in the risk of death at 10 years (5 RCTs, 3006 women; OR breast conservation *v* mastectomy 0.91, 95% CI 0.78 to 1.05). Where more than half of node-positive women in both mastectomy and breast conservation groups received adjuvant nodal radiotherapy, both groups had similar survival rates. Where fewer than half of node-positive women in both groups received adjuvant nodal radiotherapy, survival was better with breast conservation (OR of death: breast conservation *v* with mastectomy 0.69, 95% CI 0.49 to 0.97).

The third review (search date 2007, 18 RCTs, 9388 women) found no significant difference between mastectomy and breast-conserving surgery with or without radiotherapy in overall survival at 3, 5, 10, 15, and 20 years' follow-up (at 3 years: 9 RCTs; 1419/1503 [95%] with mastectomy *v* 1975/2129 [93%] with breast-conserving surgery; OR for breast-conserving surgery *v* mastectomy 0.84, 95% CI 0.63 to 1.12; at 20 years: 5 RCTs; 661/1468 [45%] with mastectomy *v* 938/2128 [44%] with breast-conserving surgery; OR for breast-conserving surgery *v* mastectomy 1.14, 95% CI 0.89 to 1.45; P = 0.31). [53] It also found no significant difference in locoregional recurrence at 3, 5, 15, and 20 years, but found a significant difference at 10 years' follow-up with locoregional recurrence being higher in women receiving breast-conserving surgery with or without radiotherapy (at 10 years: 8 RCTs; 218/2736 [8%] with mastectomy *v* 385/3691 [10%] with breast-conserving surgery; OR 1.55, 95% CI 1.05 to 2.30; P = 0.003; at 20 years: 4 RCTs; 115/1144 [10%] with mastectomy *v* 288/2477 [12%] with breast-conserving surgery; OR 2.02, 95% CI 0.85 to 4.79; P = 0.11). [53]

One RCT that had not reached 20-year follow-up at the time of the review by Yang et al has now reported 20-year follow-up results. [54] The RCT, which originally included some women who were not randomised but elected the treatment they were to receive, reported a subgroup analysis of the 793 women who were correctly randomised to either breast-conserving surgery or mastectomy with or without radiotherapy. [54] It found no significant difference between breast-conserving surgery and mastectomy in 10-year recurrence-free survival (P = 0.57; absolute results presented graphically) and 20-year overall survival (P = 0.20; absolute results presented graphically). [54]

Different extents of local excision in breast conservation:
We found no systematic review but found one RCT (705 women), which compared lumpectomy versus quadrantectomy. [55] There were significantly more local recurrences with lumpectomy than with quadrantectomy (7% with lumpectomy *v* 2% with quadrantectomy), but a major factor associated with local recurrence in the lumpectomy group was incomplete excision (see comment below). [56] We found no RCTs comparing wide local excision (complete excision microscopically) versus quadrantectomy.

Harms:

Less- versus more-extensive mastectomy:
More extensive surgery results in a poorer cosmetic result. Between 60% and 90% of women having breast conservation have an excellent or good cosmetic result (median 83%, 95% CI 67% to 87%). [55] [57] [58] [59] [60] [61] [62] [63] [64] [65] The most important factor influencing cosmetic outcome is the volume of tissue excised; the larger the amount of tissue excised, the worse the

cosmetic result. [55] The RCT of different extents of local excision in breast conservation found that, in a subset of 148 women, there was a significantly higher rate of poor cosmetic outcome with quadrantectomy (RR quadrantectomy *v* lumpectomy 3.1, 95% CI 1.2 to 8.1). [55] Only isolated small studies have shown no correlation between extent of surgical excision and cosmesis. [63]

Mastectomy versus breast conservation with or without radiotherapy:
The first review did not report on the harms of breast-conserving surgery plus radiotherapy compared with mastectomy. However, overall, the review found that adding radiotherapy to mastectomy or breast-conserving surgery increased the risk of non-breast cancer death compared with surgery alone (AR 7.7% with radiotherapy *v* 5.7% with no radiotherapy; OR 1.24, 95% CI 1.09 to 1.42). [49]

Comment: The link between completeness of excision and local recurrence after breast conservation has been evaluated in 16 centres. [56] In 13 of these, incomplete excision significantly increased the risk of local recurrence compared with complete excision (RR 1.03, 95% CI 1.03 to 1.05). The three centres not reporting increased rates of local recurrence after incomplete excision gave much higher doses of local radiotherapy (65–72 Gy) to people with involved margins. Two centres also used re-excision, and women with involved margins had only focal margin involvement.

Clinical guide: The main aim of surgical excision is to remove the tumour with microscopically clear margins. The width of what constitutes an adequate margin remains unclear. As a bare minimum, excision should aim to excise all disease with no microscopic extension to the edge of the specimen. The extent of the disease, the size of the breast, the location of the tumour in the breast and the desires of the patient will all have a role in what is then considered appropriate in terms of choice of surgical procedure. Complete excision of breast cancer achieved by less than radical mastectomy or by breast conservation may give an improved cosmetic outcome over more radical surgery without any detriment to outcome.

OPTION OVARIAN ABLATION

Treatment success
Compared with no ablation Ovarian ablation by irradiation or surgery is more effective at 15 years at improving recurrence-free survival in premenopausal women (irrespective of nodal status) with early breast cancer (moderate-quality evidence).

Mortality
Compared with no ablation Ovarian ablation by irradiation or surgery is more effective at increasing overall survival at 15 years in premenopausal women (irrespective of nodal status) with early breast cancer (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: **Ovarian ablation versus no ablation:**
We found one systematic review (search date not reported, 12 RCTs with at least 15-years' follow-up, 2102 premenopausal women with early breast cancer), which compared ovarian ablation by irradiation or surgery versus no ablation. [66] It found that ovarian ablation by irradiation significantly increased overall survival and recurrence-free survival versus surgery alone after 15 years (overall survival: 52% with ablation *v* 46% with no ablation; P = 0.001; disease-free survival: 45% with ablation *v* 39% with no ablation; P = 0.0007). Benefit was independent of nodal status.

Harms: We found no good evidence on long-term adverse effects. Concerns exist about late sequelae of ovarian ablation, especially effects on bone mineral density and cardiovascular risk. Acute adverse effects are likely to be menopausal symptoms.

Comment: Five of the RCTs compared ovarian ablation plus chemotherapy versus chemotherapy alone. [66] In these, the absolute benefit of ablation was smaller than in RCTs of ovarian ablation alone. It may be that cytotoxic chemotherapy itself suppresses ovarian function, making the effect of ablation difficult to detect in combined RCTs. When only premenopausal women who did not have chemotherapy were considered, there was a 27% improvement in the odds of recurrence-free survival. RCTs are underway of reversible oophorectomy using gonadotrophin-releasing hormone analogues, which would allow preservation of fertility in younger women with oestrogen receptor-positive tumours.

Clinical guide: Oophorectomy in premenopausal women with oestrogen receptor-positive cancers improves survival independent of node status. The addition of chemotherapy may further improve survival.

OPTION RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY FOR PRIMARY OPERABLE BREAST CANCER

Treatment success

Breast-conserving surgery plus radiotherapy compared with breast-conserving surgery alone Breast-conserving surgery plus radiotherapy is more effective at 15 to 20 years at reducing local recurrence (moderate-quality evidence).

Breast-conserving surgery with or without radiotherapy compared with mastectomy Breast-conserving surgery with or without radiotherapy seems to be as effective as mastectomy at 10 years at reducing recurrences and at improving disease-free survival at 20 years (moderate-quality evidence).

Mortality

Breast-conserving surgery with or without radiotherapy compared with breast-conserving surgery alone Breast-conserving surgery with or without radiotherapy is more effective at 15 years at reducing mortality owing to breast cancer and all-cause mortality (moderate-quality evidence).

Breast-conserving surgery with or without radiotherapy compared with mastectomy Breast-conserving surgery with or without radiotherapy seems to be as effective as mastectomy at improving overall survival at 10 to 20 years (moderate-quality evidence).

Adverse effects

Radiotherapy may rarely be associated with late adverse effects, such as pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery alone:
We found one systematic review [67] and one subsequent RCT. [68] The review compared breast-conserving surgery plus radiotherapy versus breast-conserving surgery alone. Seven RCTs included in the review used megavoltage x-rays. The review found that postoperative radiotherapy significantly reduced the risk of breast cancer mortality, all-cause mortality, and isolated local recurrence compared with no radiotherapy (search date not reported, 10 RCTs; 7311 women; 15-year risk of breast cancer mortality: 31% with breast-conserving surgery plus radiotherapy *v* 36% with breast-conserving surgery alone, rate ratio 0.83, CI presented graphically; P = 0.0002; 15-year risk of all-cause mortality: 35% with breast-conserving surgery plus radiotherapy *v* 40% with breast-conserving surgery alone; P = 0.005; 5-year risk of recurrence: 7% with breast-conserving surgery plus radiotherapy *v* 26% with breast-conserving surgery alone, rate ratio 0.31, CI presented graphically; P <0.00001). Subgroup analyses suggested that the proportional reduction in local recurrence was similar in women of different ages and tumour characteristics. [67] One RCT included in the review has now reported long-term results with a median follow-up period of 13.7 years. [69] The improvement in local control with the addition of radiotherapy to breast-conserving surgery was confirmed (400 women; 20-year local breast recurrence: 29% with breast-conserving surgery plus radiotherapy *v* 50% with breast-conserving surgery and no radiotherapy; HR 0.45, 95% CI 0.31 to 0.64; P = 0.0001). It found no significant difference in survival between groups (HR 0.91, 95% CI 0.64 to 1.28; P = 0.59). [69]

The subsequent RCT (264 women) compared surgery (lumpectomy plus dissection of ipsilateral axilla) plus radiotherapy versus surgery alone in women with good prognostic features (defined as age over 40 years, unifocal tumours 20 mm and less in diameter, low to moderate histological grade, low cell proliferation rate, positive steroid hormone receptor status, and margins clear by at least 1 cm) to determine whether there was a favourable subgroup in which radiotherapy might reasonably be omitted. [68] At a median follow-up of 12.1 years, the RCT found that surgery plus radiotherapy significantly reduced local recurrence compared with surgery alone (16/138 [12%] with surgery plus radiotherapy *v* 34/125 [27%] with surgery alone; P = 0.0013). It found no significant difference between surgery plus radiotherapy and surgery alone in distant recurrence, breast cancer-specific mortality, and overall mortality (distant recurrence: 17/138 [12.3%] with surgery plus radiotherapy *v* 15/125 [12.0%] with surgery alone; P = 0.93; breast cancer-specific mortality: 10/138 [7%] with surgery plus radiotherapy *v* 10/125 [8%] with surgery alone; P = 0.82; overall mortality: 21/138 [15%] with surgery plus radiotherapy *v* 26/125 [21%] with surgery alone; P = 0.24). [68]

Breast-conserving surgery with or without radiotherapy versus mastectomy:
See option on less extensive mastectomy, p 17 .

Harms:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery alone:
The review [67] did not perform a separate meta-analysis of non-breast cancer deaths for radiotherapy plus breast-conserving surgery versus breast-conserving surgery alone (see general adverse events of adding radiotherapy to breast surgery below for overall analyses). However, it found that radiotherapy plus breast-conserving surgery reduced all-cause mortality compared with breast-conserving surgery alone (see benefits above).

Breast-conserving surgery plus radiotherapy versus mastectomy:
See option on less extensive mastectomy, p 17 .

Quality of life:
One old prospective study of quality of life after breast-conserving surgery has been reported and is based on an RCT in which participants were randomised to either radiotherapy or no further local treatment after surgery. [70] The study (1984–1989; 837 women) [70] reported that radiotherapy significantly reduced quality of life compared with no radiotherapy at 1 and 2 months (17-item modified Breast Cancer Chemotherapy Questionnaire, higher score indicating better quality of life; mean score change at 1 month: –0.07 with radiotherapy *v* +0.21 without radiotherapy; mean score change at 2 months: –0.05 with radiotherapy *v* +0.30 without radiotherapy; P = 0.0001 for both time points). Radiotherapy significantly increased breast pain at 6 months and breast skin irritation at 3 months (AR for breast pain: 33% with radiotherapy *v* 20% without radiotherapy; P = 0.0002; skin irritation: 28% with radiotherapy *v* 14% without radiotherapy; P = 0.0001). However, there was no significant difference between groups in the risk of breast pain, skin irritation, or upset because of breast appearance at 2 years (AR for breast pain: about 15% for both groups; P reported as not significant; skin irritation: 7% in both groups; P reported as not significant; upset with breast appearance: 5% in both groups; P = 0.62). [70]

One systematic review (search date 2007) attempted to identify the prevalence and severity of upper limb problems following surgery and radiotherapy for early breast cancer. [71] The study was complicated by the diversity of studies available, the variable end points evaluated, and the extent of surgery and radiotherapy in the studies incorporated into the review. The review (32 RCTs) found that upper limb symptoms occurred with varying frequency (shoulder restriction: <1% to 67% of people; lymphoedema: 0−34% of people; shoulder and arm pain: 9−68% of people; arm weakness: 9−28% of people; significance and absolute numbers not reported). It also found that radiotherapy plus surgery significantly increased the risk of lymphoedema and shoulder restriction compared with no radiotherapy (lymphoedema: OR 1.46, 95% CI 1.16 to 1.84; shoulder restriction: OR 1.67, 95% CI 0.98 to 2.86; absolute numbers not reported). Two identified RCTs reported Global Health Status scores from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires were high and unchanged from pre-radiotherapy scores. For patients undergoing surgery and radiation for breast cancer, the prognosis is good in terms of the upper limb and quality of life. [71]

General adverse effects of adding radiotherapy to breast surgery:
One systematic overview (search date 2001) found limited data on radiotherapy-related morbidity and reported that no conclusions could be drawn. [72] A consensus document published in 1998 (mainly of women having breast-conserving surgery or mastectomy with variation in radiotherapy techniques, doses, and fractionation) reported two severe adverse effects of radiotherapy, namely acute pneumonitis (0.7–7.0%) and pericarditis (0–0.3%), and the following long-term adverse effects: significant arm oedema (1% without axillary clearance), radionecrotic rib fracture (1.1–1.5%), and brachial plexopathy (0–1.8%). [73] The risk and severity of adverse effects increased with volume irradiated, total dose received, dose per fraction, previous surgery (e.g., axillary dissection), and radiotherapy techniques that caused overlap in irradiated tissues. A more recent systematic review found that adding radiotherapy to surgery (breast-conserving surgery or mastectomy) increased the risk of non-breast cancer mortality (mainly from heart disease and lung cancer) compared with no radiotherapy (search date not reported, 63 RCTs; 32,800 people; 15-year risk of non-breast cancer mortality: 16% with radiotherapy *v* 15% with no radiotherapy, rate ratio 1.12, CI not reported; P = 0.001; rate ratio for heart disease mortality 1.27, CI not reported; P = 0.0001; rate ratio for lung cancer mortality 1.78, CI not reported; P = 0.0004). [67] Three RCTs included in the review, with data beyond 10 years, did not find an excess of cardiac deaths. [74] [75] [76] This may be because great care was taken in these RCTs to reduce the radiotherapy dose to the heart and to measure morbidity and mortality from cardiac disease. It may also be because more modern techniques in planning and treatment delivery are capable of reducing incident dose to the heart. Studies assessing cosmetic results have mainly been retrospective, using poorly validated outcomes. The effects of social, psychological, and financial disruption from attending 5 to 6 weeks of radiotherapy have not been assessed well. There is an extremely low reported incidence of radiotherapy-induced malignancy, usually soft tissue sarcomas, in the irradiated breast.

Comment: RCTs comparing breast-conserving surgery with and without radiotherapy, as well as retrospective case series, have found that prognostic factors for local recurrence after breast-conserving surgery include positive tumour margins, an extensive intraduct component, younger age, lymphovascular invasion, histological grade, and systemic therapy. The only consistent independent risk factor is avoiding radiotherapy. One systematic review of radiotherapy effects in breast cancer by the Swedish Council of Technology Assessment in Health Care, which did not carry out meta-analysis, supports the above conclusions for post-mastectomy radiotherapy, radiotherapy after breast-conserving surgery for ductal carcinoma in situ, and for the comparability of breast-conserving surgery with radiotherapy and modified radical mastectomy alone for invasive breast cancer for disease-free survival and overall survival. [72] It concluded that there are conflicting data about the effects of breast conservation surgery plus radiotherapy compared with modified radical mastectomy on local recurrence in people with invasive cancer.

Clinical guide: For women with early breast cancer, there seems to be no survival difference whether breast-conserving surgery and radiotherapy or mastectomy is chosen. Radiotherapy following breast-conserving therapy may substantially reduce local disease recurrence without detriment to survival when modern radiotherapy techniques are used. The pros and cons of these approaches need to be discussed with the patient before surgery. The addition of tamoxifen to breast-conserving surgery, with or without radiotherapy, leads to better local control. The best local control outcome is when breast-conserving surgery, radiotherapy, and tamoxifen (if oestrogen receptor-positive) are all part of the treatment. Chemotherapy seems to have little effect on local control in the absence of radiotherapy. Randomised data suggest that even patients with relatively good prognosis tumours derive a local control benefit by having radiotherapy.

