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 IIIB)? We searched: Medline, Embase, The Cochrane Library and other important databases up to February 2006 (BMJ 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 79 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

What are the effects of interventions after breast-conserving surgery for ductal carcinoma *in situ*? 4

What are the effects of treatments for primary operable breast cancer? 6

What are the effects of interventions in locally advanced breast cancer (stage III B)? 32

INTERVENTIONS

DUCTAL CARCINOMA IN SITU

Likely to be beneficial

Radiotherapy (reduced recurrence) 4

Unknown effectiveness

Tamoxifen plus radiotherapy (reduced recurrence in women with oestrogen receptor-positive tumours) . . 5

PRIMARY OPERABLE BREAST CANCER

Beneficial

Adjuvant aromatase inhibitors 6

Adjuvant combination chemotherapy (better than no chemotherapy) 7

Adjuvant tamoxifen (in women with oestrogen receptor-positive tumours) 11

Anthracycline regimens as adjuvant chemotherapy (better than standard CMF [cyclophosphamide, methotrexate, and fluorouracil] regimens) 10

Chemotherapy plus monoclonal antibody (trastuzumab) in women with overexpressed *HER2/neu* oncogene . . 1 2

Less-extensive mastectomy (similar survival to more extensive surgery, and better cosmetic outcome) . . 1 4

Ovarian ablation in premenopausal women 16

Radiotherapy after breast-conserving surgery (reduced local recurrence and breast cancer mortality compared with breast-conserving surgery alone) 17

Radiotherapy after mastectomy in women at high risk of local recurrence 21

Likely to be beneficial

Adjuvant taxanes New 13

Primary chemotherapy (reduced mastectomy rates and had similar survival rates to adjuvant chemotherapy) . . 2 3

Radiotherapy plus tamoxifen compared with breast-conserving surgery alone (reduced local recurrence and breast cancer mortality compared with breast-conserving surgery alone) 19

Total nodal radiotherapy 25

Trade off between benefits and harms

Axillary management 25

Radiotherapy after mastectomy in women not at high risk of local recurrence 23

Unknown effectiveness

Different primary chemotherapy regimens (insufficient evidence regarding which regimen is most effective) . . 2 7

Less than whole-breast radiotherapy plus breast-conserving surgery 28

Radiotherapy to the internal mammary chain 29

Radiotherapy to the ipsilateral supraclavicular fossa . . 3 0

Sentinel node biopsy (versus axillary dissection plus sentinel node dissection) 31

Unlikely to be beneficial

Enhanced dose regimens of adjuvant combination chemotherapy 9

Prolonged adjuvant combination chemotherapy (8–12 months *v* 4–6 months) 8

Likely to be ineffective or harmful

High-dose chemotherapy plus autologous stem cell transplantation 32

LOCALLY ADVANCED BREAST CANCER

Likely to be beneficial

Postoperative radiotherapy (in women also receiving postoperative systemic treatment) 32

Radiotherapy (similar effectiveness to surgery) . . . 34

Surgery (similar effectiveness to radiotherapy) . . . 34

Systemic treatment plus radiotherapy (Adding hormonal treatment to radiotherapy improves survival compared with radiotherapy alone) 35

Unknown effectiveness

Adding chemotherapy (cyclophosphamide/methotrexate/fluorouracil or anthracycline based regimens) to radiotherapy 37

Radiotherapy (low-dose versus tamoxifen) 35

Unlikely to be beneficial

Multimodal treatment versus hormonal treatment . . 3 6

Covered elsewhere in Clinical Evidence

See review on breast cancer (metastatic).

To be covered in future updates

What are the effects of local treatments for early breast cancer in the elderly?

What are the effects of different protocols for follow up after treatment?

What are the effects of different breast reconstruction techniques?

Primary aromatase inhibitors in primary operable breast cancer

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,* radiotherapy reduces local recurrence and invasive carcinoma after breast-conserving surgery, but may not improve survival.
- 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 overexpress *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, but adverse effects begin to outweigh benefit after 5 years of treatment.

  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 4–6 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, but may increase mortality in node-negative women.

  Adjuvant aromatase inhibitors improve disease-free survival compared with tamoxifen, but their effect on overall survival is unclear.Adjuvant taxoid 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.

  Chemotherapy alone, while widely used, does not improve survival in women with locally advanced breast cancer.

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 apparently restricted to the breast and to local lymph nodes, 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 cm or with multifocal cancers that are usually treated by mastectomy, and those with tumours less than 4 cm cancers 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 IIIB (includes T4 a–d; N2 disease, but absence of metastases [see table 1, p 43]). 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 1/10–1/11 women in the UK and causes about 21,000 deaths a year. Prevalence is about five 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, doubling every 10 years up to the menopause. Risk factors include an early age at menarche, 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*, is currently less well established.

PROGNOSIS

Non-metastatic carcinoma of the breast is potentially curable. The risk of relapse depends on various clinicopathological features, of which axillary node involvement, tumour grade, tumour size, and oestrogen receptor status are the most prognostically important. Of women with operable disease, 80% are alive 5 years after diagnosis and treatment (adjuvant treatment is given to most women after surgery). Risk of recurrence is highest during the first 5 years, but the risk remains even 15–20 years after surgery. Recurrence at 10 years, according to one large systematic review, [4] is 60–70% in node-positive women, and 25–30% in node negative women. The prognosis for disease-free survival at 5 years is worse for stage IIIB (33%) than that for stage IIIA (71%). Overall survival at 5 years is 44% for stage IIIB and 84% for stage IIIA. [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

Survival; rates of local and regional recurrence; rates of mastectomy after breast-conserving treatment; rates of development of metastases; cosmetic outcomes; quality of life; incidence of adverse effects of treatment, including upper-limb lymphoedema.