OPTION RADIOTHERAPY WITH OR WITHOUT ENDOCRINE THERAPY AFTER BREAST-CONSERVING SURGERY

Treatment success

Breast-conserving surgery plus radiotherapy compared with breast-conserving surgery plus endocrine therapy Radiotherapy is more effective than tamoxifen at reducing ipsilateral or local recurrences at 7.5 years in women who have undergone breast-conserving surgery (high-quality evidence).

Breast-conserving surgery plus radiotherapy plus endocrine therapy versus breast-conserving surgery plus endocrine therapy only The combination of both radiotherapy and endocrine therapy after breast-conserving surgery may be more effective than endocrine therapy alone at reducing recurrence and increasing disease-free survival but may not reduce time to mastectomy (low-quality evidence).

Mortality

Breast-conserving surgery plus radiotherapy compared with breast-conserving surgery plus endocrine therapy Radiotherapy and tamoxifen seem to be equally effective at improving survival in women who have undergone breast-conserving surgery (moderate-quality evidence).

Breast-conserving surgery plus radiotherapy plus endocrine therapy versus breast-conserving surgery plus endocrine therapy only The combination of both radiotherapy and endocrine therapy after breast-conserving surgery may not confer additional benefit over endocrine therapy alone in increasing survival (moderate-quality evidence).

Adverse effects

Radiotherapy may be associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: **Breast-conserving surgery plus radiotherapy versus breast-conserving surgery plus endocrine therapy:**

We found no systematic review but found one RCT. [70]

The RCT (1009 women after lumpectomy for node-negative invasive breast cancer 1 cm or less, 80% were aged 50 years or over) compared three treatments: radiotherapy (50 Gy over 5 weeks with or without external beam boost), radiotherapy plus tamoxifen, and tamoxifen alone. [70] It found that radiotherapy alone significantly reduced ipsilateral breast cancer recurrence compared with tamoxifen alone after a median follow-up of 87 months (23/332 [7%] with radiotherapy alone *v* 45/334 [14%] with tamoxifen alone; HR 0.51, 95% CI 0.31 to 0.84; P = 0.008). It found no significant difference in survival or other events (tumour recurrence, contralateral breast cancer, other second primary breast cancer, or death with no evidence of cancer) between radiotherapy alone and tamoxifen alone (survival: 312/332 [94%] with radiotherapy alone *v* 314/334 [94%] with tamoxifen alone; P = 0.93 between three arms; events: 61/332 [18%] with radiotherapy alone *v* 74/334 [22%] with tamoxifen alone; P = 0.08 between three arms). [70]

Breast-conserving surgery plus radiotherapy plus endocrine therapy versus breast-conserving surgery plus endocrine therapy only:
We found no systematic review. We found 4 RCTs assessing effects on recurrence/relapse and survival that met *Clinical Evidence* inclusion criteria. [70] [77] [78] [79] [79]

The first RCT (1009 women after lumpectomy for node-negative invasive breast cancer 1 cm or less, 80% were aged 50 years or over) compared three treatments: radiotherapy (50 Gy over 5 weeks with or without external beam boost), radiotherapy plus tamoxifen, and tamoxifen alone. [70] It found that radiotherapy plus tamoxifen significantly reduced ipsilateral breast cancer recurrence compared with tamoxifen alone after a median follow-up of 87 months (9/334 [3%] with radiotherapy plus tamoxifen *v* 45/334 [14%] with tamoxifen alone; HR 0.19, 95% CI 0.09 to 0.39; P <0.001). It found no significant difference in survival or other events (tumour recurrence, contralateral breast cancer, other second primary breast cancer, or death with no evidence of cancer) between radiotherapy plus tamoxifen and tamoxifen alone (survival: 312/334 [93%] with radiotherapy plus tamoxifen *v* 314/334 [94%] with tamoxifen alone; P = 0.93; events: 52/334 [16%] with radiotherapy plus tamoxifen *v* 74/334 [22%] with tamoxifen alone; P = 0.08). [70]

The second RCT (769 women with primary breast cancer, aged over 50 years, who had undergone breast-conserving surgery for histologically node-negative disease unless aged 65 years or over, when a clinically negative axilla was acceptable) compared radiotherapy plus tamoxifen versus tamoxifen alone (20 mg/day for 5 years). [77] It found that radiotherapy plus tamoxifen increased disease-free survival rates and reduced recurrence and rate of relapse in the ipsilateral breast compared with tamoxifen alone after 5 years (HR for relapse 1.7, 95% CI 1.2 to 2.5; P = 0.004; recurrence: 7.7% with tamoxifen alone *v* 0.6% with radiotherapy plus tamoxifen; HR 8.3, 95% CI 3.3 to 21.1; P <0.001; AR for disease-free survival: 84% with tamoxifen alone *v* 91% with radiotherapy plus tamoxifen; P = 0.004). [77] A subgroup analysis found greater benefits in local relapse rates in women with T1, receptor-positive tumours at 5 years (3% with receptor-positive tumours *v* 8% with receptor-negative or T2 tumours). [77]

The third RCT (women aged 70 years or over with clinical stage 1 breast cancer, who had undergone lumpectomy for receptor-positive tumour) compared postoperative radiotherapy versus no radiotherapy in women taking tamoxifen (20 mg/day) for 5 years. [78] It found that radiotherapy significantly reduced local or regional recurrence rate, but found no significant difference in time to mastectomy versus no radiotherapy (recurrence rate: 2/317 [0.6%] with radiotherapy plus tamoxifen *v* 16/319 [5.0%] with tamoxifen alone; P <0.01; time to mastectomy: P = 0.15, no further details reported). [78] There was no significant difference between treatment groups in time to distant metastasis (P = 0.97) or overall survival rates (P = 0.94). [78]

The fourth RCT (869 women, median follow-up 53.8 months) compared two interventions: breast-conserving surgery plus radiotherapy plus adjuvant hormone therapy (tamoxifen for 2 years followed by anastrozole for 3 years) versus breast-conserving surgery plus adjuvant hormone therapy (tamoxifen for 2 years followed by anastrozole for 3 years). [79] It found that radiotherapy plus adjuvant hormone therapy significantly reduced local recurrence compared with adjuvant hormone therapy alone (2/414 [0.4%] with radiotherapy plus adjuvant hormone therapy *v* 19/417 [5%] with adjuvant hormone therapy alone; HR 10.21, 95% CI 2.38 to 43.84). Radiotherapy plus adjuvant hormone therapy also significantly improved disease-free survival compared with adjuvant hormone therapy alone (overall relapse events: 7/414 [2%] with radiotherapy plus adjuvant hormone therapy *v* 23/417 [6%] with adjuvant hormone therapy alone; HR 3.48, 95% CI 1.49 to 8.12). There was no significant difference in overall survival between the groups (mortality: 11/414 [3%] with radiotherapy plus adjuvant hormone therapy *v* 18/417 [4%] with adjuvant hormone therapy alone; P = 0.18). [79]

Harms:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery plus endocrine therapy:
The RCT (1009 women after lumpectomy in node-negative invasive breast cancer 1 cm or less) compared radiotherapy, radiotherapy plus tamoxifen, and tamoxifen alone, and found no significant difference between treatments in endometrial cancer or other second primary cancers (endometrial cancer: 1/332 [0.3%] with radiotherapy alone *v* 1/334 [0.3%] with tamoxifen alone *v* 5/334 [1.5%] with radiotherapy plus tamoxifen; P = 0.12; other second primary cancer: 10/332 [3.0%] with radiotherapy alone *v* 14/334 [4.2%] with tamoxifen alone *v* 15/334 [4.5%] with radiotherapy plus tamoxifen; P = 0.65). [70]

Breast-conserving surgery plus radiotherapy plus endocrine therapy versus breast-conserving surgery plus endocrine therapy:
Adverse effects for the first RCT are reported under breast-conserving surgery plus radiotherapy versus breast-conserving surgery plus endocrine therapy. [70] The second RCT reported no significant difference in grade 3 adverse events between tamoxifen plus radiotherapy and tamoxifen alone (39/386 [10%] with radiotherapy plus tamoxifen *v* 30/383 [8%] with tamoxifen alone; P = 0.33).

Hot flushes were reported to be the most common adverse effects, followed by fatigue, fluid retention, and skin erythema owing to radiation. [77] The third RCT found that more women experienced breast pain and skin fibrosis or retraction following treatment with tamoxifen plus radiotherapy compared with tamoxifen alone (P <0.05 for both outcomes). Physicians rated worse cosmesis, oedema, and skin colour in women who had received radiotherapy in addition to tamoxifen compared with those who received tamoxifen alone (P <0.05 for all outcomes). [78] The fourth RCT found found that 2/414 (0.5%) women receiving radiotherapy plus adjuvant hormone therapy developed contralateral breast cancer compared with 5/417 (1.2%) receiving adjuvant hormone therapy alone (significance not assessed). [79]

Quality of life:
We found one RCT (255 women) evaluating the effect of radiotherapy on quality of life. [80] The RCT compared breast-conserving surgery plus hormone therapy versus breast-conserving surgery plus hormone therapy plus radiotherapy in women defined as "minimum-risk" (65 years or more, receiving adjuvant hormone therapy, medically suitable to attend treatment and follow-up, node negative, T1–T2, had breast-conserving surgery with clear surgical margins, and able and willing to give informed consent). The trial reported no significant difference between the two arms in overall quality of life scores, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (P = 0.64; absolute numbers not reported). Radiotherapy significantly improved several quality of life subscales within the first 15 months of follow-up compared with no radiotherapy, including insomnia (P = 0.01; absolute numbers not reported) and systemic therapy adverse effects (P = 0.03; absolute numbers not reported), although radiotherapy was associated with significantly increased breast symptom scores compared with no radiotherapy (P <0.001; absolute numbers not reported). [80]

One prospective study (1992–2000) [81] assessed whether breast pain affected quality of life in women who received breast-conserving surgery plus tamoxifen plus either radiotherapy or no further treatment. It found no significant difference between groups in pain, physical function, breast symptoms, or global health quality of life at 12 months (measured using the Quality of Life Questionnaire Core 30 Items [QLQ-C30] and breast-cancer-specific Quality of Life Questionnaire [QLQ-BR23]; mean scores presented graphically; pain: P = 0.33; physical function: P = 0.76; breast symptoms: P = 0.27; quality of life: P = 0.45). [81]

General adverse effects of adding radiotherapy to breast surgery:
One systematic overview (search date 2001) found limited data on radiotherapy-related morbidity and reported that no conclusions could be drawn. [72]

The RCT of breast-conserving surgery plus hormone therapy versus breast-conserving surgery plus hormone therapy plus radiotherapy in women with minimum-risk breast cancer examined women for acute and late toxicity. [80] Observer findings included a significant increase in breast erythema, breast oedema, and telangiectasia observed in those women randomised to receive radiotherapy. Late toxicity data are not available as yet. [80]

One consensus document published in 1998 (mainly of women having breast-conserving surgery or mastectomy with variation in radiotherapy techniques, doses, and fractionation) reported two severe adverse effects of radiotherapy, namely acute pneumonitis (0.7–7.0%) and pericarditis (0–0.3%), and the following long-term adverse effects: significant arm oedema (1% without axillary clearance), radionecrotic rib fracture (1.1–1.5%), and brachial plexopathy (0–1.8%). [73] The risk and severity of adverse effects increased with volume irradiated, total dose received, dose per fraction, previous surgery (e.g., axillary dissection), and radiotherapy techniques that caused overlap in irradiated tissues. One more recent systematic review found that adding radiotherapy to surgery (breast-conserving surgery or mastectomy) increased the risk of non-breast cancer mortality (mainly from heart disease and lung cancer) compared with no radiotherapy (search date not reported, 63 RCTs; 32,800 people; 15-year risk of non-breast cancer mortality: 16% with radiotherapy *v* 15% with no radiotherapy, rate ratio 1.12, CI not reported; P = 0.001; rate ratio for heart disease mortality 1.27, CI not reported; P = 0.0001; rate ratio for lung cancer mortality 1.78, CI not reported; P = 0.0004). [67] Three RCTs included in the review, with data beyond 10 years, did not find an excess of cardiac deaths. [74] [75] [76] This may be because great care was taken in these RCTs to reduce the radiotherapy dose to the heart and to measure morbidity and mortality from cardiac disease. Studies assessing cosmetic results have mainly been retrospective, using poorly validated outcomes. The effects of social, psychological, and financial disruption from attending 5 to 6 weeks of radiotherapy have not been assessed well. There is an extremely low reported incidence of radiotherapy-induced malignancy, usually soft tissue sarcomas, in the irradiated breast.

Comment: We found one RCT (361 women with receptor-positive breast cancer), which had a 2 x 2 factorial trial that randomised women to radiotherapy or no radiotherapy, and tamoxifen or no tamoxifen after breast-conserving surgery. [82] It found that any combination of treatment significantly reduced

local recurrence rates compared with breast-conserving surgery alone after a median follow-up of 5.9 years (RR of recurrence for combination treatment *v* breast-conserving surgery alone 0.35, 95% CI 0.19 to 0.62 for breast-conserving surgery plus radiotherapy *v* breast-conserving surgery alone; RR 0.25, 95% CI 0.12 to 0.56 for breast-conserving surgery plus tamoxifen *v* breast-conserving surgery alone; RR 0.38, 95% CI 0.19 to 0.74 for breast-conserving surgery plus radiotherapy plus tamoxifen *v* breast-conserving surgery alone; multivariate analysis adjusting for age, tumour size, and tumour grade, absolute numbers not reported). There was no significant difference between any combination of treatment and breast-conserving surgery alone in distant disease-free survival. [82] The RCT did not assess adverse effects. The RCT reported difficulties in trial execution owing to poor cooperation from some participating centres and was closed in 1998 owing to slow recruitment, having recruited just over half of its original target sample size of 700 participants. This means that the trial was underpowered to detect a clinically important difference between combination treatment groups and instead presented results for any combination treatment compared with breast-conserving surgery alone. In order to increase recruitment, the trial was opened to centres with a "strong preference for tamoxifen"; this may also have affected the results.

Clinical guide:
RCTs comparing breast-conserving surgery with and without radiotherapy, as well as retrospective case series, have found that prognostic factors for local recurrence after breast-conserving surgery include positive tumour margins, an extensive intraduct component, younger age, lymphovascular invasion, histological grade, and systemic therapy. The only consistent independent risk factor is avoiding radiotherapy. One systematic review of radiotherapy effects in breast cancer by the Swedish Council of Technology Assessment in Health Care, which did not carry out meta-analysis, supports the above conclusions for post-mastectomy radiotherapy, radiotherapy after breast-conserving surgery for ductal carcinoma in situ, and for the comparability of breast-conserving surgery with radiotherapy and modified radical mastectomy alone for invasive breast cancer for disease-free survival and overall survival. [72] It concluded that there are conflicting data about the effects of breast conservation surgery plus radiotherapy compared with modified radical mastectomy on local recurrence in people with invasive cancer.

For women with early breast cancer, there seems to be no survival difference whether breast-conserving surgery and radiotherapy or mastectomy is chosen. Radiotherapy following breast-conserving therapy may substantially reduce local disease recurrence without detriment to survival when modern radiotherapy techniques are used. The pros and cons of these approaches need to be discussed with the patient before surgery. The addition of tamoxifen to breast-conserving surgery, with or without radiotherapy, leads to better local control. The best local control outcome is when breast-conserving surgery, radiotherapy, and tamoxifen (if oestrogen receptor-positive) are all part of the treatment. Chemotherapy seems to have little effect on local control in the absence of radiotherapy.

OPTION RADIOTHERAPY AFTER MASTECTOMY FOR PRIMARY OPERABLE BREAST CANCER

Treatment success
Compared with mastectomy Radiotherapy after mastectomy is more effective at reducing the 5-year risk of isolated local recurrence in women with node-positive disease (moderate-quality evidence).

Mortality
Compared with mastectomy alone In women with node-positive disease, radiotherapy is more effective than no radiotherapy after mastectomy plus axillary clearance at reducing the 15-year risk of breast cancer mortality, particularly in women with tumours >5 cm (moderate-quality evidence).

Adverse effects
Radiotherapy may be associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, radionecrotic rib fracture, and radiation-induced malignancy.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Radiotherapy after mastectomy versus mastectomy:
We found 5 systematic reviews, which compared radiotherapy after mastectomy versus mastectomy. [83] [84] [67] [85] [86] The first review also reported updated results. [87] Each of the reviews had differing inclusion criteria and often included small under-powered studies, spanning a long period of time. Identified RCTs frequently had differing treatment regimens, with various radiotherapy treatment volumes (including total nodal irradiation) and doses used, with or without systemic therapy. The first two reviews reflect earlier treatment patterns so we report them in brief below. [83] [84] The third review identified all of the RCTs included in the other systematic reviews and provides a meta-analysis of all the trials. [67] The fourth and fifth reviews performed different meta-analyses; one assessing post-mastectomy radiotherapy in only those women that received concur-

rent systemic therapy, [85] and the other assessing only those women that received an "optimal" radiation dose and volume. [86] We also found two subsequent reports of an RCT identified by the review. [88] [89]

The first review examined RCTs before 1975 and mainly included RCTs of women not treated with systemic therapy (10 RCTs). [83] It followed up participants in these early trials for 10 years and reported updated results. [87] The review reported that locoregional radiation after mastectomy decreased cancer-specific death but this decrease was offset by an increase in cardiac deaths. The excess cardiac mortality seems to be greatest for trials that used older radiation techniques where myocardial doses may have been relatively high. This review has been criticised on the basis that radiotherapy was not always given to the same treatment area and that the RCTs were of antiquated radiotherapy planning and treatment techniques.

The second review focused primarily on RCTs published between 1987 and 1997 (10 RCTs, 10,862 women) and found that adding radiotherapy to mastectomy significantly reduced the risk of local recurrence (OR 0.33, 95% CI 0.27 to 0.39) and reduced the risk of cancer-related mortality (OR 0.94, 95% CI 0.88 to 1.0; P values not reported). [84] However, this cause-specific mortality benefit was offset by an increase in non-cancer mortality for those treated with radiotherapy (OR 1.24, 95% CI 1.1 to 1.4; P = 0.02). There was no difference in overall mortality. Indicators identified for increased risk of locoregional recurrence were increasing number of positive axillary nodes, increasing tumour size, involvement of margins, high tumour grade, and presence of lymphovascular invasion.

The third review (search date 1995, 36 RCTs) compared mastectomy versus mastectomy followed by radiotherapy to the chest wall. [67] Seven RCTs were of mastectomy alone (5597 women; 3318 node-negative; 2279 node-positive), 4 RCTs were of mastectomy plus axillary sampling (647 women; 449 node-negative; 198 node-positive), and 25 were of mastectomy plus axillary clearance (9933 women; 1428 node-negative; 8505 node-positive). Some of the identified RCTs also included women treated with systemic therapy; however, the review reported that only unconfounded RCTs, where both arms received the same systemic treatment, were included in the meta-analysis. In women with node-positive disease, the review found that radiotherapy significantly reduced 5-year risk of isolated local recurrence compared with no radiotherapy after mastectomy plus axillary clearance (6% with radiotherapy *v* 23% with no radiotherapy; rate ratio 0.28, CI presented graphically; P <0.00001), after mastectomy plus axillary sampling (14% with radiotherapy *v* 50% with no radiotherapy; rate ratio 0.23, CI presented graphically; P <0.00001), and after mastectomy alone (12% with radiotherapy *v* 34% with no radiotherapy; rate ratio 0.34, CI presented graphically; P <0.00001). In women with node-positive disease, radiotherapy significantly reduced the 15-year risk of breast cancer mortality compared with no radiotherapy after mastectomy plus axillary clearance (55% with radiotherapy *v* 60% with no radiotherapy; rate ratio 0.89, CI presented graphically; P = 0.0002). However, there was no significant difference in 15-year risk of breast cancer mortality between radiotherapy and no radiotherapy after mastectomy alone (rate ratio 0.81, CI presented graphically; P = 0.3) or after mastectomy plus axillary sampling (rate ratio 0.92, CI presented graphically; P = 0.2). In women with node-negative disease, the review found that radiotherapy significantly reduced 5-year risk of isolated local recurrence compared with no radiotherapy after mastectomy plus axillary clearance (2% with radiotherapy *v* 6% with no radiotherapy; rate ratio 0.41, CI presented graphically; P = 0.0002), after mastectomy plus axillary sampling (6% with radiotherapy *v* 25% with no radiotherapy; rate ratio 0.32, CI presented graphically; P <0.00001), and after mastectomy alone (6% with radiotherapy *v* 23% with no radiotherapy; rate ratio OR 0.33, CI presented graphically; P <0.00001). In women with node-negative disease, radiotherapy significantly increased 15-year risk of breast cancer mortality compared with no radiotherapy after mastectomy plus axillary clearance (31% with radiotherapy *v* 28% with no radiotherapy; rate ratio 1.26, CI presented graphically; P = 0.01). However, it found no significant difference in 15-year risk of breast cancer mortality between radiotherapy and no radiotherapy after mastectomy plus axillary sampling (rate ratio 0.88, CI presented graphically; P = 0.4), or after mastectomy alone (rate ratio 0.98, CI presented graphically; P = 0.8). In those trials where systemic therapy was given to participants, the review found that tamoxifen given for 5 years significantly reduced the local recurrence risk for oestrogen-positive cancers (OR 0.47, CI not reported) and polychemotherapy reduced the local recurrence risk irrespective of oestrogen-receptor status (OR 0.63, CI not reported for women aged <50 years and OR 0.70, CI not reported for women aged 50–69 years). Among the women treated with systemic therapy, the 15-year absolute reduction in breast-cancer mortality was 6% with radiotherapy (mortality: 49% with radiotherapy *v* 55% with mastectomy; P <0.000001).

The fourth review (search date 1999, 18 RCTs, 6367 women) analysed only RCTs that included women who were treated with systemic therapy and where the randomisation involved locoregional radiotherapy following definitive surgery. [85] It found that radiation significantly reduced the risk of any recurrence (OR 0.69, 95% CI 0.58 to 0.83; P = 0.00004), reduced locoregional recurrence (OR

0.25 95% CI 0.19 to 0.34; P<0.000001), and improved overall survival (OR 0.83, 95% CI 0.74 to 0.94; P = 0.004).

The fifth review (search date not reported, 25 RCTs, 13,199 women) confined the analysis to RCTs involving women treated by mastectomy, where radiotherapy was the sole variable studied, and where the radiotherapy dose and target volume was considered optimal (i.e., included the chest wall, axilla, and supraclavicular fossa with or without the internal mammary nodes and of adequate radiotherapy dose). [86] Analysis of the 17 trials with at least 5 years' follow-up found that optimal adjuvant radiotherapy significantly increased overall survival compared with mastectomy (1122/3626 [31%] with radiotherapy *v* 1262/3704 [34%] with mastectomy alone; OR 0.87, 95% CI 0.79 to 0.96; P = 0.006). Analysis of the 13 trials with follow-up of more than 10 years found that the difference in survival rates between groups had increased and remained significant (1609/3434 [47%] with radiotherapy *v* 1864/3512 [53%] with mastectomy alone; OR 0.78, 95% CI 0.70 to 0.85; P <0.001).

Two subsequent reports updated one of the RCTs included in the reviews. [88] [89] The first report (3083 women, median follow-up 18 years) pooled results from the premenopausal and post-menopausal subgroups reported in the original publication to perform an analysis of the whole group. [88] It found that post-mastectomy radiotherapy increased disease-free survival compared with no radiotherapy (proportion of women alive at 18 years with no recurrence: 462/1538 [30%] with radiotherapy *v* 297/1545 [19%] with no radiotherapy; significance not assessed). It also found that compared with no radiotherapy, post-mastectomy radiotherapy significantly improved locoregional recurrence, time to distant metastases, distant recurrence, and the risk of distant metastasis subsequent to any local recurrence (locoregional recurrence: 79/1538 [5%] with radiotherapy *v* 456/1545 [30%] with no radiotherapy; RR 0.15, 95% CI 0.12 to 0.19; time to distant metastases: 12.3 years with radiotherapy *v* 6.5 years with no radiotherapy; P = 0.04; distant recurrence: 53% with radiotherapy *v* 64% with no radiotherapy; RR 0.78, 95% CI 0.71 to 0.86; risk of distant metastasis subsequent to any local recurrence: 6% with radiotherapy *v* 35% with no radiotherapy; RR 0.15, 95% CI 0.11 to 0.20; absolute numbers not reported). [88]

The second further report assessed a subgroup of women from the same RCT in an attempt to identify those most at risk of recurrence and therefore most likely to benefit from adjuvant post-mastectomy radiotherapy. [89] The study examined the outcomes of 1000 of the 3083 women (32%) with node-positive breast cancer according to their receptor status. It found that locoregional recurrence rates were reduced with radiotherapy compared with no radiotherapy irrespective of receptor status. However, significantly improved survival with post-mastectomy radiotherapy compared with no radiotherapy was confined to those women with good prognostic markers, such as oestrogen-receptor positive, progesterone-receptor positive, or HER-2 negative (oestrogen-receptor positive: HR 0.74, 95% CI 0.62 to 0.89; P = 0.002; progesterone-receptor positive: HR 0.69, 95% CI 0.56 to 0.85; P = 0.001; HER-2 negative: HR 0.79, 95% CI 0.66 to 0.83; P = 0.007). The authors of the study suggested that node-positive women with poor prognosis tumours were more likely to harbour distant metastatic disease and therefore were unlikely to derive a survival benefit, whereas node-positive women with better prognosis disease were more likely to be harbouring locoregional disease only, with locoregional control leading to a survival benefit. [89]

Radiotherapy after mastectomy versus mastectomy plus adjuvant chemotherapy:
Two RCTs reported in one report compared mastectomy plus radiotherapy versus mastectomy plus chemotherapy (one trial was in premenopausal women [547 participants] and one trial was in postmenopausal women [679 participants]). [90] It found that radiotherapy reduced locoregional recurrences among both premenopausal and postmenopausal women compared with chemotherapy (relative hazard [RH] radiotherapy group *v* chemotherapy group: premenopausal women, RH 0.67, 95% CI 0.44 to 1.0; P <0.05; postmenopausal women, RH 0.43, 95% CI 0.30 to 0.63; P <0.001). Among premenopausal women, it found that distant metastases occurred less frequently in the chemotherapy group compared with the radiotherapy group (HR 1.68, 95% CI 1.3 to 2.2; P <0.001) resulting in an improved recurrence-free survival (P = 0.04). It found that overall survival in premenopausal women was better with chemotherapy but the difference between groups was not statistically significant (cumulative survival at 15 years: 50% in chemotherapy group *v* 44% in radiotherapy group; reported as not significant; P value not reported). Among postmenopausal women, it reported that there was no significant difference between the treatment groups in terms of recurrence-free (P = 0.28) or overall survival (P = 0.38). [90] However, the period of enrolment of the RCTs was long (between 1976 to 1990), inclusion criteria and randomisation were modified over the course of the studies, and the chemotherapy regimen used was modified on a number of occasions. [90] Also, the report noted that the trials had to some extent a mainly historical interest, since some of the regimens tested were no longer relevant to routine medical practice. [90]

Radiotherapy after mastectomy versus mastectomy plus tamoxifen:
We found one phase 3 RCT (724 post-menopausal women treated between 1978 and 1985, 20-year follow-up), which compared three arms: mastectomy plus tamoxifen 30 mg daily for 12 months

versus mastectomy plus postoperative radiotherapy to the chest wall, axilla, supraclavicular fossa, and internal mammary chain versus mastectomy, postoperative radiotherapy to the chest wall, axilla, supraclavicular fossa, and internal mammary chain plus tamoxifen 30 mg daily for 12 months. [91] A total of 131 participants were oestrogen-receptor negative and progesterone-receptor negative, a group now identified as unlikely to benefit from endocrine therapy. Cumulative local recurrence risk was 6.7% (95% CI 3.8% to 10.4%) for radiotherapy alone, 5.3% (95% CI 2.8% to 8.9%) for radiotherapy plus tamoxifen and 18.5% (95% CI 13.8% to 23.8%) for tamoxifen alone.The benefit in local control with postoperative radiotherapy was seen in the lymph-node-positive group only. Overall mortality at 20 years was 71% in the radiotherapy arm, 68% in the radiotherapy plus tamoxifen arm, and 62% in the tamoxifen arm. The difference between radiotherapy plus tamoxifen and tamoxifen alone was not significant except in the receptor-positive subgroup in favour of non-irradiated patients (P = 0.047). The cumulative incidence of systemic disease at 20 years was lower in the radiotherapy plus tamoxifen arm than in the radiotherapy arm (40% with radiotherapy plus tamoxifen *v* 50% with radiotherapy; P = 0.047). [91]

Harms: See harms of radiotherapy after breast-conserving surgery, p 20 .

Radiotherapy after mastectomy versus mastectomy:
Three RCTs included in the review of total nodal irradiation after mastectomy in high-risk disease found no significant increase in cardiac mortality. [74] [75] [76] [92] One systematic review evaluated toxicity. [85] Acute toxicity reported in people receiving radiotherapy included severe skin toxicity in 2.7% to 5% of women, myelosuppression attributed to radiotherapy in 2% to 32%, and radiation pneumonitis in 1% to 23%. Late toxicity included arm oedema (0% to 25% in non-irradiated women and 10% to 54% in irradiated women). No increased rates of brachial plexopathy, cardiac disease, or second malignancies were found in irradiated compared with non-irradiated women.

Radiotherapy after mastectomy versus mastectomy plus tamoxifen:
The RCT found similar rates of second malignancy, contralateral breast cancer, and endometrial cancer in all of the treatment arms; frequency ranged from 4% to 6% (no further data reported). [91] More women who underwent radiotherapy developed lymphoedema (73/435 [7%] with radiotherapy *v* 9/233 [4%] with mastectomy; significance not assessed). Radiation pneumonitis was reported in 3.9% and brachial plexopathy in 0.5% of people receiving radiotherapy (no further data reported).

Comment: Two systematic reviews have attempted to address the issues about variable quality by confining analysis to very specific groups of patients. [85] [86] The reviews suggest that there are locoregional control, overall survival, and cancer-specific survival advantages for post-mastectomy radiotherapy. The patients that benefit most from radiotherapy in terms of local recurrence prevention following mastectomy are those patients with greater risk of recurrence. This includes node-positive disease and larger tumours (stage 3 patients were included in some of the trials but none had sufficient power to analyse this separately). There is a lack of high-quality evidence to support post-mastectomy radiotherapy for node-negative patients with tumours <5 cm outside of a clinical trial. However, in terms of patient selection when the goal is improving survival, the situation differs from that described for locoregional control. Patients with node-positive disease who have a low likelihood of distant micro-metastases, such as oestrogen-receptor positive, progesterone-receptor positive, or HER2 negative may be the patients that derive the overall survival benefit of locoregional therapy, although this has only been noted in a subset of one RCT and has not, as yet, been validated by other studies.

Clinical guide: Current expert opinion and evidence-based treatment guidelines suggest that high-risk patients for locoregional recurrence should be recommended for radiotherapy. These patients would include those with lymph node positivity (particularly when >3 axillary nodes are involved with tumour), positive surgical margins post mastectomy, and larger tumour size (especially >5 cm). Post-mastectomy radiotherapy should also be considered when patients have fewer nodes involved, as there may be a survival benefit from receiving postoperative radiotherapy.

OPTION PRIMARY CHEMOTHERAPY

Treatment success
Compared with adjuvant chemotherapy Primary chemotherapy seems to more effective at reducing mastectomy rates but not at reducing locoregional recurrences at 4 years (moderate-quality evidence).

Mortality
Compared with adjuvant chemotherapy Primary chemotherapy and adjuvant chemotherapy seem to be equally effective at improving overall survival (moderate-quality evidence).

Adverse effects

Adverse effects of chemotherapy include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Survival:

We found no systematic review but found 5 RCTs, which compared primary chemotherapy versus adjuvant chemotherapy. [93] [94] [95] [96] [97] The first RCT (272 women with tumours 3 cm or more in whom mastectomy was indicated) compared primary EVMTV (epirubicin, vincristine, mitomycin C, thiotepa, vindesine) chemotherapy versus mastectomy followed by the EVMTV regimen. [93] At an initial median follow-up of 34 months, a significant survival difference was reported in favour of primary chemotherapy (results presented graphically; log rank P = 0.04). [93] However, the final analysis at 124 months showed that the survival improvement was no longer significant, with survival of about 55% in both groups. [98]

The second RCT (414 women) compared 4 cycles of FAC (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) as primary or adjuvant chemotherapy. [94] At 54 months' follow-up, the primary chemotherapy group had a better overall survival (86% with primary *v* 68% with adjuvant; P = 0.039); however, a subsequent analysis at 105 months did not show a long-term survival benefit. [99]

The third RCT (309 women) compared 4 cycles of primary MM (mitoxantrone [mitozantrone], methotrexate) chemotherapy followed by surgery and 4 further cycles of MM versus surgery followed by 8 cycles of adjuvant MM. [95] At 48 months' follow-up, there was no difference in survival between the primary and adjuvant groups (84% with primary *v* 82% with adjuvant; reported as not significant).