METHODS

BMJ Clinical Evidence search and appraisal January 2007. The following databases were used to identify studies for this review: Medline 1966 to January 2007, Embase 1980 to January 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the authors for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, any level of blinding, 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. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. 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 comments sections. Phase 3 randomised published data are included. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 44).

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

OPTION RADIOTHERAPY

Treatment success
Compared with no radiotherapy Radiotherapy after breast-conserving surgery for ductal carcinoma in situ is more effective at 2, 4, 8 and at 10 years at reducing local recurrence and invasive carcinoma (high-quality evidence).

Compared with tamoxifen plus radiotherapy Radiotherapy alone and radiotherapy plus tamoxifen seem to be equally effective at 1 year at reducing invasive or ductal carcinoma in situ events in women undergoing local excision (moderate-quality evidence).

Mortality
Compared with no radiotherapy Radiotherapy after breast-conserving surgery for ductal carcinoma in situ is no more effective at 2, 4, 8 or at 10-years at prolonging survival (moderate-quality evidence).

Adverse effects
Radiotherapy has been associated with an increased risk in contralateral breast cancer at 4 years.

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits:

Radiotherapy versus no radiotherapy:
We found one systematic review (search date 2001, 2 RCTs), which compared radiotherapy versus no radiotherapy after surgery for ductal carcinoma *in situ* (DCIS). [6] The first RCT identified by the review (814 women) found no significant difference in survival at 8 years with radiotherapy compared with no radiotherapy (survival 95% with radiotherapy *v* 94% with no radiotherapy, reported as not significant). [7] It found significant reductions in risk of local recurrence, recurrent DCIS, and invasive carcinoma with radiotherapy compared with no radiotherapy (local recurrence: 12.1% with radiotherapy *v* 26.8% with no radiotherapy, P less than 0.0005; risk of recurrent DCIS: 8.2% with radiotherapy *v* 13.4% with no radiotherapy, P = 0.007; risk of invasive carcinoma: 3.9% with radiotherapy *v* 13.4% with no radiotherapy, P less than 0.0001). [7] The second RCT identified by the review (1002 women) found that surgery plus radiotherapy significantly increased the proportion of women free of local recurrence at 4 years compared with surgery alone (91% with surgery plus radiotherapy *v* 84% with surgery alone; P = 0.005; HR 0.62, 95% CI 0.44 to 0.87). [8] More women were free of DCIS recurrence after 4 years with radiotherapy, but the difference was not significant (95% with surgery plus radiotherapy *v* 92% with surgery alone; HR 0.65, 95% CI 0.43 to 1.03). Added radiotherapy significantly reduced invasive recurrence (96% with surgery plus radiotherapy *v* 92% with surgery alone; HR 0.60, 95% CI 0.37 to 0.97). [8] There was no significant difference between groups in survival at 4 years (survival rates presented graphically; P = 0.94). A subsequent update of this RCT at 10 years' median follow-up found persistence of the benefit of radiotherapy in significantly reducing local recurrence (85% local control with surgery plus radiotherapy *v* 74% with surgery alone; P less than 0.0001; HR 0.53, 95% CI 0.4 to 0.7). [9] It found no significant difference between groups in survival. [9] One subsequent RCT included 1046 women with screen-detected DCIS. [10] It found that, after a minimum follow-up period of 2 years, surgery plus post-operative radiotherapy significantly reduced recurrence rates compared with surgery alone (local recurrence: 8% with surgery plus radiotherapy *v* 22% with surgery alone; P less than 0.0001; HR 0.33, 95% CI 0.24 to 0.47). [10] It found no significant difference between groups in survival. [10]

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

Harms:

Radiotherapy versus no radiotherapy:
The second 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). [8] 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). [9] The subsequent RCT did not report on harms. [10]

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 sub-groups. [11] 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). [11] 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

Treatment success
Compared with placebo Adjuvant treatment with tamoxifen seems to be more effective at 6 years at reducing invasive ipsilateral or contralateral breast cancers and breast cancer events in women who have been treated with wide excision and radiotherapy (moderate-quality evidence). However, this benefit may be limited to women with oestrogen receptor-positive tumours.

Compared with radiotherapy alone Radiotherapy plus tamoxifen, and radiotherapy alone seem to be equally effective at 1 year at reducing invasive or ductal carcinoma in situ events (moderate-quality evidence).

Mortality
Compared with placebo Adjuvant treatment with tamoxifen seems to 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 44 .

Benefits: **Tamoxifen plus radiotherapy versus placebo:**
We found no systematic review but found one RCT (2 publications). [12] [13] The 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. [12] 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. [13]

Tamoxifen plus radiotherapy versus radiotherapy alone:
We found no systematic review but found one RCT. [14] The RCT (1694 women having local excision) compared four treatments in a factorial design: no adjuvant treatment, tamoxifen alone, radiotherapy alone, and tamoxifen plus radiotherapy (See comment on radiotherapy, p 4). [14] It found no significant difference between tamoxifen plus radiotherapy and radiotherapy alone in ipsilateral invasive disease, ipsilateral DCIS, and invasive or DCIS events after median follow-up of 1 year (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). [14]

Harms: **Tamoxifen plus radiotherapy versus radiotherapy plus placebo:**
The RCT found a higher, but non-significant rate of endometrial cancers associated with tamoxifen (RR 3.4, 95% CI 0.6 to 33.4). [12]

Tamoxifen plus radiotherapy versus radiotherapy alone:
The RCT did not report results comparing harms of tamoxifen plus radiotherapy versus radiotherapy alone. [14] 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 they choose to omit radiotherapy, or 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)

Treatment success

Compared with placebo Letrozole seems to be 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).