The fourth, and largest, RCT (National Surgical Adjuvant Breast and Bowel Project [NSABP] 18), in which 1523 women were randomised to 4 cycles of AC (doxorubicin [adriamycin], cyclophosphamide) as primary or adjuvant chemotherapy, found identical survival rates (67%) in the two groups at 60 months. [96]

The fifth RCT (698 women) compared 4 cycles of fluorouracil, epirubicin, and cyclophosphamide, as primary or adjuvant chemotherapy. [97] It found no significant difference between primary and adjuvant chemotherapy in overall survival, progression-free survival, or locoregional recurrence at 4 years (overall survival: 82% with primary *v* 84% with adjuvant; HR 1.16, 95% CI 0.83 to 1.63; progression-free survival: 65% with primary *v* 70% with adjuvant; HR 1.15, 95% CI 0.89 to 1.48; locoregional recurrence at 4 years: 21.5% with primary *v* 17.8% with adjuvant; HR 1.13, 95% CI 0.70 to 1.81).

Mastectomy rates:

We found no systematic review but found three RCTs, which compared mastectomy rates with primary chemotherapy versus adjuvant chemotherapy. [96] [100] [101] The first RCT (309 women receiving MM chemotherapy) found that primary chemotherapy significantly reduced the mastectomy rate compared with adjuvant chemotherapy (13% with primary *v* 28% with adjuvant; P <0.005). [100] The second RCT (1523 women receiving AC chemotherapy) found that breast conservation rates were lower in the adjuvant arm (60% with adjuvant *v* 67% with primary), although this was not significant. [96] The third RCT assessed 272 women at diagnosis in terms of the recommended surgical procedure, and two of three women who were initially advised to have mastectomy were able to have breast-conserving surgery after primary chemotherapy with FAC. [101]

Harms:

We found no evidence that primary chemotherapy has a negative impact on survival. None of the RCTs examining effects on mastectomy rates reported a significantly higher local recurrence rate with primary chemotherapy compared with adjuvant chemotherapy. [96] [100] [101] See harms of adjuvant combination chemotherapy, p 8 .

Comment:

We found no evidence to support the use of primary chemotherapy to improve the chances of survival for operable breast cancers outside the context of an RCT. With an increased number of conservative operations being performed after downstaging by primary chemotherapy for large primary tumours, there are theoretical concerns that this may result in an increased rate of local recurrence. However, primary chemotherapy can lead to a reduction in the requirement for mastectomy and, as such, an increase in breast-conserving surgery and sequential tissue biopsies can be obtained within the context of clinical trials. In the three RCTs of women with operable breast cancer receiving breast-conserving surgery, use of primary chemotherapy has not been associated with a significant increase in the rate of local recurrence. [96] [100] [101]

OPTION TOTAL NODAL RADIOTHERAPY

Treatment success

Radiotherapy after mastectomy compared with mastectomy alone Radiotherapy, including total irradiation, after mastectomy is effective at reducing the 5-year risk of isolated local recurrence in women with node-positive disease (moderate-quality evidence).

Mortality
Radiotherapy after mastectomy compared with mastectomy alone In women with node-positive disease, radiotherapy, including total nodal irradiation, is more effective than no radiotherapy after mastectomy plus axillary clearance at reducing the 15-year risk of breast cancer mortality, particularly in women with tumours >5 cm (moderate-quality evidence).

Note
The relative contributions that chest wall radiotherapy and nodal radiotherapy make to the outcomes reported above are unclear.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: We found one systematic review (search date not reported, 36 RCTs of post-mastectomy radiotherapy), which included 26 RCTs of total nodal irradiation to the internal mammary chain, supraclavicular fossa, and axilla. [67] It found that postoperative radiotherapy reduced locoregional recurrence in people with node-negative and node-positive disease. However, it found conflicting evidence on breast cancer mortality. See benefits of radiotherapy after mastectomy, p 25 . These results should be interpreted with caution because they include some RCTs that did not give total nodal irradiation. The benefits of treating any one particular nodal area has not been addressed adequately to date.

Harms: See harms of radiotherapy to the internal mammary chain, p 35 ; See harms of radiotherapy to the ipsilateral supraclavicular fossa, p 36 ; and See harms of axillary management, p 30 . Three RCTs included in the review found no increase in cardiac mortality because of radiotherapy. [74] [75] [76] [92]

Comment: **Clinical guide:** Total nodal radiotherapy may reduce local recurrence but with an uncertain effect on survival. The RCTs that showed a survival benefit for post-mastectomy radiotherapy usually used nodal irradiation to the internal mammary chain, supraclavicular fossa, and axilla as well as chest wall radiation. However, what the relative benefits and risks associated with each of these treatment areas are remains unanswered. In terms of risk, the greatest risk of recurrence in most high-risk patients is the chest wall, with smaller recurrence risks for supraclavicular fossa, internal mammary chain, and axilla. RCTs are currently being conducted to answer some of these questions.

OPTION AXILLARY MANAGEMENT

Treatment success
Axillary clearance compared with axillary radiotherapy Axillary clearance (level I, II, and III dissection) and axillary radiotherapy (regardless of axillary nodal status) seem to be equally effective at 10 years at reducing recurrence (moderate-quality evidence).

Total axillary dissection plus sentinel node biopsy compared with sentinel node biopsy alone (with axillary node dissection only if the sentinel contains metastases) We don't know whether total axillary dissection plus sentinel node biopsy is more effective at reducing breast cancer events, postoperative pain, arm swelling, seroma formation, and loss of sensation (low-quality evidence).

Mortality
Axillary clearance compared with axillary sampling Axillary clearance (level I, II, and III dissection) and 4-node axillary sampling (followed by axillary radiotherapy in women found to be node-positive) seem to be equally effective at improving survival (moderate-quality evidence).

Axillary clearance compared with axillary radiotherapy Axillary clearance (level I, II, and III dissection) and axillary radiotherapy (regardless of axillary nodal status) seem to be equally effective at 10 years at reducing the annual risk of mortality (moderate-quality evidence).

Total axillary dissection plus sentinel node biopsy compared with sentinel node biopsy alone (with axillary node dissection only if the sentinel contains metastases) We don't know whether total axillary dissection plus sentinel node biopsy is more effective at improving overall survival in women undergoing quadrantectomy (low-quality evidence).

Note
There is consensus that axillary clearance reduces regional recurrence compared with no axillary management. We found no direct information about the effects of radiotherapy in addition to axillary clearance (level I and II or level I, II, or III dissection) in regional disease control.

Adverse effects
Axillary surgery has been associated with seroma formation, arm swelling, damage to the intercostobrachial nerve, and shoulder stiffness.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Axillary clearance versus axillary sampling:
We found no systematic review but found one RCT (466 women) in women having breast-conserving surgery. [102] The RCT compared complete axillary clearance (level I, II, and III dissection) versus 4-node axillary sampling followed by axillary radiotherapy if the nodes were involved. It found that axillary sampling was associated with improved survival compared with axillary clearance, but the difference was not significant (overall survival figures presented graphically; P = 0.2; estimated 5-year survival: 89% with axillary sampling *v* 82% with axillary clearance). Rates of node positivity were similar in both groups.

Axillary clearance versus axillary radiotherapy:
We found one systematic review (search date not reported, 8 RCTs, 4370 women) comparing axillary clearance (level I, II, and III dissection) versus axillary radiotherapy (regardless of axillary nodal status). [49] It found no significant difference in annual risk of mortality over 10 years or in recurrence (mortality: OR 0.96, CI presented graphically; P = 0.3; recurrence: OR 1.01, CI not reported). Radiotherapy was associated with fewer isolated local recurrences, but this difference did not reach significance (OR 0.85, CI not reported; P = 0.06). [49]

Axillary clearance alone versus axillary clearance plus radiotherapy:
We found no systematic review or RCTs assessing the effect of radiotherapy in addition to axillary clearance (level I and II, or level I, II, and III dissection) in regional control of disease.

Axillary dissection versus sentinel node biopsy:
See benefits of sentinel node biopsy, p 36 .

Harms:

Axillary clearance versus axillary sampling:
Adverse effects of axillary surgery include seroma formation, arm swelling, damage to the intercostobrachial nerve, and shoulder stiffness. We found one RCT, which compared the morbidity of different axillary procedures. [102] It compared complete axillary clearance (level I, II, and III dissection) versus 4-node axillary sampling, followed by radiotherapy if the nodes were involved. It found that the rate of arm swelling was higher after clearance than after sampling, whether or not women received postoperative radiotherapy (at 3 years, forearm girth was significantly greater with clearance than with sampling alone [P = 0.005] or sampling plus radiotherapy [P = 0.04]). After removal of axillary drains, 25% to 50% of women who had had a level I and II, or level I, II, and III axillary clearance developed seromas requiring aspiration. The RCT found that women who received axillary clearance or axillary sampling plus radiotherapy (not to the shoulder joint) had significantly reduced shoulder movement compared with women receiving axillary sampling alone at 6 months (clearance *v* sampling alone: P = 0.003; sampling plus radiotherapy *v* sampling alone: P = 0.004). However, by 3 years, the axillary clearance group had improved and was not significantly different from the sampling alone group (P = 0.1). [102]

Arm lymphoedema:
One Australian systematic review (search date 1996) of lymphoedema prevalence, risks, and management found that, although current information is of poor quality, the combination of axillary dissection (to or beyond level II) and axillary radiotherapy was associated with a risk of lymphoedema of 12% to 60%, with most studies suggesting that at least a third of women are affected. [103] Studies of axillary sampling followed by irradiation found lower rates of lymphoedema (6–32%), and for axillary sampling alone, the rates were lower still (0–21%). Studies of dissection beyond level I found rates of lymphoedema between 0% and 42%, with most studies reporting a rate of 20% to 30% 1 year after operation. [103] In women who receive axillary radiotherapy without axillary surgery, the overall lymphoedema rate is about 8%.

Comment:

Axillary staging:
Both clearance and sampling provide important prognostic information on which decisions on local and systemic treatment can be based. A decision on axillary management should be based on the risk of involvement of axillary nodes (which varies according to tumour size, grade, and the presence of vascular/lymphatic invasion) and potential treatment-related morbidity. Two retrospective cohort studies found that level I dissection accurately assessed axillary lymph node status, providing that at least 10 nodes were removed. [104] [105] One RCT found that a sample of 4 nodes provided sufficient information to categorise an axilla as histologically positive or negative. [106] Removal of nodes at level I and II, or removal of all nodes below the axillary vein (level I, II, and III), accurately stages the axilla. [104] [105]

Clinical guide: The probability of axillary lymph node metastasis should be assessed and a selective surgical approach to the axilla (clearance or sampling) employed balancing local disease control and prognostic information against morbidity.

OPTION DIFFERENT PRIMARY CHEMOTHERAPY REGIMENS VERSUS EACH OTHER

Treatment success

Standard compared with dose-intensified anthracycline-based regimens A standard-based regimen (cyclophosphamide, epirubicin, fluorouracil) and a dose-intensified regimen (epirubicin, cyclophosphamide, filgrastim) seem to be equally effective at increasing time to progression in women with locally advanced breast cancer (moderate-quality evidence).

FAC regimen (fluorouracil, doxorubicin [adriamycin], and cyclophosphamide) compared with single-agent paclitaxel We don't know whether FAC regimens are more effective at improving response rates (low-quality evidence).

MPEMi (methotrexate, cisplatin, etoposide, mitomycin C), MPEpiE (methotrexate, cisplatin, epirubicin, etoposide), and MPEpiV (methotrexate, cisplatin, epirubicin, vincristine) regimens compared with each other We don't know which regimen is more effective at improving response rates (low-quality evidence).

Sequencing of anthracycline-based chemotherapy and docetaxel Further treatment with docetaxel may be more effective than further treatment with CVAP (cyclophosphamide, doxorubicin [adriamycin], vincristine, prednisolone) at improving clinical response rates in women who have achieved complete or partial response to 4 cycles of CVAP (low-quality evidence). Primary treatment with docetaxel may be more effective than no primary treatment in women who have received 4 cycles of AC (doxorubicin [adriamycin], cyclophosphamide) at improving clinical complete response rates (low-quality evidence).

Intra-arterial compared with intravenous administration Although intra-arterial epirubicin may be more effective than intravenous epirubicin at improving response rates, this benefit does not lead to an improvement in survival in women with locally advanced breast cancer (low-quality evidence).

Mortality

Standard compared with dose-intensified anthracycline-based regimens A standard-based (cyclophosphamide, epirubicin, fluorouracil) and a dose-intensified anthracycline regimen (epirubicin, cyclophosphamide, filgrastim) seem to be equally effective at increasing time to death, or 5-year survival rates in women with locally advanced breast cancer (moderate-quality evidence).

FAC regimen (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) compared with single-agent paclitaxel We don't know whether FAC regimens are more effective at improving survival (low-quality evidence).

Note

We found no clinically important results from RCTs about the effects of navelbine-based regimens in women with breast cancer.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Standard versus dose-intensified anthracycline-based regimens:

We found no systematic review but found one RCT. [107] The RCT (448 women with locally advanced breast cancer) compared a CEF (cyclophosphamide, epirubicin, fluorouracil) regimen versus a dose-intensified ECFi (epirubicin, cyclophosphamide, filgrastim) regimen. It found no significant difference between the regimens in time to progression (recurrence or death) or 5-year survival (median time to progression: 34 months with CEF *v* 33.7 months with ECFi; P = 0.68; 5-year survival: 53% with CEF *v* 51% with ECFi; P = 0.94). Complete clinical response rates were similar with both regimens (31% with CEF *v* 27% with ECFi; P value and RR not reported).

FAC regimen versus paclitaxel:

We found no systematic review but found one RCT. [108] The RCT (174 women in the USA) compared conventional FAC (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) versus single-agent paclitaxel, and found similar response rates in both groups (79% with FAC *v* 80% with paclitaxel), with no significant difference in survival rates.

Comparison between MPEMi (methotrexate, cisplatin, etoposide, mitomycin C), MPEpiE (methotrexate, cisplatin, epirubicin, etoposide), and MPEpiV (methotrexate, cisplatin, epirubicin, vincristine) regimens:

We found no systematic review but found one RCT. [109] The RCT (101 women) compared three different primary chemotherapy regimens: MPEMi versus MPEpiE versus MPEpiV. It found that the response rate was 89% in all three groups.

Sequencing of anthracycline-based chemotherapy and docetaxel:
We found no systematic review but found two RCTs. [110] [111] The first RCT (104 women who had achieved complete or partial clinical response to 4 cycles of CVAP [cyclophosphamide, doxorubicin {adriamycin}, vincristine, prednisolone]) compared a further 4 cycles of CVAP versus 4 cycles of docetaxel. [110] It found that further treatment with docetaxel significantly improved clinical complete response rate compared with further CVAP (clinical complete response rate: 85% with docetaxel *v* 64% with CVAP; P = 0.03). [110] In the second RCT (2411 people), all women received 4 cycles of AC (doxorubicin [adriamycin], cyclophosphamide) and were then randomly allocated to three regimens: surgery alone, 4 cycles of docetaxel followed by surgery, or surgery followed by 4 cycles of docetaxel. [111] The preliminary results of this RCT found that, at the time of surgery, primary docetaxel improved clinical complete response rate compared with no primary docetaxel (65% with docetaxel *v* 40% with no docetaxel; P <0.001). The final results, which will also examine the effects of adjuvant docetaxel, are awaited.

Navelbine-based regimens:
We found no systematic review or fully published RCTs (see comment below).

Comparison between routes of administration:
We found no systematic review but found one RCT. The RCT (73 women with locally advanced breast cancer) compared routes of administration of primary chemotherapy. [112] It compared no primary treatment, primary intravenous epirubicin, or primary intra-arterial epirubicin. The RCT found that response rates were higher in women receiving intra-arterial epirubicin compared with intravenous epirubicin (68% with intra-arterial epirubicin *v* 36% with intravenous epirubicin; P <0.05); however, this was not associated with a survival benefit. [112]

Harms:

Standard versus dose-intensified anthracycline-based regimens:
In the RCT comparing a CEF versus a dose-intensified ECFi regimen, there were similar numbers of serious adverse events requiring admission to hospital in the groups (60 events with CEF *v* 68 events with ECFi; absolute numbers of women affected in each group and P value not reported). [107] The dose-intensified ECFi regimen increased nausea and vomiting, and induced more grade 3 and 4 anaemia, but there were fewer febrile neutropenic episodes with ECFi compared with CEF (AR for nausea: 12% with CEF *v* 22% with ECFi; vomiting: 11% with CEF *v* 19% with ECFi; anaemia: 16% with CEF *v* 51% with ECFi; febrile neutropenia: 14% with CEF *v* 8% with ECFi; P values not reported for any outcome).

FAC versus paclitaxel:
In the RCT comparing FAC versus paclitaxel, rates of septic neutropenia and use of granulocyte colony-stimulating factor were higher in women taking paclitaxel (neutropenia: 53% with paclitaxel *v* 21% with FAC; use of granulocyte colony-stimulating factor: 56% with paclitaxel *v* 25% with FAC). [108]

Comment:

More research is needed to determine the optimal regimen for primary treatment. We found little evidence in the literature comparing different combinations, but anthracycline-based combinations probably remain the treatment of choice, with dose intensification not proved to confer additional clinical benefit. [107] Ongoing RCTs are investigating the role of taxane sequencing after anthracycline-based treatment (National Surgical Adjuvant Breast and Bowel Project [NSABP] 27) and anthracycline in combination with fluorouracil infusion.