Mortality

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

Adverse events

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 44 .

Benefits:

Adjuvant aromatase inhibitors versus placebo:

We found no systematic review but found one RCT. [15] 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 versus 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). [15]

Adjuvant aromatase inhibitors versus tamoxifen:

We found no systematic review but found two RCTs (4 publications), which compared adjuvant aromatase inhibitors versus tamoxifen. [16] [17] [18] [19] The first RCT (3 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. [16] [17] [18] It found that anastrozole 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; [17] HR at 4 years: 0.86, 95% CI 0.76 to 0.99, P = 0.03; [16] HR at 5 years: 0.87, 95% CI 0.78 to 0.97, P = 0.01 [18]). Anastrozole also prolonged time to recurrence, and reduced time to distant metastases at 5 years (time to recurrence: 402 days with anastrozole *v* 498 days with tamoxifen, HR 0.87, 95% CI 0.78 to 0.97, P = 0.01; distant metastases: 324 days with anastrozole *v* 375 days with tamoxifen, RR 0.79, 95% CI 0.70 to 0.90, P = 0.0005). [18] It also found that contralateral breast cancer was reduced with anastrozole versus tamoxifen (35 with anastrozole *v* 59 with tamoxifen; P = 0.01). [18] A combination of tamoxifen and anastrozole did not significantly improve outcomes versus tamoxifen alone at 3 or 4 years (3 years: HR 1.02, 95% CI 0.89 to 1.18, P = 0.8; [17] 4 years: HR 1.08, 95% CI 0.98 to 1.24, P = 0.3 [16]). The second RCT (4742 recurrence-free postmenopausal women, who had completed 2–3 years of tamoxifen treatment following surgery for primary, oestrogen receptor-positive breast cancer) compared exemestane versus continuing tamoxifen treatment for the recommended 5 years. [19] 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 less than 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). [19] It found no significant difference in overall survival

between treatments (HR 0.88, 95% CI 0.67 to 1.16; P = 0.41) at the time of analysis. [19] 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). [20]

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 less than 0.05 for each). Vaginal bleeding was more common with placebo (P = 0.01). [15] 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). [15]

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 less than 0.0001; hot flushes: OR 0.80, 95% CI 0.73 to 0.89, P less than 0.0001; vaginal discharge: OR 0.24, 95% CI 0.19 to 0.30, P less than 0.0001; fracture rate: OR 1.49, 95% CI 1.25 to 1.77, P less than 0.0001; arthralgia: OR 1.32, 95% CI 1.19 to 1.47, P less than 0.001). [18] Increases in adverse musculoskeletal events are probably best explained as being due to a "second menopause" induced by lower levels of oestrogen, and appear 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 on anastrozole, compared with small increases in bone mineral density on 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. [21] 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 less than 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 less than 0.001). [19] 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 less than 0.0001). [22]

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. [15]

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. [16] [17] [18] 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, [19] although a significant survival benefit was observed with switching in the oestrogen receptor positive group, [20] at the expense of some loss in bone mineral density. [22] 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. [23]

Clinical guide: Aromatase inhibitors have an increased disease-free (but not overall) survival for oestrogen receptor-positive cancers 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, in postmenopausal women with oestrogen receptor-positive breast cancer, than 5 years of tamoxifen: firstly, tamoxifen for 5 years followed by letrozole for 5 years; secondly, anastrazole for 5 years; thirdly, 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 44 .

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. [24] Chemotherapy was associated with significantly lower rates of any kind of recurrence and death from all causes (recurrence: 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 43).

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 adriamycin (doxorubicin) does not exceed 300–350 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 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. [25]

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

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 44 .

Benefits:

Duration of treatment:
We found one systematic review (as above, 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. [24] 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). [24]

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 adriamycin (doxorubicin) does not exceed 300–350 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 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. [25]

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 44 .

Benefits:

Different doses:
We found no systematic review, but found two RCTs, which compared enhanced versus standard-dose chemotherapy regimens. The first RCT (2305 women with primary breast cancer) compared four 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). [26] The second RCT (1572 women with node-positive, stage II breast cancer) compared cyclophosphamide (400 mg/m^2 of body-surface area), doxorubicin (40 mg/m^2 once every 28 days), and fluorouracil (400 mg/m^2 twice every 28 days) for six cycles versus 50% higher doses of the three drugs (600 mg cyclophosphamide, 60 mg doxorubicin, and 600 mg fluorouracil), but for only four cycles versus half the total dose used in the other two groups, and at half the dose intensity used in the second group. [27] 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 medium and high doses. [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 adriamycin (doxorubicin) does not exceed 300–350 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 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. [25]

OPTION ADJUVANT ANTHRACYCLINE CHEMOTHERAPY

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

Mortality
Anthracycline regimens compared with standard CMF regimens Adjuvant regimens containing an anthracycline are modestly more effective than a standard multidrug chemotherapy regimen (cyclophosphamide, methotrexate, and 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 44 .

Benefits: **Anthracycline regimens versus standard CMF (cyclophosphamide, methotrexate, and fluorouracil) regimen:**
We found one systematic review (as above, search date not reported, 11 RCTs, 5942 women), which compared regimens containing anthracycline (including the drugs adriamycin [doxorubicin] or 4-epidoxorubicin) versus standard CMF regimens. [24] 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 regimen; P = 0.02).

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 adriamycin (doxorubicin) does not exceed 300–350 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 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. [25]

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 to be 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 to be 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 aromatose inhibitors (letrozole, anastrozole, and exemestane) but is less likely to cause arthralgia and fractures.

Note

We found no clinically important results 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 44 .

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. [28] 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 less than 0.00001). [28] 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 (as above, search date not reported, 55 RCTs, 37,000 women) [28] 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 *v* 0.94 with oestrogen receptor-negative), 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 *v* 14.9% with node-negative). 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 43). [28]

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 less than 0.0001). [28] One RCT included in the review (3887 women) compared 2 and 5 years of treatment and found similar results. [29] The RCT found that 5 years of adjuvant tamoxifen therapy improved event-free and overall survival rates versus 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 or 5 more years of tamoxifen. [30] It found that placebo increased disease-free survival versus 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. [31]

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). [28] For 5 years of tamoxifen treatment, this resulted in a cumulative risk over 10 years of two 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. [32] 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). [28]

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 [33] 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. [34] Women completed loco-regional therapy and at least four 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 disease-free survival event: 127/1694 [7.5%] with 1 year of trastuzumab *v* 220/1693 [13.0%] with observation; HR 0.54, 95% CI 0.43 to 0.67). [34] 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). [34] Outcomes with 2 years of trastuzumab were not reported.

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). [35] 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). [35]

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 [7.9%] with 1 year of trastuzumab *v* 75/1710 [4.4%] with observation, P less than 0.001; severe congestive heart failure: 9/1677 [0.54%] with 1 year of trastuzumab *v* 0/1710 [0%] with observation, P = 0.002). [34] It found that left ventricular ejection fraction decreased in a significantly higher proportion of women with trastuzumab than with observation (113/1677 [6.7%] with trastuzumab *v* 34/1710 [2.0%] with observation; P less than 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). [35] The RCT found no differences in any other common toxicity criteria (data not reported). [35]

Comment: In two of the RCTs, enrolment was closed after first interim analysis by the data safety monitoring boards of each trial. [34] [35] Trastuzumab, a monoclonal antibody, led to decreases in the initial peak of recurrences during the first 2–3 years, with a projected absolute benefit of 18% at 5 years. [36] 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, [35] 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) individuals about whether to start trastuzumab during or after chemotherapy, and current expert opinion appears to favour continuing the trastuzumab for 1 year with 3-monthly ECHOs to assess cardiac function. Patients with HER 2+ tumours by immunohistochemistry should have the appropriate HER2 status assess by FISH.

OPTION ADJUVANT TAXANES New

Treatment success
Adjuvant taxoid regimens compared with standard anthracycline based regimens Adjuvant taxoid regimens are more effective at increasing disease-free survival in women with breast cancer who are at high risk of relapse, as defined by node positivity (moderate-quality evidence).

Mortality
Adjuvant taxoid regimens compared with standard anthracycline based regimens Adjuvant taxoid regimens are more effective at improving 5-year overall survival rates in women with node-positive early breast cancer (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits: We found six RCT phase III trials (1016 to 3121 participants) in women with breast cancer at high risk of relapse, as defined by node positivity, that found a statistically significant disease-free survival

benefit, or improved response rate, for adjuvant taxoid regimens compared with standard anthracycline-based therapy in the adjuvant setting. [37] [38] [39] [40] [41] [42] Out of these six studies, four involved docetaxel. [37] [39] [41] [42] The RCTs used a variety of trial designs and comparisons of different regimens. We have reported two of the most robust studies in detail below. [39] [41] The first RCT randomised 1491 women with axillary node-positive breast cancer to six cycles of treatment with either docetaxel plus doxorubicin and cyclophosphamide (TAC) or fluorouracil plus doxorobucin and cyclophosphamide (FAC) as adjuvant chemotherapy after surgery. [39] The primary end-point was disease-free survival. The median follow-up was 55 months. The RCT found that TAC significantly increased the estimated rates of disease-free survival compared with FAC at 5 years (75 % with TAC *v* 68 % with FAC; P = 0.001). [39] After adjustment for nodal status, TAC was associated with a statistically significant 28% reduction in the risk of relapse compared with FAC (HR 0.72, 95% CI 0.59 to 0.88). The estimated rates of overall survival at 5 years were 87% with TAC compared with 81% with FAC. The RCT found that treatment with TAC resulted in a significant reduction in the risk of death compared with FAC (30% reduction; HR 0.7, 95% CI 0.53 to 0.91; P = 0.008). The second RCT compared six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) versus a sequential regimen of three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant treatment in 1999 women with node-positive early breast cancer. [41] Women who were hormone receptor-positive received tamoxifen for 5 years after chemotherapy. Median follow-up was 60 months. The RCT found that 5-year disease-free survival rates were significantly improved with FEC-D compared with FEC alone (78.4% with FEC-D *v* 73.2% with FEC; P = 0.012). A multivariate analysis adjusted for prognostic factors found an 18% reduction in the relative risk of relapse with FEC-D (HR 0.82, 95% CI 0.69 to 0.99; P = 0.34). The RCT found that FEC-D significantly improved 5-year overall survival rates compared with FEC (5-year overall survival rates: 90.7% with FEC-D *v* 86.7% with FEC; HR 0.73, 95% CI 0.56 to 0.94). [41]

Harms:

In one RCT, the incidence of grade 3 or 4 neutropenia was significantly higher with docetaxel plus doxorubicin and cyclophosphamide (TAC) compared with fluorouracil plus doxorobucin and cyclophosphamide (FAC) (66% with TAC *v* 49% with FAC; absolute numbers not reported; P less than 0.001). [39] The RCT found that rates of febrile neutropenia were 25% with TAC compared with 3% with FAC (P less than 0.001), and that grade 3 or 4 infections occurred in 4% of women with TAC compared with 2.% of women with FAC (P = 0.05). It reported that no deaths occurred as a result of infection. It reported that two women in each group died during treatment, and congestive heart failure and acute myeloid leukemia occurred in less than 2% of the women in each group. [39] In another RCT, the incidence of grade 3 to grade 4 neutropenia, and the incidence of nausea and vomiting, were significantly higher with FEC (fluororubacin, epirubicin, and cyclophosphamide) compared with FEC followed by docetaxel (neutropenia on day 21: 33.6% with FEC *v* 28.1% with FEC-D, P = 0.008; nausea and vomiting grade 3–4: 20.5% *v* 11.2%, P less than 0.001). [41] It found that docetaxel was associated with more febrile neutropenia in the fourth cycle, stomatitis, oedema, and nail disorders (febrile neutropenia in the 4th cycle: 1% with FEC *v* 4.6% with FEC-D, P value not reported; stomatitis grade 3–4 cycles 4–6: 2% *v* 4.0%, P = 0.03; moderate or severe oedema: 0.3% *v* 4.8%, P less than 0.001; nail disorders: 1% *v* 10.3%, P less than 0.001). Although rare, it found that there were fewer cardiac events after FEC-D (any cardiac events reported as serious adverse event: 1.3% with FEC *v* 0.4% with FEC-D, P = 0.03), attributable mainly to the lower anthracycline cumulative dose. [41]

Comment:

Clinical guide: While in England and Wales the National Institute of Clinical Excellence has approved TAC, nearly all clinicians however have indicated their preference to use docetaxel as part of the FEC-T regimen as per the PACS 01 study. [41] The rationale for favouring FEC-T over TAC is based on cost, capacity issues, and data reported in the PACS 01 [41] and BCIRG 001 [39] studies, in particular the rate of haematological toxicities, specifically febrile neutropenia and the need for 7 days of primary prophylactic 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 favorable safety profile. In other words, FEC followed by docetaxel, FEC-T, buys efficacy with lower toxicity and costs (less G-CSF).

OPTION LESS EXTENSIVE MASTECTOMY

Treatment success

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

Mastectomy compared with breast conservation 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).

Radical mastectomy compared with quandrantectomy plus radiotherapy Radical mastectomy, and quandrantectomy plus radiotherapy seem to be equally effective at reducing all-cause mortality at 20 years (moderate-quality evidence).

Lumpectomy (with or without radiotherapy) compared with total mastectomy Lumpectomy (with or without radiotherapy) and total mastectomy seem to be equally effective at reducing mortality at 20 years (moderate-quality evidence).

Modified radical mastectomy compared with lumpectomy plus axillary dissection plus radiotherapy Modified radical mastectomy, and lumpectomy plus axillary dissection plus radiotherapy seem to be equally effective at improving overall survival at 20 years (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits:

Comparisons between supraradical, radical, and total mastectomy:
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). [43] 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).

Comparisons between radical, total, and simple mastectomy:
We found one systematic review (as above, search date not reported, 4 RCTs, 1296 women with operable breast cancer), which compared radical or total mastectomy versus simple mastectomy. [43] 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 = 0.8). 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). [44]

Mastectomy versus breast conservation:
We found two systematic reviews. [43] [45] The first review (search date 1995, 6 RCTs) compared breast conservation versus mastectomy. [45] 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 second 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). [43] 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). Three RCTs included in the reviews have now reported 20-year follow-up results. [46] [47] [48] The first RCT (701 women with breast cancer less than 2 cm diameter) found no significant difference between radical mastectomy and quadrantectomy plus radiotherapy for all-cause mortality at 20 years (death rate about 42% in both groups; P = 1.0). [46] The second RCT (1851 women) compared lumpectomy alone,

lumpectomy plus radiotherapy, and total mastectomy. [47] It found no significant difference between lumpectomy (with or without radiotherapy) and total mastectomy in mortality at 20 years (HR lumpectomy alone *v* mastectomy 1.05, 95% CI 0.90 to 1.23; HR lumpectomy plus radiotherapy *v* mastectomy 0.97, 95% CI 0.77 to 1.06). The third RCT (237 women) found no significant difference between modified radical mastectomy and lumpectomy plus axillary dissection plus radiotherapy in overall survival or in disease-free survival at 20 years (AR for overall survival: 58% with mastectomy *v* 54% with lumpectomy, P = 0.67; AR for disease-free survival: 67% with mastectomy *v* 63% with lumpectomy, P = 0.64). [48]

Different extents of local excision in breast conservation:
We found no systematic review but found one RCT (705 women), which compared lumpectomy versus quadrantectomy. [49] 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). [50] We found no RCTs comparing wide local excision (complete excision microscopically) versus quadrantectomy.

Harms:

More extensive surgery results in a poorer cosmetic result. Between 60–90% of women having breast conservation have an excellent or good cosmetic result (median 83%, 95% CI 67% to 87%). [49] [51] [52] [53] [54] [55] [56] [57] [58] [59] 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. [49] 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). [49] Only isolated small studies have shown no correlation between extent of surgical excision and cosmesis. [57]

Comment:

The link between completeness of excision and local recurrence after breast conservation has been evaluated in 16 centres. [50] 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 play 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 44 .

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. [60] 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 with chemotherapy alone. [60] 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

Treatment success

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

Breast-conserving surgery plus radiotherapy compared with mastectomy Breast-conserving surgery plus radiotherapy seems to be equally 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 plus radiotherapy compared with breast-conserving surgery alone Breast-conserving surgery plus radiotherapy is more effective at 15 years at reducing mortality due to breast cancer, and all-cause mortality (moderate-quality evidence).