Navelbine-based regimens:
We found one RCT (published as an abstract, 147 women), which compared AC (doxorubicin [adriamycin], cyclophosphamide), NM (navelbine, mitoxantrone), and NE (navelbine, epirubicin). Response rates were 65% with AC, 73% with NM, and 86% with NE. The time to outcome was not reported. The trial is ongoing, although the NM arm has been stopped because of haematological toxicity. [113] Clinical trials are currently underway to address different regimens in the primary setting, including the use of taxane-platinum regimens, which may be associated with lower long-term toxicities, including leukemia and cardiac failure when compared with anthracyclines.

Comparison of different methods of sequencing chemotherapy and radiotherapy:
We found one systematic review (search date 2005, 3 RCTs) comparing two different methods of sequencing chemotherapy and radiotherapy. [114] There were no significant differences between the various methods of sequencing adjuvant therapy for survival, distant metastases, or local recurrence, based on 853 randomised patients in two trials. Different methods of sequencing chemotherapy and radiotherapy did not seem to have a major effect on survival or recurrence for women with breast cancer if radiotherapy was commenced within 7 months after surgery. The systematic review reported adverse effects from one RCT (647 women). Haematological toxicity (OR 1.43, CI 1.01 to 2.03) and oesophageal toxicity (OR 1.44, CI 1.03 to 2.02) were significantly increased with concurrent therapy, and nausea and vomiting were significantly decreased (OR

0.70, CI 0.50 to 0.98). Other measures of toxicity did not differ between the two types of sequencing. On the basis of one trial (244 women), radiotherapy before chemotherapy was associated with a significantly increased risk of neutropenic sepsis (OR 2.96, 95% CI 1.26 to 6.98) compared with chemotherapy before radiotherapy, but other measures of toxicity were not significantly different. [114]

OPTION LESS THAN WHOLE-BREAST RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY

Treatment success
Less than whole-breast radiotherapy compared with whole-breast radiotherapy We don't know whether less than whole-breast radiotherapy after breast-conserving surgery is more effective at reducing recurrences at 8 years (low-quality evidence).

Mortality
Less than whole-breast radiotherapy compared with whole-breast radiotherapy We don't know whether tumour-bed radiotherapy after breast-conserving surgery is more effective at 8 years at improving survival (low-quality evidence).

Adverse effects
We don't know whether less than whole-breast radiotherapy reduces adverse effects.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

We found two systematic reviews (search date 2002 [115] and search date 2006 [116]), one further report of an RCT identified by the second review, [117] and two additional RCTs [118] [119] assessing the effects of less than whole-breast radiotherapy after breast-conserving surgery.

The first systematic review (search date 2002) compared intra-operative radiotherapy versus standard postoperative radiotherapy in women receiving breast-conserving surgery, and found no fully published RCTs (see comment). [115] The second review (search date 2004–2006) compared accelerated partial-breast radiotherapy with standard radiotherapy following breast-conserving surgery. [116] One RCT was identified with short follow-up of 50 months. [116] The review found that recurrence rates were similar between the two treatments (absolute numbers and significance not reported). The reviewers recommended that further evidence be gathered before accelerated partial-breast radiotherapy can be recommended for routine use and that 8 years' follow-up was required to demonstrate equivalence. [116]

One follow-up report provided long-term data for the RCT included in the second review (258 people with T1 N0–1mi, grade 1–2, non-lobular breast cancer without the presence of extensive intra-lobular component; median follow-up 66 months). [117] The RCT compared partial-breast irradiation using either electron beams or brachytherapy implants versus standard whole-breast irradiation. Long-term follow-up found no significant difference in the 5-year actuarial rate of local recurrence between partial-breast radiotherapy and whole-breast radiotherapy (5% with partial-breast radiotherapy *v* 3% with whole-breast radiotherapy; P = 0.50; absolute numbers not reported). Similarly, there was no significant difference between groups in overall survival at 5 years, cancer-specific survival at 5 years, and disease-free survival (overall survival at 5 years: 95% with partial-breast radiotherapy *v* 92% with whole-breast radiotherapy; cancer-specific survival at 5 years: 98% with partial-breast radiotherapy *v* 96% with whole-breast radiotherapy; disease-free survival: 89% with partial-breast radiotherapy *v* 90% with whole-breast radiotherapy; absolute numbers and significance not reported). [117]

The first additional RCT found that localised-field radiotherapy significantly increased breast recurrence compared with wide-field radiotherapy at 8 years (713 women; 69/353 [20%] with localised-field radiotherapy *v* 35/355 [10%] with wide-field radiotherapy; P = 0.00008). [118] [119] It found no significant difference in disease-specific survival between localised-field radiotherapy and wide-field radiotherapy at 8 years (73% with localised-field radiotherapy *v* 72% with wide-field radiotherapy; P = 0.91). [118] [119]

The second additional RCT found no significant difference in local recurrence, distant recurrence, or survival between tumour-bed radiotherapy and whole-breast radiotherapy at a median follow-up of 8 years (174 women; local recurrence: 10/84 [12%] with tumour-bed radiotherapy *v* 4/90 [4%] with whole-breast radiotherapy; P = 0.07; distant recurrence: 19/84 [23%] with tumour-bed radiotherapy *v* 24/90 [27%] with radiotherapy; P = 0.70; mortality: 25/84 [30%] with tumour-bed radiotherapy *v* 24/90 [27%] with whole-breast radiotherapy; P = 0.75). [120] The RCT aimed to recruit 400 women, but it closed early because of problems with recruitment, and therefore may have been underpowered to detect a clinically important difference. [120]

Harms: The first RCT found that localised-field radiotherapy increased marked fibrosis and marked telangiectasia compared with wide-field radiotherapy (fibrosis: 51/353 [15%] with localised-field radiotherapy *v* 18/355 [5%] with wide-field radiotherapy; telangiectasia: 116/353 [33%] with localised-field radiotherapy v 43/355 [12%] with wide-field radiotherapy; significance assessment not performed). [118] [119] The differences may be related to radiation fractionation, rather than the target field area. The systematic reviews and the second and third RCTs gave no information on adverse effects. [115] [116] [120] [117]

Comment: The first review found one RCT, which was published in abstract form only, making it difficult to assess study quality. [115] The abstract reported similar levels of "good to excellent" cosmetic result with intra-operative radiotherapy plus postoperative radiotherapy and postoperative therapy plus external beam boost radiotherapy. Local cancer recurrence, disease-free survival, and overall survival results were not reported in the abstract. The RCT has been criticised as having had poor selection criteria (for example, lobular breast cancer cases were included). [119] The follow-up report of the RCT identified by the second review suggests no significant difference in breast cancer outcome in women receiving partial breast irradiation and superior cosmetic outcome. Follow-up for this study is still short given the overall good prognostic group of women being studied. [117]

Less than whole-breast radiotherapy may reduce toxicity because less tissue in the breast, chest wall, and thorax is irradiated. It may also be possible to take advantage of the radiobiological effects of irradiating a smaller volume in order to deliver the treatment in a shorter period of time. If an intra-operative technique is used, it may be possible to place radiotherapy dose more accurately within the excision area. [121] There are several techniques under consideration for less than whole-breast radiotherapy: intra-operative brachytherapy; delayed brachytherapy, intra-operative external beam techniques (electrons, low energy x-rays), and delayed external beam techniques. We found only two fully published RCTs, [118] [119] [120] but there are several international trials of different technologies underway. Each technique of less than whole-breast radiotherapy will be associated with its own adverse effects. Invasive intra-operative or implantation techniques may require anaesthesia and expose the person to wound infections. Radiotherapy effects on skin, subcutaneous fat, muscle, and ribs will depend on technique, dose, and fractionation. Localisation of a limited volume of irradiation may also be a problem, and various radiological, clinical, and ultrasonographic techniques are advocated to overcome this problem. [121]

Clinical guide: Studies are currently attempting to address the question as to whether partial-breast irradiation may be sufficient treatment for some favourable subgroups of breast cancer. Until those studies are complete, and the follow-up data sufficiently mature, it is not possible to recommend partial breast irradiation as an appropriate treatment for breast cancer outside of a properly conducted trial.

OPTION RADIOTHERAPY TO THE INTERNAL MAMMARY CHAIN

Relapse
Compared with no internal mammary chain irradiation We don't know whether radiotherapy to the internal mammary chain is more effective at reducing relapses in women treated with breast-conserving surgery and radiotherapy (moderate-quality evidence).

Mortality
Compared with no internal mammary chain irradiation We don't know whether radiotherapy to the internal mammary chain is more effective at improving survival in women treated with breast-conserving surgery and radiotherapy (moderate-quality evidence).

Note
Radiotherapy to the internal mammary chain may increase radiation-induced cardiac morbidity.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: We found no systematic review but found one RCT. The RCT (270 women treated with breast-conserving surgery and radiotherapy) compared internal mammary chain irradiation versus no internal mammary chain irradiation. [122] At a median follow-up of 2.7 years, there was no significant difference in relapse or survival (numbers not reported).

Harms: See harms of radiotherapy after breast-conserving surgery, p 20 . Radiotherapy to the internal mammary chain is more likely to affect the heart compared with other types of radiotherapy. [123]

Comment: The risk of internal mammary chain node involvement is related to the location and size of the primary tumour and, most importantly, histopathological axillary nodal status. Up to 30% of women with axillary involvement will also exhibit internal mammary chain nodal metastases. Central or

medial breast cancers are more likely to metastasise to the internal mammary chain, as are larger tumours and tumours that have axillary node involvement. [124] [125] The risk of internal mammary chain recurrence is low, and after modified radical mastectomy alone is 2%. [126] Modern radiotherapy planning and delivery should involve an assessment of the position and depth of the internal mammary chain nodes to be treated (using computerised tomography or ultrasound), and computer-assisted placement, arrangement, and determination of dose distribution; these technologies were unavailable at the time of most RCTs included in the reviews. [49] [87] [127] Indirect evidence from RCTs suggests improved survival from nodal irradiation (including radiation to the internal mammary chain) after modified radical mastectomy combined with systemic treatment. [74] [75] [92]

Clinical guide: Internal mammary node chain irradiation remains of uncertain benefit and should be the subject of RCTs.

OPTION RADIOTHERAPY TO THE IPSILATERAL SUPRACLAVICULAR FOSSA

Treatment success
Compared with no radiotherapy We don't know whether radiotherapy to the chest wall and lymph nodes is more effective at reducing recurrence in the supraclavicular fossa at 123 months in postmenopausal women who have received tamoxifen after mastectomy and are at high risk of local recurrence (moderate-quality evidence).

Note
We found no direct information about radiotherapy to the ipsilateral supraclavicular fossa in the treatment of women with breast cancer. Morbidity associated with irradiation of the supraclavicular fossa is rare and, where it occurs, is mild and temporary.

Benefits: We found no systematic review or RCTs on radiotherapy to the ipsilateral supraclavicular fossa. One systematic review (search date not reported) found that postoperative radiotherapy to the chest wall and lymph nodes was associated with reduced locoregional recurrence: see benefits of radiotherapy after breast-conserving surgery, p 20 ; radiotherapy after mastectomy, p 25 ; and radiotherapy to the internal mammary chain, p 35 . [67] RCTs indicate reduced recurrence in the supraclavicular fossa following radiotherapy to the peripheral lymphatics. One RCT in postmenopausal women at high risk of local recurrence who received tamoxifen after mastectomy found that radiotherapy (chest wall and total nodal irradiation) was associated with lower recurrence in the supraclavicular fossa at a median follow-up of 123 months (9/689 [1%] with radiotherapy *v* 37/686 [5%] with no radiotherapy; CI not reported). [92]

Harms: The acute morbidity of irradiation to the supraclavicular fossa is mild and includes temporary upper oesophagitis in nearly all women. The risk of radiation pneumonitis increases with the volume of lung irradiated. Treatment irradiates the lung apex in addition to any lung included in the breast or chest wall fields. Possible late morbidity includes brachial plexopathy, but this should not exceed 1.8% if attention is paid to limiting the total dose to 50 Gy, limiting the dose per fraction to 2 Gy or less, and avoiding field junction overlaps. [73] [128] Late apical lung fibrosis is common and usually of no clinical importance. Demyelination of the cervical cord is an extremely rare complication of supraclavicular fossa radiotherapy.

Comment: **Clinical guide:** There is insufficient evidence to give a definite recommendation for or against supraclavicular fossa node irradiation. In the absence of good-quality randomised trial data it might be considered reasonable to include the supraclavicular fossa for patients that are deemed at high risk of involvement. This would be in the group with three or more nodes involved in their axillary surgery.

OPTION SENTINEL NODE BIOPSY

Treatment success
Sentinel node biopsy plus total axillary dissection compared with sentinel node biopsy alone (with axillary node dissection only if the sentinel contains metastases) We don't know whether sentinel node biopsy is more effective at reducing breast cancer events. Sentinel lymph node biopsy may be more effective than axillary dissection plus sentinel node biopsy at reducing postoperative pain, arm swelling, seroma formation, and loss of sensation (low-quality evidence).

Mortality
Sentinel node biopsy plus total axillary dissection compared with sentinel node biopsy alone (with axillary node dissection only if the sentinel contains metastases) We don't know whether sentinel node biopsy is more effective at improving overall survival in women undergoing quadrantectomy (low-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Sentinel node biopsy versus axillary procedures (sampling or clearance):
We found three RCTs, which compared sentinel node biopsy plus total axillary dissection versus sentinel node biopsy alone (with axillary node dissection only if the sentinel node contained metastases or as a comparator trial). [129] [130] [131] In the first RCT, both groups received radiotherapy after surgery for 8 weeks. It found that sentinel node biopsy improved postoperative pain and arm mobility compared with axillary dissection and non-significantly reduced breast cancer events (516 women, aged 45–70 years, primary tumour 2 cm or less, undergoing quadrantectomy; no pain at 24 months: 92/100 [92%] with sentinel node biopsy *v* 61/100 [61%] with axillary dissection; P value not reported; 80–100% arm mobility: 100/100 [100%] with sentinel node biopsy *v* 79/100 [79%] with axillary dissection; P value not reported; breast cancer events: 13/259 [5%] with sentinel node biopsy *v* 21/257 [8%] with axillary dissection; P = 0.13; see comment below). [129] It found no significant difference in overall survival between treatments (P = 0.15). [129]

The second RCT (298 people with early breast cancer) found that sentinel node biopsy significantly reduced postoperative arm swelling and loss of sensation compared with axillary dissection (OR for subjective arm swelling 0.30, 95% CI 0.18 to 0.68; P = 0.004; absolute numbers not reported; AR of no loss of sensation: 48/143 [34%] with sentinel node biopsy *v* 25/155 [16%] with axillary dissection; OR 0.36, 95% CI 0.20 to 0.66). Sentinel node biopsy did not significantly reduce seroma formation overall, but did significantly reduce seroma formation in node-negative women, who did not need subsequent axillary dissection (overall risk of seroma formation: 20/143 [14%] with sentinel node biopsy *v* 33/155 [21%] with axillary dissection; OR 0.60, 95% CI 0.33 to 1.11; risk of seroma formation in node-negative women, 209 women: 10/94 [11%] with sentinel node biopsy *v* 28/115 [24%] with axillary dissection; OR 0.37, 95% CI 0.16 to 0.82). It found a trend towards reduced impairment of shoulder mobility and psychological morbidity (Beck Depression Inventory, Global Severity Index of the Brief Symptom Inventory, State-Trait Anxiety Inventory, Mental Adjustment to Cancer Scale) with sentinel node biopsy soon after the operation, but the differences were not consistently significant over different measures, and differences between groups reduced with time. [130]

The third RCT reported only surgical complications (see harms).

Harms:

One prospective cohort study found that the blue dye used in sentinel lymph node mapping caused some allergic reaction (31/1728 [2%]). The study found a trend towards fewer allergic reactions with smaller volumes of blue dye, although this was not significant. [132]

Sentinel node biopsy versus axillary procedures:
Two of the RCTs did not report on harms specific to sentinel node biopsy. [129] [130] The third RCT (891 women with invasive breast cancer) found that sentinel node biopsy significantly reduced adverse surgical effects compared with axillary dissection (103/411 [25%] with sentinel lymph node biopsy alone *v* 278/399 [70%] with axillary dissection; P = 0.001). [131] Compared with sentinel lymph node biopsy, axillary dissection was also associated with significantly more wound infections, seromas, and paraesthesia at 12 months (wound infections: 11/371 [3%] with sentinel lymph node biopsy alone *v* 31/373 [8%] with axillary dissection; P = 0.016; seromas: 21/371 [6%] with sentinel lymph node biopsy alone *v* 53/373 [14%] with axillary dissection; P = 0.0001; paraesthesia: 24/268 [9%] with sentinel lymph node biopsy alone *v* 113/287 [39%] with axillary dissection; P <0.0001). There was no significant difference in objective lymphoedema at 12 months (12/226 [6%] with sentinel lymph node biopsy alone *v* 26/242 [11%] with axillary dissection; P = 0.08). [131]

Comment:

We have not included RCTs comparing specific techniques of sentinel node biopsy versus each other. An evidence-based guideline from the American Society of Clinical Oncology recommends sentinel lymph node biopsy as an appropriate alternative to axillary dissection for women with early-stage breast cancer and clinically negative axillary nodes. [133] The guidelines also point out that the clinical significance of isolated cancer cells detected by detailed pathological examination of sentinel nodes is unknown. We found one RCT (5611 women within the NSABP B-32 trial), which has to date only reported on the secondary endpoint of technical success and accuracy. [134] It reported 97.1% accuracy, 95% CI 96.4% to 97.7% (2544 /2619), with a false-negative rate of 9.8%, 95% CI 7.8% to 12.2% (75/766).