Breast-conserving surgery plus radiotherapy compared with mastectomy Breast-conserving surgery plus radiotherapy seems to be equally effective as mastectomy at improving overall survival at 10–20 years (moderate-quality evidence).

Radical mastectomy compared with quandrantectomy plus radiotherapy Radical mastectomy seems to be equally effective as quandrantectomy plus radiotherapy at reducing all-cause mortality at 20 years (moderate-quality evidence).

Lumpectomy (with or without radiotherapy) compared with total mastectomy Lumpectomy (with or without radiotherapy), and total mastectomy seem to be equally effective at reducing mortality at 20 years (moderate-quality evidence).

Modified radical mastectomy compared with lumpectomy plus axillary dissection plus radiotherapy Modified radical mastectomy seems to be equally effective as lumpectomy plus axillary dissection plus radiotherapy at improving overall survival at 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 44 .

Benefits: **Breast-conserving surgery plus radiotherapy versus breast-conserving surgery alone:** We found one systematic review, [61] which 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 less than 0.00001). Subgroup analyses suggested that the proportional reduction in local recurrence was similar in women of different ages and tumour characteristics.One RCT included in the review has now reported long-term results with a median follow-up period of 13.7 years. [62] The improvement in local control with the addition of radiotherapy to breast-conserving surgery was confirmed (400 women; 20 year local breast recurrence: 28.6% with breast-conserving surgery plus radiotherapy *v* 49.8% 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 to1.28; P = 0.59). [62]

Breast-conserving surgery plus radiotherapy versus mastectomy:
We found one systematic review (search date not reported, 9 RCTs, 4891 women) [43] and one additional RCT, [63] which compared breast radiotherapy after breast-conserving surgery versus simple or modified radical mastectomy in women with invasive breast cancer. The review found no significant difference in annual risk of death over 10 years (OR 1.02, CI presented graphically; P = 0.7) or annual risk of any recurrence or local recurrence (6 RCTs, 3107 women; overall OR for any recurrence: mastectomy *v* breast conservation plus radiotherapy 0.96, 95% CI 0.88 to 1.04; AR for local recurrence: 6.2% with radiotherapy after breast conservation surgery *v* 5.9% with radical mastectomy; P value reported as not significant). [43] Three RCTs included in the review have now reported 20-year follow-up results. [46] [47] [48] The first RCT (701 women with breast cancer less than 2 cm diameter) found no significant difference between radical mastectomy and quadrantectomy plus radiotherapy for all-cause mortality at 20 years (death rate about 42% in both groups; P = 1.0). [46] The second RCT (1851 women) compared lumpectomy alone, lumpectomy plus breast radiotherapy, and total mastectomy. [47] It found no significant difference between lumpectomy plus radiotherapy and total mastectomy for mortality at 20 years (HR lumpectomy plus radiotherapy *v* mastectomy 0.97, 95% CI 0.77 to 1.06). The third RCT (237 women) found no significant difference between modified radical mastectomy and lumpectomy plus axillary clearance plus radiotherapy in overall survival or disease-free survival at 20 years (AR for overall survival: 58% with mastectomy *v* 54% with lumpectomy, P = 0.67; AR for disease-free survival: 67% with mastectomy *v* 63% with lumpectomy, P = 0.64). [48] One additional RCT (187 women) found no significant difference in overall or disease-free survival between breast-conserving surgery plus radiotherapy and modified radical mastectomy at 40 months (overall survival: 94.1% with breast conservation therapy plus radiotherapy *v* 93.7% with mastectomy; disease-free survival: 93.9% with breast-conserving surgery plus radiotherapy *v* 89.2% with mastectomy; P less than 0.05 for both comparisons). [63] The incidence of loco-regional recurrence was similar in the two groups (2/76 [2.6%] with breast-conserving surgery plus radiotherapy *v* 2/111 [1.8%] with mastectomy; significance not reported).

Harms:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery alone:
The review [61] 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:
The 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). [43]

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. [64] The study (1984–1989; 837 women) [64] 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). [64]

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. [6] 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%). [65] 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 in 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). [61] Three recent RCTs included in the review, with data beyond 10 years, did not find an excess of cardiac deaths. [66] [67] [68] 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 5–6 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 postmastectomy 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. [6] 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 appears 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 prior to 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 appears to have little effect on local control in the absence of radiotherapy.

OPTION RADIOTHERAPY PLUS TAMOXIFEN AFTER BREAST-CONSERVING SURGERY (REDUCED LOCAL RECURRENCE RATES)

Treatment success

Breast conserving surgery plus radiotherapy compared with breast-conserving surgery plus tamoxifen Radiotherapy plus tamoxifen after breast-conserving surgery is more effective at 5 years at reducing ipsilateral or local recurrences (moderate-quality evidence).

Mortality

Radiotherapy plus tamoxifen compared with tamoxifen alone Radiotherapy plus tamoxifen seems to be equally effective as tamoxifen alone at improving survival in women who have undergone breast-conserving surgery (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 44 .

Benefits:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery plus tamoxifen:

We found no systematic review but found three RCTs. [64] [69] [70] The first RCT (1009 women after lumpectomy for node-negative invasive breast cancer 1 cm or less, 80% were aged 50 years or over), which compared three treatments: radiotherapy (started 2 weeks after surgery, 50 Gy over 5 weeks with or without external beam boost), radiotherapy plus tamoxifen, and tamoxifen alone. [64] It found that radiotherapy (with or without tamoxifen) 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* 9/334 [3%] with radiotherapy plus tamoxifen *v* 45/334 [14%] with tamoxifen alone; HR for radiotherapy alone *v* tamoxifen alone 0.51, 95% CI 0.31 to 0.84, P = 0.008; HR for radiotherapy plus tamoxifen *v* tamoxifen alone 0.19, 95% CI 0.09 to 0.39, P less

than 0.001; HR for radiotherapy plus tamoxifen *v* radiotherapy alone 0.37, 95% CI 0.17 to 0.80, P = 0.01). 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 the three treatments (survival: 312/332 [94%] with radiotherapy alone *v* 314/334 [94%] with tamoxifen alone *v* 312/334 [93%] with radiotherapy plus tamoxifen, P = 0.93; events: 61/332 [18%] with radiotherapy alone *v* 74/334 [22%] with tamoxifen alone *v* 52/334 [16%] with radiotherapy plus tamoxifen, P = 0.08). [71] The second RCT (769 women with primary breast cancer, aged over 50 years, who had undergone breast-conserving surgery for an invasive adenocarcinoma, tumour diameter 5 cm or less, histologically node-negative 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). It found that radiotherapy plus tamoxifen increased disease-free survival rates and reduced recurrence and rate of relapse in the ipsilateral breast versus 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 less than 0.001; AR for disease-free survival: 84% with tamoxifen alone *v* 91% with radiotherapy plus tamoxifen, P = 0.004). [69] A subgroup analysis found greater benefits in local relapse rates in women with T1, receptor-positive tumours at 5 years (3.2% with receptor-positive tumours *v* 7.8% with receptor-negative or T2 tumours). [69] The third RCT (women aged 70 years or over with clinical stage I 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. It found that radiotherapy 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 less than 0.01; time to mastectomy: P = 0.15, no further details reported). [70] There was no significant difference between treatment groups in time to distant metastasis (P = 0.97) or overall survival rates (P = 0.94). [70]

Harms:

Breast-conserving surgery plus radiotherapy versus breast-conserving surgery plus tamoxifen:

The first 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). [64] The third RCT found that more women experienced breast pain and skin fibrosis or retraction following treatment with tamoxifen plus radiotherapy (P less than 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 less than 0.05 for all outcomes). [70]

Quality of life:

A more recent prospective study (1992–2000) [72] 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). [72]

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. [6] 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%). [65] 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 in 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). [61] Three recent RCTs included in the review, with data beyond 10 years, did not find an excess of cardiac deaths. [66] [67] [68] 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 5–6 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:

One poor quality RCT (361 women with receptor positive breast cancer) compared the effects of radiotherapy versus tamoxifen versus radiotherapy plus tamoxifen on recurrence rates after breast-conserving surgery. It found no significant difference between treatments after a median follow-up of 5.9 years (risk of recurrence: 0.35 with breast-conserving surgery plus radiotherapy *v* 0.25 with breast-conserving surgery plus tamoxifen *v* 0.38 with breast-conserving surgery plus radiotherapy plus tamoxifen *v* 1.00 with breast-conserving surgery alone [reference group]). [73] 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 postmastectomy 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. [6] 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 appears 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 prior to 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 appears to have little effect on local control in the absence of radiotherapy.

OPTION RADIOTHERAPY AFTER MASTECTOMY

Treatment success

Radiotherapy after mastectomy compared with mastectomy alone Radiotherapy after mastectomy (alone, with axillary clearance, or with axillary sampling) may be more effective at reducing the 5-year risk of isolated local recurrence in women with node-positive disease (low-quality evidence).

Mortality

Radiotherapy after mastectomy compared with mastectomy alone In women with node-positive disease, radiotherapy may be more effective than no radiotherapy after mastectomy plus axillary clearance at reducing the 15-year risk of breast cancer mortality but may be equally effective as radiotherapy alone or after mastectomy plus axillary sampling (low-quality evidence).

Note

Women at high risk of recurrence include those with more axillary node involvement, larger tumours, higher histological grade, lymphovascular invasion, and involvement of tumour margins.

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 44 .

Benefits:

Radiotherapy after mastectomy versus mastectomy alone:

We found one systematic review (search date not reported, 36 RCTs; see comment below), which compared mastectomy versus mastectomy followed by radiotherapy to the chest wall. [61] Seven RCTs were of mastectomy alone (5597 women; 3318 node-negative; 2279 node-positive), four RCTs of mastectomy plus axillary sampling (647 women; 449 node-negative; 198 node-positive), and 25 of mastectomy plus axillary clearance (9933 women; 1428 node-negative; 8505 node-positive). 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 less than 0.00001), after mastectomy plus axillary sampling (14% with radiotherapy *v* 50% with no radiotherapy; rate ratio 0.23, CI presented graphically; P less than 0.00001), and after mastectomy alone (12% with radiotherapy *v* 34% with no radiotherapy; rate ratio 0.34, CI presented graphically; P less than 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 (2.3% with radiotherapy *v* 6.3% with no radiotherapy; rate ratio 0.41, CI presented graphically; P = 0.0002), after mastectomy plus axillary sampling (6.1% with radiotherapy *v* 24.5% with no radiotherapy; rate ratio 0.32, CI presented graphically; P less than 0.00001), and after mastectomy alone (6% with radiotherapy *v* 23% with no radiotherapy; rate ratio OR 0.33, CI presented graphically; P less than 0.00001). In women with node-negative disease, radiotherapy 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).