Assessment of performance of sentinel node biopsy test:
We found one systematic review (search date not reported, 69 studies, 8059 people), which included studies assessing the diagnostic performance of sentinel node biopsy. [135] It found that 96% of people had successful lymph node mapping (range 41% to 100%) and 42% of people had lymph node involvement (range 17% to 74%). The mean false-negative rate was 8.4% (range 0% to 29%), with a significantly higher false-negative rate in smaller studies (P <0.01) and studies with fewer successfully mapped nodes (P = 0.009). [135]

Sentinel node biopsy versus axillary procedures (sampling or clearance):
In the first RCT, which compared sentinel node biopsy versus sentinel node biopsy plus axillary dissection, 36% of women in the sentinel node biopsy group also received axillary dissection because of positive sentinel node status. These women were included in the analysis for the sentinel node group. [129] We found 4 preliminary publications of three RCTs comparing sentinel node biopsy versus axillary procedures. [136] [137] [138] [139] The first RCT (abstract only, 5611 women with node-negative breast cancer) compared sentinel node resection plus immediate axillary dissection versus sentinel node resection without axillary dissection. Preliminary technical results suggest similar sentinel node identification between treatment groups. [136] The second RCT (Axillary Lymphatic Mapping Against Nodal Axillary Clearance [ALMANAC] study, preliminary results only, women with clinically node-negative invasive breast cancer) compared sentinel node biopsy versus conventional axillary treatment. [137] [138] The results of the randomisation phase have not been fully published, but preliminary results suggest that sentinel node biopsy significantly reduces lymphoedema (circumferential arm measurements) and improves sensory deficit versus standard axillary treatment (clearance or radiotherapy) at 18 months after treatment (P <0.0001 for both outcomes). [137] The RCT found no significant difference between treatments in shoulder flexion and abduction, and internal and external rotation of the shoulder. [137] Results of the validation phase of this RCT suggest that indiscriminate removal of axillary nodes may worsen the morbidity of sentinel node biopsy. [137] The third RCT, the Sentinel Node biopsy or Axillary Clearance [SNAC] trial demonstrated significantly lower ratings for arm swelling (P <0.001), arm symptoms (P <0.001) and dysfunction (P = 0.02) in the sentinel node group with an increase in arm volume of 2.8% in the sentinel lymph node biopsy group and 4.2% in the axillary clearance group. [139]

Clinical guide: Axillary sentinel lymph node biopsy or axillary node sampling should be considered a preferential approach to managing the axilla in clinically axillary node-negative breast cancer.

OPTION HIGH-DOSE CHEMOTHERAPY PLUS AUTOLOGOUS STEM CELL TRANSPLANTATION

Treatment success
Compared with conventional chemotherapy High-dose chemotherapy plus autologous stem cell transplantation seems no more effective than conventional chemotherapy at increasing event-free survival at up to 6 years' follow-up (moderate-quality evidence).

Mortality
Compared with conventional chemotherapy High-dose chemotherapy plus autologous stem cell transplantation seems no more effective than conventional chemotherapy at prolonging 3-year or 5-year overall survival rates in women with early, poor prognosis breast cancer, multiple positive axillary lymph nodes, and no distant metastasis (moderate-quality evidence).

Adverse effects
Compared with conventional chemotherapy High-dose chemotherapy plus autologous stem cell transplantation is more likely to increase treatment-related deaths compared with conventional chemotherapy (high-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

We found one systematic review (search date 2004) [140] and two subsequent RCTs. [141] [142] The review (13 RCTs, 5064 women with early, poor prognosis breast cancer, multiple positive axillary lymph nodes, and no distant metastasis) compared high-dose chemotherapy plus bone marrow or peripheral blood stem cell autograft versus conventional chemotherapy (see comment below). [140] It found no significant difference between regimens in overall survival at 3, 4, or 5 years (3 years: 5 RCTs, 2465 women, RR 1.01, 95% CI 0.97 to 1.05; 4 years: 3 RCTs, 743 women, RR 1.08, 95% CI 0.98 to 1.19; 5 years: 6 RCTs, 3015 women, RR 1.01, 95% CI 0.96 to 1.05). It found that high-dose chemotherapy significantly increased event-free survival compared with conventional chemotherapy at 3 years but not at 5 years (3 years: 5 RCTs, 2465 women, RR 1.12, 95% CI 1.06 to 1.19; 5 years: 6 RCTs, 3017 women, RR 1.05, 95% CI 0.99 to 1.11). [140]

The first subsequent RCT (307 women with primary breast cancer and >10 axillary lymph nodes, median follow-up 6.1 years) compared high-dose chemotherapy versus standard-dose chemotherapy. [141] All women received 4 cycles of epirubicin plus cyclophosphamide, and were then randomised to either high-dose chemotherapy (cyclophosphamide plus thiotepa plus mitoxantrone for 4 days followed by stem cell transplantation) or standard-dose chemotherapy (3 cycles of cyclophosphamide plus methotrexate plus fluorouracil). The RCT found no significant difference between high-dose chemotherapy and standard-dose chemotherapy in event-free survival or overall survival (event-free survival: 75 events with high-dose chemotherapy *v* 91 events with standard-dose chemotherapy; HR 0.80, 95% CI 0.59 to 1.08; mortality: 57/150 [38%] with high-dose chemotherapy *v* 66/152 [43%] with standard-dose chemotherapy; HR 0.84, 95% CI 0.59 to 1.20).

The second subsequent RCT (536 women with operable breast cancer involving 4 or more axillary lymph nodes and recent mastectomy or breast-conserving surgery) compared high-dose chemotherapy (anthracycline-based chemotherapy followed by high-dose regimen with autologous haematopoietic progenitor cell support) versus intensive dose-dense chemotherapy (including both an anthracycline and a taxane). [142] It found no significant difference between the two arms in disease-free survival or overall survival at a median follow-up of 70 months (disease-free survival: 70/265 [26%] with high-dose chemotherapy *v* 58/271 [21%] with intensive dose-dense chemotherapy; P = 0.35; overall survival: 46/265 [17%] with high-dose chemotherapy *v* 36/271 [13%] with intensive dose-dense chemotherapy; P = 0.40). [142]

Harms: The systematic review found that high-dose chemotherapy significantly increased treatment-related mortality compared with conventional chemotherapy (treatment-related deaths: 13 RCTs; 65/2535 [2.6%] with high-dose chemotherapy *v* 4/2529 [0.2%] with conventional chemotherapy; RR 8.58, 95% CI 4.13 to 17.80). [140] The first subsequent RCT did not report adverse effects. [141] The second subsequent RCT reported that grade 4 haematological toxicity was more common with high-dose chemotherapy (62–92% with high-dose chemotherapy *v* 59% with intensive dose-dense chemotherapy; absolute numbers and significance not reported). [142] Four deaths occurred as a result of treatment-related adverse effects. [142]

Comment: Most of the RCTs included in the systematic review have only been published as abstracts or have reported only preliminary results, and reporting of follow-up is incomplete. [140] Further results are awaited. Overall survival rates quoted in the review were predominantly based on results to date and showed no differences in overall survival. The systematic review concluded that there was insufficient evidence to support the routine use of high-dose chemotherapy with autograft for women with early poor prognosis breast cancer. Transplantation may be associated with an inferior outcome owing to the treatment-related toxicity.

QUESTION What are the effects of interventions in locally advanced breast cancer (stage 3B)?

OPTION POSTOPERATIVE RADIOTHERAPY IN WOMEN ALSO RECEIVING POSTOPERATIVE SYSTEMIC TREATMENT

Treatment success
Compared with no radiotherapy Postoperative radiotherapy may be more effective at reducing recurrences and improving disease-free survival at 10 years in women who also receive chemotherapy or hormone therapy following mastectomy (very low-quality evidence).

Mortality
Compared with no radiotherapy Postoperative radiotherapy may be more effective at improving overall survival at 10 years in women who also receive chemotherapy or hormone therapy following mastectomy (very low-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: The data discussed earlier on post-mastectomy radiotherapy also applies to the stage 3B group of patients who have operable disease and undergo mastectomy. Some of the studies incorporated into the reviews on post-mastectomy radiotherapy included stage 3B patients, although discrete analyses of outcomes for stage 3B patients are not provided. Stage 3B patients usually made up the minority of patients on these trials. We found no systematic review or RCTs of postoperative radiotherapy and systemic therapy solely in stage 3B. We found one systematic review (search date 1999, 18 RCTs, 6367 people) comparing post-mastectomy radiotherapy studies plus systemic therapy in women with stage 2 or stage 3 disease. [85] For full details, see radiotherapy after mastectomy in primary operable breast cancer, p 25 .

We found 4 additional RCTs where people with stage 3B disease were a subgroup of the entire study population. [75] [92] [143] [144] The first RCT (184 women, all with T3–4 tumours, receiving pre-mastectomy and post-mastectomy chemoendocrine treatment) compared post-mastectomy radiotherapy to the chest wall and regional lymphatics (45–50 Gy in 5 weeks) versus no radiotherapy. [143] However, 43% of the 184 women were excluded and there were more exclusions in the radiotherapy group, There were numerous chemotherapy complications, including one death. The RCT found no significant difference in local or distant failures. However, it found that overall crude survival was significantly higher with no radiotherapy compared with radiotherapy (28.7 months with no radiotherapy *v* 21.7 months with radiotherapy; P <0.05). [143] Because of poor study quality, conclusions cannot be drawn from this RCT.

The second RCT (332 women who were recurrence-free after modified radical mastectomy and 6 cycles of chemohormone treatment for operable locally advanced breast cancer; 38% stage T4 and 14% N2) [144] compared postoperative radiotherapy versus no further treatment. It found no significant difference in time to relapse or median overall survival (time to relapse: 4.7 years with radiotherapy *v* 5.2 years with no further treatment; P = 0.68; median overall survival: 8.3 years with radiotherapy *v* 8.1 years with no further treatment; P = 0.94). [144] Radiotherapy reduced locoregional sites as first recurrence by 9%.

The third RCT (1708 premenopausal women who had undergone mastectomy for stage 2 or 3 breast cancer, 234/1708 [14%] with tumours >5 cm) compared 8 cycles of CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy plus radiotherapy to the chest wall and regional lymph nodes versus chemotherapy alone. [75] It found that addition of postoperative radiotherapy to adjuvant chemotherapy after surgery significantly reduced locoregional recurrence and improved overall and disease-free survival versus chemotherapy alone after 10 years (recurrence: RR 0.27, 95% CI 0.21 to 0.34; overall survival: 54% with radiotherapy plus chemotherapy *v* 45% with chemotherapy alone; disease-free survival: 48% with radiotherapy plus chemotherapy *v* 34% with chemotherapy alone; all comparisons reported as significant). [75]

The fourth RCT (1375 postmenopausal women, all with high-risk breast cancer, receiving adjuvant tamoxifen, 14% had skin invasion, 12% with tumours >5 cm) found that postoperative radiotherapy significantly reduced locoregional recurrence and improved disease-free survival versus no radiotherapy at a median follow-up of 123 months (recurrence: 52/689 [8%] with radiotherapy *v* 242/686 [35%] without radiotherapy; P <0.001; disease-free survival: 36% with radiotherapy *v* 24% without radiotherapy; P <0.001). [92] It found that radiotherapy also improved overall survival versus no radiotherapy at 10 years (survival: 45% with radiotherapy *v* 36% without radiotherapy; P = 0.03). [92] Subgroup analysis of 189 postmenopausal women with skin invasion found that radiotherapy plus tamoxifen reduced local recurrence and increased overall and disease-free survival after 5 and 10 years (recurrence: 8% with radiotherapy *v* 34% with tamoxifen alone, significance not reported; 5-year disease-free survival: 41% with radiotherapy *v* 37% with tamoxifen; 10-year disease-free survival: 23% with radiotherapy *v* 22% with tamoxifen; 5-year survival: 51% with radiotherapy *v* 61% with tamoxifen; 10-year survival: 31% with radiotherapy *v* 27% with tamoxifen; P values not reported). However, the studies used small and retrospective subgroup analyses, making conclusions uncertain.

Harms: The type of harms from radiotherapy for locally advanced breast cancer were similar to those from radiotherapy after mastectomy or breast-conserving surgery (see harms of radiotherapy after breast-conserving surgery, p 20). However, in stage 3B disease with skin involvement (T4 b, c, d), the skin is usually given a higher dose of radiotherapy. In addition, a higher dose (60 Gy) is often given to more of the breast volume. Acute skin toxicity (including moist desquamation) and late skin toxicity (pigmentation and telangiectasia) are also more likely than in women without skin involvement.

Comment: The lack of good-quality, large RCTs that directly address stage 3B breast cancer and the role of radiotherapy renders it difficult to draw firm conclusions on its value. The published RCTs are small and have varying approaches to management. It is more difficult to detail the possible benefits of postoperative radiotherapy in women whose locally advanced breast cancers have been rendered operable by systemic treatment and who have had surgery, usually modified radical mastectomy. However, there are strong benefits identified for postoperative radiotherapy for stage 2 and 3 patients based on the post-mastectomy systematic reviews and RCTs (see radiotherapy after mastectomy in primary operable breast cancer, p 25). It is likely that such postoperative radiotherapy will reduce the risk of local and regional recurrence. It is not possible to conclude whether it will affect survival.

OPTION SURGERY

Treatment success
Compared with radiotherapy Surgery compared with radiotherapy as sole local treatments seem to have equal durations of disease control and remission in women with locally advanced disease (stage 3B) rendered operable by prior chemotherapy (moderate-quality evidence).

Mortality
Compared with radiotherapy Surgery compared with radiotherapy as sole local treatments seem to be equally effective at prolonging overall survival at 3 to 4 years in women with locally advanced disease (stage 3B) rendered operable by prior chemotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: **Surgery alone versus radiotherapy alone:**
We found no systematic review but found two RCTs, which compared surgery alone with radiotherapy alone as local treatment. [145] [146] In the first RCT (113 women with stage 3 breast cancer, 67% stage 3B), women were given chemotherapy and 81% became operable; then 87 women were randomised to surgery or radiotherapy. [145] After local treatment, a further 2 years of chemotherapy was given. Both groups had a similar duration of disease control (29.2 months with surgery *v* 24.4 months with radiotherapy; P = 0.5), similar overall median survival (39.3 months with surgery *v* 39.0 months with radiotherapy), and similar sites of first relapse. [145] In the second RCT (132 women, 91% stage 3B, 9% stage 3A), all women received chemotherapy before randomisation to either surgery or radiotherapy. [146] The total response rate was 75% in each group. There was no significant difference in the duration of remission (15 months with surgery *v* 22 months with radiotherapy; P = 0.58). Survival was similar at 4 years (49.1 months with surgery *v* 52 months with radiotherapy). [146]

Harms: The type of harms from radiotherapy for locally advanced breast cancer were similar to those from radiotherapy after mastectomy or breast-conserving surgery (see harms of radiotherapy after breast-conserving surgery, p 20). However, in stage 3B disease with skin involvement (T4 b, c, d), the skin is usually given a higher dose of radiotherapy. In addition, a higher dose (60 Gy) is often given to more of the breast volume. Acute skin toxicity (including moist desquamation) and late skin toxicity (pigmentation and telangiectasia) are also more likely than in women without skin involvement.

Comment: From the results of two RCTs, [145] [146] it can be concluded that in terms of overall response (which includes the response from local treatments such as surgery, radiotherapy, or both, and the effects of any initial systemic treatment), duration of that response, and overall survival, there is no advantage of either surgery alone or radiotherapy alone as sole local treatment over the other. It is more difficult to detail the possible benefits of postoperative radiotherapy in women whose locally advanced breast cancers have been rendered operable by systemic treatment and who have had surgery, usually modified radical mastectomy. It is likely that such postoperative radiotherapy will reduce the risk of local (and regional, if nodal areas are irradiated) recurrence. It is not possible to conclude that it will affect survival.

OPTION RADIOTHERAPY

Treatment success
Compared with surgery Radiotherapy and surgery as sole local treatments seem to have equal durations of disease control and remission in women with locally advanced disease (stage 3B) rendered operable by prior chemotherapy (moderate-quality evidence).

Mortality
Compared with surgery Radiotherapy and surgery as sole local treatments seem to be equally effective at prolonging overall survival at 3 to 4 years in women with locally advanced disease (stage 3B) rendered operable by prior chemotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: **Radiotherapy alone versus surgery alone:**
See benefits of surgery alone versus radiotherapy alone, p 40 .

Harms: The type of harms from radiotherapy for locally advanced breast cancer were similar to those from radiotherapy after mastectomy or breast-conserving surgery (see harms of radiotherapy after breast-conserving surgery, p 20). However, in stage 3B disease with skin involvement (T4 b, c, d), the skin is usually given a higher dose of radiotherapy. In addition, a higher dose (60 Gy) is often given to more of the breast volume. Acute skin toxicity (including moist desquamation) and late skin toxicity (pigmentation and telangiectasia) are also more likely than in women without skin involvement.

Comment: The lack of good-quality, large RCTs that directly address stage 3B breast cancer and the role of radiotherapy renders it difficult to draw firm conclusions on its value. The published RCTs are small and have varying approaches to management. From the results of two RCTs, [145] [146] it can be concluded that in terms of overall response (which includes the response from local treatments such as surgery, radiotherapy, or both, and the effects of any initial systemic treatment), duration of that response, and overall survival, there is no advantage of either surgery alone or radiotherapy alone as sole local treatment over the other. It is more difficult to detail the possible benefits of postoperative radiotherapy in women whose locally advanced breast cancers have been rendered operable by systemic treatment and who have had surgery, usually modified radical mastectomy.

It is likely that such postoperative radiotherapy will reduce the risk of local (and regional, if nodal areas are irradiated) recurrence. It is not possible to conclude whether it will affect survival.

OPTION HYPOFRACTIONATED RADIOTHERAPY

Mortality
Hypofractionated radiotherapy compared with tamoxifen We don't know whether radiotherapy (40 Gy in 15 fractions) is more effective at prolonging survival in women with locally advanced breast cancer (low-quality evidence).

Adverse effects
Radiotherapy may rarely be associated with late adverse effects, such as pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Hypofractionated radiotherapy versus tamoxifen:
We found no systematic review but found one small RCT. [147] The RCT (143 women with locally advanced breast cancer) compared hypofractionated radiotherapy (40 Gy in 15 fractions) versus tamoxifen 20 mg twice daily. Women were given the alternative treatment on relapse. The RCT found no significant difference in response rates (P = 0.34), duration of response (P = 0.76), or survival (P = 0.38). [147]

Harms:

The type of harms from radiotherapy for locally advanced breast cancer were similar to those from radiotherapy after mastectomy or breast-conserving surgery (see harms of radiotherapy after breast-conserving surgery, p 20). However, in stage 3B disease with skin involvement (T4 b, c, d), the skin is usually given a higher dose of radiotherapy. In addition, a higher dose (60 Gy) is often given to more of the breast volume. Acute skin toxicity (including moist desquamation) and late skin toxicity (pigmentation and telangiectasia) are also more likely than in women without skin involvement.

Comment:

The lack of good-quality, large RCTs that directly address stage 3B breast cancer and the role of radiotherapy render it difficult to draw firm conclusions on its value. The published RCTs are small and have varying approaches to management. From the results of two RCTs, [145] [146] it can be concluded that in terms of overall response (which includes the response from local treatments such as surgery, radiotherapy, or both, and the effects of any initial systemic treatment), duration of that response, and overall survival, there is no advantage of either surgery alone or radiotherapy alone as sole local treatment over the other. It is more difficult to detail the possible benefits of postoperative radiotherapy in women whose locally advanced breast cancers have been rendered operable by systemic treatment and who have had surgery, usually modified radical mastectomy. It is likely that such postoperative radiotherapy will reduce the risk of local (and regional, if nodal areas are irradiated) recurrence. It is not possible to conclude that it will affect survival, although some RCTs and systematic reviews on patients treated with mastectomy and subsequent chemotherapy and/or endocrine therapy show a survival benefit (see postoperative radiotherapy, p 39).

OPTION SYSTEMIC TREATMENT (HORMONE TREATMENT, CHEMOTHERAPY, OR BOTH)

Treatment success
Systemic treatment plus radiotherapy compared with radiotherapy alone We don't know whether adding chemotherapy or hormone treatment (ovarian irradiation for premenopausal women, tamoxifen for postmenopausal women) to radiotherapy is more effective at reducing locoregional recurrences in women with locally advanced breast cancer (very low-quality evidence).

Mortality
Systemic treatment plus radiotherapy compared with radiotherapy alone Adding hormone treatment (ovarian irradiation for premenopausal women, tamoxifen for postmenopausal women) may improve median survival but we don't know whether adding chemotherapy improves overall survival in women with locally advanced breast cancer (very low-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Systemic treatment plus radiotherapy versus radiotherapy alone:
We found no systematic review but found three RCTs, [148] [149] [150] which compared radiotherapy versus radiotherapy plus systemic treatment (hormone treatment, chemotherapy, or both). The first RCT (410 women, most stage 3B) [148] compared 4 treatments in a factorial design: radiotherapy; radiotherapy plus chemotherapy (CMF [cyclophosphamide, methotrexate, fluorouracil] for 12

cycles); radiotherapy plus hormone treatment (ovarian irradiation for premenopausal women, tamoxifen for postmenopausal women); and radiotherapy plus chemotherapy plus hormone treatment. [148] Adding chemotherapy (P = 0.0002) or hormone treatment (P = 0.0007) to radiotherapy significantly delayed locoregional recurrence, and adding both chemotherapy and hormone treatment had the greatest effect on delaying locoregional recurrence (P = 0.0001). Adding chemotherapy or hormone treatment to radiotherapy reduced locoregional recurrence at 6 years (AR about 60% with radiotherapy alone *v* about 50% with radiotherapy plus chemotherapy or hormonal treatment). The effect of adding chemotherapy or hormone treatment to radiotherapy on distant metastases was similar but less marked. Adding hormone treatment to radiotherapy significantly increased median survival, but adding chemotherapy did not significantly increase survival (median survival: 4.3 years with hormone treatment *v* 3.3 years without hormone treatment after 8 years; HR death 0.75, 95% CI 0.59 to 0.96; median survival: 3.8 years with chemotherapy *v* 3.6 years without chemotherapy; HR death 0.84, 95% CI 0.66 to 1.08).

The second RCT (118 women with stage 3B breast cancer) [149] compared three treatments: radiotherapy; radiotherapy plus chemotherapy (CMF for 12 cycles) plus tamoxifen; and chemotherapy (CMF alternating with doxorubicin [adriamycin] and vincristine) followed by radiotherapy and further similar chemotherapy plus tamoxifen. The radiotherapy in the third treatment group delivered a lower dose to the skin and a lower total dose than delivered in the other two treatment groups. After a minimum follow-up of 14 years, the RCT found no significant difference in survival, disease-free survival, or type of first recurrence between groups (figures presented graphically; survival: P = 0.38; disease-free survival: P = 0.26; first recurrence: P = 0.4). [149]

The third RCT (52 women with T4 breast cancer) compared an anthracycline chemotherapy regimen before radiotherapy versus similar radiotherapy alone. [150] Chemotherapy plus radiotherapy significantly increased initial locoregional control rate (complete response defined as no palpable, visible, or radiological evidence of cancer in the breast or regional lymph node areas) compared with radiotherapy alone (complete response: 79% with chemotherapy plus radiotherapy *v* 46% with radiotherapy alone; P = 0.03). However, the proportion of women free of locoregional spread at death or final follow-up was similar (57% with chemotherapy plus radiotherapy *v* 50% with radiotherapy alone). Overall survival and time to distant recurrence were not significantly different between groups.

Harms: In many RCTs, harms of treatment were not reported (see harms of adjuvant combination chemotherapy, p 8).

Comment: The lack of large RCTs and the frequent inclusion of less locally advanced disease (T3) with locally advanced breast cancer (defined here as stage 3B) make it difficult to draw conclusions. There is, however, no evidence from the studies using CMF chemotherapy or various regimens incorporating anthracyclines that cytotoxic chemotherapy improves survival, disease-free survival, or long-term locoregional control in stage 3B breast cancer. Chemotherapy is often used in the management of locally advanced breast cancer (as defined here), despite a lack of evidence of measurable benefit. The lack of evidence may in part be caused by small sample sizes in RCTs.

OPTION MULTIMODAL TREATMENT

Recurrence

Compared with hormone treatment Multimodal treatment (primary chemotherapy, surgery, radiotherapy, and tamoxifen) seems more effective than initial treatment with tamoxifen plus salvage treatments upon tumour progression at improving remission rates at 6 months but not at reducing the development of metastases, or controlling disease at 52 months (low-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits:

Multimodal treatment versus hormone treatment:

We found no systematic review but found one RCT (two publications). [151] [152] The RCT (108 women) compared multimodal treatment (primary chemotherapy, surgery, radiotherapy, and tamoxifen) with initial hormone treatment plus subsequent salvage treatments upon tumour progression. [151] [152] The objective remission after 6 months was higher with multimodal treatment than with tamoxifen alone (31/54 [57%] with multimodal treatment *v* 19/53 [36%] with tamoxifen alone; OR 2.4, 95% CI 1.1 to 5.0). [151] However, at a median follow-up of 52 months, there was no significant difference in survival, the development of metastases, the time to metastases, or uncontrolled local disease. Women with oestrogen receptor-positive tumours had a higher overall objective response rate (49% with oestrogen receptor-positive *v* 7% with oestrogen receptor-negative; P value not reported) and increased survival (numbers not reported). [152]

Harms: In many RCTs, harms of treatment were not reported (see harms of adjuvant combination chemotherapy, p 8).

Comment: None.

OPTION CHEMOTHERAPY PLUS RADIOTHERAPY

Mortality
Adjuvant chemotherapy compared with primary plus adjuvant chemotherapy Adjuvant chemotherapy and primary plus adjuvant chemotherapy are equally effective at 25 months at improving disease-free survival, and overall survival in women also receiving radiotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 52 .

Benefits: **Adjuvant chemotherapy versus primary plus adjuvant chemotherapy:**
We found no systematic review but found one RCT. [153] The RCT (101 women with operable T4bN0–2 breast cancer) compared 6 cycles of adjuvant CEF (cyclophosphamide, epirubicin, fluorouracil) after surgery (standard or modified radical mastectomy) versus three cycles of primary CEF followed by surgery plus three cycles of adjuvant CEF; both groups received chest wall and total nodal radiotherapy. [153] At a median follow-up of 25 months, there was no significant difference in overall survival or disease-free survival (overall survival: 82% with adjuvant *v* 76% with primary plus adjuvant chemotherapy; P = 0.42; disease-free survival: 76% with adjuvant *v* 61% with primary plus adjuvant chemotherapy; P = 0.18). [153]

Harms: In many RCTs, harms of treatment were not reported (see harms of adjuvant combination chemotherapy, p 8).

Comment: None.

GLOSSARY

Adjuvant treatment (also known as postoperative chemotherapy) This usually refers to systemic chemotherapy, hormonal treatment, or both, given to people after removal of a primary tumour (in this case, surgery for early breast cancer), with the aim of killing any remaining micrometastatic tumour cells and thus preventing recurrence.

Anthracyclines These are also known as cytotoxic antibiotics, and are used as adjuvant treatment with radiotherapy. Examples of anthracyclines are aclarubicin, daunorubicin, adriamycin (doxorubicin), epirubicin, and idarubicin.

Axillary clearance Clearance of level I, II, and usually level III axillary lymph nodes. Level I nodes are lateral to the pectoralis minor muscle, level II nodes are under it, and level III nodes are medial to it at the apex of the axilla.

Axillary radiotherapy This usually includes irradiation of the supraclavicular fossa. Irradiation of this area incorporates some underlying lung, which increases the risk of radiation pneumonitis. By increasing the volume of the lung irradiated, compared with chest wall or breast radiotherapy alone, the risk of acute pneumonitis is increased.

Axillary sampling Aims to remove the four largest, most easily palpable axillary lymph nodes for histological examination.

Brachial plexopathy Damage — usually permanent and often progressive — to the brachial plexus. It may arise from radiotherapy as a delayed or late event. It may also be caused by tumour infiltration.

CMF (classical) Chemotherapy regimen containing cyclophosphamide, methotrexate, and fluorouracil.

FAC Chemotherapy regimen containing fluorouracil, adriamycin (doxorubicin), and cyclophosphamide.

Modified radical mastectomy Modified radical mastectomy is a total mastectomy with removal of all axillary nodes from level I medial to the pectoralis minor, level II underneath the pectoralis minor, and up to the apex and including level III nodes medial to the pectoralis minor but below the axillary vein up to the first rib. Traditionally, a modified radical mastectomy included excision of the pectoralis minor, but most surgeons performing a modified radical mastectomy nowadays preserve the pectoralis minor.

Radical mastectomy Removal of the breast and pectoralis major and minor muscles and axillary contents.

Radiotherapy Part of initial local and regional treatment. In early stage disease, it may be an adjunct to surgery; in locally advanced disease (T4, N2), it may be the sole locoregional treatment. Radiotherapy may be delivered to the breast or postmastectomy chest wall, as well as to the lymphatic areas of the axilla, supraclavicular fossa, or internal mammary node chain.

Sentinel node biopsy A procedure whereby the first nodes in the draining lymphatic basin are removed and examined by a pathologist for cancer cells.

Simple mastectomy Removal of the breast tissue, usually in association with an ellipse of skin which includes the nipple and areolar complex. Dissection continues down to, but does not usually include, the pectoral fascia. It includes removal of the axillary tail of the breast. Lymph nodes are not usually removed other than by an additional procedure.

Supraradical mastectomy Removal of breast, pectoralis major and minor muscles, axillary contents, and internal mammary chain of nodes.

Total mastectomy Surgery to remove the entire breast.

Total nodal irradiation Radiotherapy to the regional lymph nodes, including supraclavicular, infraclavicular, axillary nodes, and internal mammary nodes in the upper intercostal spaces.

UICC International Union against Cancer.

Brachytherapy Delivery of a radiation dose over a short distance either from a low-energy x-ray source, a low-energy electron source, or a radioactive source.

Breast-conserving surgery Surgery consisting of lumpectomy (minimal cancer-free margins), wide local excision (wider free margins), or segmental or quadrant resection (usually with wide-free margins).

Combination chemotherapy Two or more cytotoxic drugs given intravenously every 3 to 4 weeks for 4 to 6 months.

Disease-free survival Means being alive with no local or distant recurrence or contralateral disease.

Early invasive breast cancer (stage 1 or 2) is M0 with T1 or T2 (tumour diameter 5 cm or less, no involvement of skin or chest wall) and N0 or N1 (mobile axillary nodes); or M0 with T3 (tumour diameter over 5 cm, no skin or chest wall involvement), but only N0.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Less than whole-breast radiotherapy The delivery of radiotherapy by either temporary internal placement of a radiation source or by external beam treatment to part of the breast (area of wide local excision after breast-conserving surgery).

Locally advanced breast cancer Operable locally advanced breast cancer (stage 3A) is T3 (tumours >5 cm) and N1 (non-matted involved axillary nodes). Locally advanced breast cancer (stage 3B) is M0 with T4 (skin or chest wall infiltration by tumour), N2 (matted axillary nodes)/N3 (internal mammary node involvement) disease, or both, not classified as non-invasive or early invasive breast cancer. Metastatic breast cancer (stage 4) is M1 (any supraclavicular fossa node involvement or distant metastases to bone, lung, liver, etc.) with any combination of tumour and node parameters.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Milan regimen A sequential regimen of single agent anthracycline followed by CMF (cyclophosphamide, methotrexate, and fluorouracil).

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Ovarian ablation Surgical, medical, or radiation-induced suppression of ovarian function in premenopausal women.

Overall objective response rate The proportion of treated people in whom a complete response (disappearance of all known lesions on 2 separate measurements at least 4 weeks apart), or partial response (>50% reduction in the size of lesions) is observed.

Primary chemotherapy (also known as neoadjuvant or preoperative chemotherapy) involves the use of chemotherapy to treat breast cancer before locoregional treatment (surgery, radiotherapy, or both) to the breast to downstage large primary cancers that would require mastectomy to improve chances of survival.

Quadrantectomy Tumour excised with 2 cm or more of normal surrounding breast tissue and with a segment of breast tissue from the periphery of the breast to the nipple.

Systemic therapy Use of oral or intravenous treatments that affect the whole body.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adjuvant aromatase inhibitors (for primary operable breast cancer) Two follow-up studies added comparing adjuvant aromatase inhibitors versus placebo, which found that letrozole remained beneficial when analysing results by HER2 status [15] and by age. [16] One follow-up study added comparing adjuvant aromatase inhibitors versus tamoxifen, which found that anastrozole improved disease-free survival, time to recurrence, and time to distant recurrence compared with tamoxifen at 8.5 years. [20] Categorisation unchanged (Beneficial).

Adjuvant combination chemotherapy (for primary operable breast cancer) One new systematic review added, which compared combination chemotherapy versus no chemotherapy in women with oestrogen-receptor-poor breast

cancer. [27] The review found that chemotherapy reduced recurrence compared with no chemotherapy across all age groups. [27] Categorisation unchanged (Beneficial compared with no chemotherapy).

Adjuvant tamoxifen (for primary operable breast cancer) One systematic review added, which found no significant difference in mortality and recurrence between tamoxifen and no tamoxifen in women with oestrogen-receptor-poor breast cancer. [27] Categorisation unchanged (Beneficial in women with oestrogen receptor-positive tumours).

Anthracycline regimens as adjuvant chemotherapy (for primary operable breast cancer) One large RCT added, which found no significant difference between epirubicin-based regimens and standard CMF (cyclophosphamide, methotrexate, fluorouracil) regimens in disease-free survival and overall survival at 15 years. [31] Categorisation unchanged (Beneficial) as most anthracycline-based regimens are more effective than standard CMF chemotherapy.

Chemotherapy plus monoclonal antibody (trastuzumab) in women with primary operable breast cancer who have overexpressed *HER2/neu* oncogene One subgroup analysis of an included RCT added, which found that trastuzumab after chemotherapy reduced relapse similarly across subpopulations defined by nodal status and steroid hormone receptor status. [40] Categorisation unchanged (Beneficial).

Different primary chemotherapy regimens versus each other (for primary operable breast cancer) One systematic review added, which found no significant difference between the various methods of sequencing adjuvant chemotherapy and radiotherapy in survival, distant metastases, or local recurrence. [114] Categorisation unchanged (Unknown effectiveness) as there is still insufficient evidence regarding which regimen is most effective.

Enhanced-dose regimens of adjuvant combination chemotherapy (for primary operable breast cancer) One RCT added, which compared epirubicin plus cyclophosphamide versus higher-dose epirubicin plus cyclophosphamide. [31] At 15 years' follow-up, the RCT found that higher-dose epirubicin improved disease-free survival compared with standard-dose epirubicin, but found no significant difference in overall survival. Categorisation unchanged (Unlikely to be beneficial).

High-dose chemotherapy plus autologous stem cell transplantation (for primary operable breast cancer) Two RCTs added, which both found that high-dose chemotherapy plus autologous stem cell transplantation did not improve disease-free survival or overall survival compared with chemotherapy alone. [141] [142] Categorisation unchanged (Likely to be ineffective or harmful).

Less extensive mastectomy (for primary operable breast cancer) One RCT added, which found no significant difference in 25-year disease-free survival and 50-year overall survival between simple mastectomy plus radiotherapy and extended radical mastectomy. [50] One subgroup analysis providing 20-year follow-up of an already included RCT added, which found no significant difference between breast-conserving surgery and mastectomy in disease-free survival and overall survival. [54] Categorisation unchanged (Beneficial).

Less than whole-breast radiotherapy plus breast-conserving surgery (for primary operable breast cancer) One systematic review added, which identified one RCT and reported no significant difference in recurrence rates between partial-breast radiotherapy and whole-breast radiotherapy. [116] Follow-up data from one already included RCT added, which found no significant difference between partial-breast radiotherapy and whole-breast radiotherapy in recurrence, disease-free survival, and overall survival at 5 years. [117] Categorisation unchanged (Unknown effectiveness) as late recurrence rates and long-term effects are not yet known.

Radiotherapy after breast-conserving surgery (for primary operable breast cancer) One RCT added, which found that at a median follow-up of 12.1 years, lumpectomy plus radiotherapy significantly reduced local recurrence compared with surgery alone in women with good prognostic features. [68] One systematic review added to the harms section, which found that lymphoedema and shoulder restriction were significantly more common with radiotherapy compared with no radiotherapy, but that quality of life and upper limb symptoms were generally favourable in women with breast-conserving surgery plus radiotherapy. [71] Categorisation unchanged (Beneficial).

Radiotherapy after mastectomy (for primary operable breast cancer) Two further reports of an included RCT added. The first report found that post-mastectomy radiotherapy significantly reduced locoregional recurrence and distant recurrence compared with no radiotherapy. [88] The second report found that locoregional recurrence rates were significantly reduced with radiotherapy compared with no radiotherapy irrespective of receptor status. Radiotherapy increased survival in people with good prognostic features, such as hormone receptor-positive and HER2-negative cancer. [89] Condition restructured to remove distinction between high-risk and low-risk people. Categorisation unchanged (Beneficial).

Adjuvant taxanes (for primary operable breast cancer) One systematic review [43] and three subsequent RCTs [44] [45] [46] added, which found that taxane-based therapies improved disease-free survival and overall survival compared with anthracycline-based regimens. Categorisation changed from Likely to be beneficial to Beneficial.

Radiotherapy after breast-conserving surgery (for ductal carcinoma in situ) One systematic review added, which found that radiotherapy after breast-conserving surgery for ductal carcinoma in situ significantly reduced ipsilateral recurrence at up to 10.5 years of follow-up. [6] Categorisation changed from Likely to be beneficial to Beneficial because of confirmation given in systematic review and maintenance of benefit with long-term follow-up.

Radiotherapy with or without endocrine therapy after breast-conserving surgery (for primary operable breast cancer) One RCT added, which found that after breast-conserving surgery, radiotherapy plus adjuvant hormone therapy reduced recurrence and improved disease-free survival compared with adjuvant hormone therapy alone. [79]

One RCT reporting no significant difference in quality of life between radiotherapy and no radiotherapy added to the harms section. [80] Categorisation changed from Likely to be beneficial to Beneficial.

Sentinel node biopsy (for primary operable breast cancer) One RCT assessing operative complications added, which found that sentinel node biopsy plus axillary dissection was associated with more surgical adverse effects, including wound infections, seromas, and paraesthesia, compared with sentinel node biopsy alone. [131] Categorisation changed from Unknown effectiveness to Likely to be beneficial.

Tamoxifen plus radiotherapy after breast-conserving surgery (for ductal carcinoma in situ) Existing evidence re-evaluated. Tamoxifen plus radiotherapy (reduced recurrence in women with oestrogen receptor-positive tumours) recategorised from Likely to be beneficial to Unknown effectiveness because the two large RCTs identified present conflicting results.

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Breast cancer (non-metastatic)

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Disclaimer

TABLE 1 **Staging of breast cancer (see text).** [1]

	TNM			Stage
Non-invasive	Tis	N0	M0	0
Early invasive	T1−2	N0−1	M0	1, 2A or B
	T3	N0	M0	2B
Advanced				
Locally advanced	Tany	N2	M0	3A
	T3	N1−2	M0	3A
	T4	N0−3	M0	3B
	Tany	N3	M0	3B
Metastatic	Tany	Nany	M1	4

TABLE 2 **Ten-year survival with combination chemotherapy versus placebo, according to nodal and age/menopausal status: results of a systematic review of RCTs (see text, p 8).** [97]

	Control (%)	Chemotherapy (%)	Absolute benefit (%)	SD (%)	Significance (two sided)
Age under 50 years					
Node +ve	41.4	53.8	+12.4	2.4	P <0.0001
Node –ve	71.9	77.6	+5.7	2.1	P = 0.01
Age 50 to 69 years					
Node +ve	46.3	48.6	+2.3	1.3	P = 0.001
Node –ve	64.8	71.2	+6.4	2.3	P = 0.0025

SD, standard deviation.

TABLE 3 **Survival at 10 years in women treated with tamoxifen for 5 years compared with control treatment (no tamoxifen): results of a systematic review (see text, p 12).** [98]

	Control (%)	Tamoxifen (%)	Absolute benefit (%)	SD (%)	Significance (two sided)
Node +ve	50.5	61.4	+10.9	2.5	P <0.00001
Node –ve	73.3	78.9	+5.6	1.3	P <0.00001

SD, standard deviation.

TABLE GRADE evaluation of interventions for breast cancer (non-metastatic)

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions after breast-conserving surgery for ductal carcinoma in situ?									
4 (3925) [6]	Treatment success	Radiotherapy *v* no radiotherapy	4	0	0	0	0	High	
2 (2327) [11] [12] [13]	Treatment success	Tamoxifen plus radiotherapy *v* radiotherapy plus placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of result. Consistency point deducted for conflicting results
1 (1804) [11] [12]	Mortality	Tamoxifen plus radiotherapy *v* radiotherapy plus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments for primary operable breast cancer?									
1 (5187 [14]	Mortality	Adjuvant aromatase inhibitors *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (14,068) [17] [18] [19] [21] [20]	Treatment success	Adjuvant aromatase inhibitors *v* tamoxifen	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (14,068) [17] [18] [19] [21] [20]	Mortality	Adjuvant aromatase inhibitors *v* tamoxifen	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (9366) [17] [18]	Treatment success	Adjuvant aromatase inhibitors plus tamoxifen *v* tamoxifen alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
47 (18,000) [26] [27]	Treatment success	Adjuvant combination chemotherapy *v* no chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
47 (18,000) [26]	Mortality	Adjuvant combination chemotherapy *v* no chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
not reported (3454) [26]	Treatment success	Different treatment durations compared with each other (prolonged adjuvant combination chemotherapy)	4	0	0	0	0	High	
not reported (3454) [26]	Mortality	Different treatment durations compared with each other (prolonged adjuvant combination chemotherapy)	4	0	0	0	0	High	
3 (4399) [29] [30] [31]	Treatment success	Different doses compared with each other (enhanced-dose regimens of adjuvant combination chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (4399) [29] [30] [31]	Mortality	Different doses compared with each other (enhanced-dose regimens of adjuvant combination chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
12 (6719) [26] [31]	Treatment success	Anthracycline regimens *v* standard CMF (cyclophosphamide, methotrexate, fluorouracil) regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
12 (6719) [26] [31]	Mortality	Anthracycline regimens *v* standard CMF regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
55 (37,000, primarily with oestrogen) [33]	Treatment success	Adjuvant tamoxifen *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
55 (37,000) [33]	Mortality	Adjuvant tamoxifen *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3887) [34]	Treatment success	Durations of treatment compared with each other (adjuvant tamoxifen)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3887) [34]	Mortality	Durations of treatment compared with each other (adjuvant tamoxifen)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3387) [39] [40]	Treatment success	Trastuzumab *v* observation (after chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3387) [39] [40]	Mortality	Trastuzumab *v* observation (after chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3351) [41]	Treatment success	Trastuzumab *v* observation (during chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3351) [41]	Mortality	Trastuzumab *v* observation (during chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
15 (26,277) [43] [154] [45]	Treatment success	Adjuvant taxane-based regimens *v* anthracycline-based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
15 (26,277) [43] [154] [45]	Mortality	Adjuvant taxane-based regimens *v* anthracycline-based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (4950) [46]	Treatment success	Different adjuvant taxane-based regimens *v* each other	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
[46]	Mortality	Different adjuvant taxane-based regimens *v* each other	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (1296) [49]	Mortality	Radical/total mastectomy *v* simple mastectomy plus radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (666) [50]	Treatment success	Radical or total mastectomy *v* simple mastectomy plus radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (2090) [49]	Mortality	Supraradical, radical, and total mastectomy *v* each other	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (3107) [49] [53]	Treatment success	Mastectomy *v* breast conservation with or without radiotherapy	4	0	0	−1	0	Moderate	Directness point deducted as unclear how many women in analysis received radiotherapy
9 (at least 4891) [49] [52] [53]	Mortality	Mastectomy *v* breast conservation with or without radiotherapy	4	0	0	−1	0	Moderate	Directness point deducted as unclear how many women in analysis received radiotherapy
1 (705) [55]	Treatment success	Different extents of local excision compared with each other	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
12 (2102) [66]	Treatment success	Ovarian ablation *v* no ablation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
12 (2102) [66]	Mortality	Ovarian ablation *v* no ablation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (7575) [67] [69] [68]	Treatment success	Breast-conserving surgery plus radiotherapy *v* breast-conserving surgery alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (7575) [67]	Mortality	Breast-conserving surgery plus radiotherapy *v* breast-conserving surgery alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (3294) [49] [155]	Mortality	Breast-conserving surgery plus radiotherapy *v* mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (666) [70]	Treatment success	Breast-conserving surgery plus radiotherapy *v* breast-conserving surgery plus endocrine therapy	4	0	0	0	0	High	
1 (666) [70]	Mortality	Breast-conserving surgery plus radiotherapy *v* breast-conserving surgery plus endocrine therapy	4	−1	0	0	0	Moderate	Quality point deducted for assessment of only among-group differences for this outcome (3-armed trial)
4 (2907) [70] [77] [78] [79] [79]	Treatment success	Breast-conserving surgery plus radiotherapy plus endocrine therapy *v* breast-conserving surgery plus endocrine therapy only	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for different results with measures of treatment success
3 (2268) [70] [78] [79] [79]	Mortality	Breast-conserving surgery plus radiotherapy plus endocrine therapy *v* breast-conserving surgery plus endocrine therapy only	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting
36 (8505 node positive) [67]	Treatment success	Radiotherapy after mastectomy *v* mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
36 (8505 node positive) [67]	Mortality	Radiotherapy after mastectomy *v* mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (2802) [96] [100] [101] [97]	Treatment success	Primary chemotherapy *v* adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (3216) [93] [94] [95] [96] [97]	Mortality	Primary chemotherapy *v* adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (466) [102]	Mortality	Axillary clearance *v* axillary sampling	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (4370) [49]	Treatment success	Axillary clearance *v* axillary radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (4370) [49]	Mortality	Axillary clearance *v* axillary radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (448) [107]	Treatment success	Standard *v* dose-intensified anthracycline based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (448) [107]	Mortality	Standard *v* dose-intensified anthracycline based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (174) [108]	Treatment success	FAC regimen (fluorouracil, doxorubicin [adriamycin], and cyclophosphamide) *v* single-agent paclitaxel	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (174) [108]	Mortality	FAC regimen (fluorouracil, doxorubicin [adriamycin], and cyclophosphamide) *v* single-agent paclitaxel	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (101) [109]	Treatment success	MPEMi (methotrexate, cisplatin, etoposide, mitomycin C), MPEpiE (methotrexate, cisplatin, epirubicin, etoposide), and MPEpiV (methotrexate, cisplatin, epirubicin, vincristine) regimens *v* each other	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (2515) [110] [111]	Treatment success	Sequencing of anthracycline-based chemotherapy and docetaxel	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for no long-term results
1 (73) [112]	Treatment success	Intra-arterial *v* intravenous administration	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (1134) [118] [119] [120] [116] [117]	Treatment success	Less than whole-breast radiotherapy *v* whole breast radiotherapy	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (426) [120] [116]	Mortality	Less than whole-breast radiotherapy *v* whole breast radiotherapy	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (270) [122]	Treatment success	Radiotherapy to the internal mammary chain *v* no internal mammary chain irradiation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (270) [122]	Mortality	Radiotherapy to the internal mammary chain *v* no internal mammary chain irradiation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1375) [92]	Treatment success	Radiotherapy *v* no radiotherapy to the ipsilateral supraclavicular fossa	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1389) [129] [130] [131]	Treatment success	Sentinel node biopsy plus total axillary dissection *v* with sentinel node biopsy alone	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for uncertainty about follow-up
1 (200) [129]	Mortality	Sentinel node biopsy plus total axillary dissection *v* with sentinel node biopsy alone	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for uncertainty about follow-up
at least 8 RCTs (at least 3858 women) [140] [142] [141]	Mortality	High-dose chemotherapy plus autologous stem cell transplantation *v* conventional chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 8 RCTs (at least 3858 women) [140] [142] [141]	Treatment success	High-dose chemotherapy plus autologous stem cell transplantation *v* conventional chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
13 (5064) [140]	Adverse effects	High-dose chemotherapy plus autologous stem cell transplantation *v* conventional chemotherapy	4	0	0	0	+2	High	Effect size points added for RR >5

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions in locally advanced breast cancer (stage 3B)?									
4 (3599) [75] [92] [143] [144]	Treatment success	Postoperative radiotherapy (in women also receiving postoperative systemic treatment) *v* no radiotherapy	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and for weak methods. Directness point deducted for inclusion of women with different disease severities
4 (3599) [75] [92] [143] [144]	Mortality	Postoperative radiotherapy (in women also receiving postoperative systemic treatment) *v* no radiotherapy	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and for weak methods. Directness point deducted for inclusion of women with different disease severities
2 (219) [145] [146]	Treatment success	Surgery alone *v* radiotherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (219) [145] [146]	Mortality	Surgery alone *v* radiotherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (143) [147]	Mortality	Low-dose radiotherapy *v* tamoxifen	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (580) [148] [149] [150]	Treatment success	Systemic treatment plus radiotherapy *v* radiotherapy	4	−1	−1	−1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inclusion of women with less severe disease
3 (580) [148] [149] [150]	Mortality	Systemic treatment plus radiotherapy *v* radiotherapy	4	−1	−1	−1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inclusion of women with less severe disease
1, 2 publications (107) [151] [152]	Treatment success	Multimodal treatment *v* hormone treatment	4	−1	−1	0	+1	Moderate	Quality point deducted for sparse data. Consistency point deducted for different results at different end points. Effect size point added for OR 2 to 5
1 (101) [153]	Mortality	Adjuvant chemotherapy *v* primary plus adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.