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]). [74] It found that radiotherapy reduced loco-regional recurrences among both pre 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 less than 0.05; postmenopausal women, RH 0.43, 95% CI 0.30 to 0.63, P less than 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 less than 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 no significant difference, P value not provided). 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). [74] However, the period of enrollment of the RCTs were long (between 1976 to 1990), inclusion criteria and randomisation were modified over the course of the studies, and the chemotherapy regimen used was modfied on a number of occasions. [74] 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. [74]

Harms: See harms of radiotherapy after breast-conserving surgery, p 17 . Three RCTs included in the review of total nodal irradiation after mastectomy in high-risk disease found no significant increase in cardiac mortality. [66] [67] [68] [75]

Comment: The RCTs in the large systematic review [61] were heterogeneous, varying in randomisation processes, areas irradiated, use of systemic treatment, radiotherapy doses, fractionation, and treatment schedules. We found little good evidence to identify which women should have postmastectomy radiotherapy to prevent local recurrence. One review of retrospective data found that extent of axillary node involvement, larger tumour size, higher histological grade, presence of lymphovascular invasion, and involvement of tumour margins increased the absolute risk of local recurrence or mortality. [76] [77] [78] [79] One non-systematic review (36 RCTs, 13,199 women) comparing radiotherapy after mastectomy versus no radiotherapy assessed the effects of dose and target volume on overall survival. [80] It found that radiotherapy after mastectomy delivered with an optimal biologically equivalent dose to an appropriate clinical target volume significantly increased overall survival at up to 10 years. We found no evidence that reduction in relative risk of local recurrence was affected by age, nodal status, receptor status, tumour grade, or tumour size, or that the effect of radiotherapy on mortality varied significantly with extent of surgery, type of radiotherapy (megavoltage or orthovoltage), years the RCTs commenced or completed recruitment, or whether systemic treatment was given. [76]

Clinical guide: Current expert opinion and evidence based treatment guidelines suggest that high-risk patients for loco-regional recurrence should be recommended for radiotherapy. These patients

would include those with lymph node positivity (particularly when more than 3 axillary nodes are involved with tumour), positive surgical margins post-mastectomy and larger tumour size (especially more than 5cm). Post-mastectomy radiotherapy should also be considered when patients have lesser nodes involved, or smaller tumours, particularly when there are a number of other adverse features (such as 1–3 nodes, receptor negativity, lymphvascular space invasion), though clinical trials are currently underway to specifically address this question, including the use of radiotherapy in elderly patients.

OPTION RADIOTHERAPY AFTER MASTECTOMY IN WOMEN NOT AT HIGH RISK OF LOCAL RECURRENCE

Treatment success

Radiotherapy after mastectomy compared with mastectomy alone Radiotherapy after mastectomy (alone, with axillary clearance, or with axillary sampling) may be more effective at reducing the 5-year risk of isolated local recurrence in women with node-negative disease (low-quality evidence).

Mortality

Radiotherapy after mastectomy compared with mastectomy alone In women with node-negative disease, radiotherapy may increase the15-year risk of breast cancer mortality compared with no radiotherapy after mastectomy plus axillary clearance but may be equally effective as radiotherapy after mastectomy plus axillary sampling (low-quality evidence).

Note

Women at high risk of recurrence include those with more axillary node involvement, larger tumours, higher histological grade, lymphovascular invasion, and involvement of tumour margins.

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 44 .

Benefits: **Radiotherapy after mastectomy versus mastectomy alone:**
See benefits of radiotherapy after mastectomy, p 21 .

Harms: See harms of radiotherapy after breast-conserving surgery, p 17 . Three RCTs included in the review of total nodal irradiation after mastectomy in high-risk disease found no significant increase in cardiac mortality. [66] [67] [68] [75]

Comment: We found little good evidence to identify which women should have postmastectomy radiotherapy to prevent local recurrence. One review of retrospective data found that extent of axillary node involvement, larger tumour size, higher histological grade, presence of lymphovascular invasion, and involvement of tumour margins increased the absolute risk of local recurrence or mortality. [76] [77] [78] [79] One non-systematic review (36 RCTs, 13,199 women) comparing radiotherapy after mastectomy versus no radiotherapy assessed the effects of dose and target volume on overall survival. [80] It found that radiotherapy after mastectomy delivered with an optimal biologically equivalent dose to an appropriate clinical target volume significantly increased overall survival at up to 10 years. We found no evidence that reduction in relative risk of local recurrence was affected by age, nodal status, receptor status, tumour grade, or tumour size, or that the effect of radiotherapy on mortality varied significantly with extent of surgery, type of radiotherapy (megavoltage or orthovoltage), years the RCTs commenced or completed recruitment, or whether systemic treatment was given. [76]

Clinical guide:

Current expert opinion and evidence based treatment guidelines suggest that high-risk patients for loco-regional recurrence should be recommended for radiotherapy. These patients would include those with lymph node positivity (particularly when more than 3 axillary nodes are involved with tumour), positive surgical margins post-mastectomy and larger tumour size (especially more than 5cm). Post-mastectomy radiotherapy should also be considered when patients have lesser nodes involved, or smaller tumours, particularly when there are a number of other adverse features (such as 1–3 nodes, receptor negativity, lymphvascular space invasion), though clinical trials are currently underway to specifically address this question, including the use of radiotherapy in elderly patients.

OPTION PRIMARY CHEMOTHERAPY

Treatment success

Primary chemotherapy compared with adjuvant chemotherapy Primary chemotherapy seems to more effective at reducing mastectomy rates but not at reducing loco-regional recurrences at 4 years (moderate-quality evidence).

Mortality

Primary chemotherapy 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 44 .

Benefits:

Survival:

We found no systematic review but found five RCTs, which compared primary chemotherapy versus adjuvant chemotherapy. [81] [82] [83] [84] [85] 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. [81] 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). [81] However, the final analysis at 124 months showed that the survival improvement was no longer significant, with survival of about 55% in both groups. [86] The second RCT (414 women) compared four cycles of FAC (fluorouracil, adriamycin [doxorubicin], and cyclophosphamide) as primary or adjuvant chemotherapy. [82] 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. [87] The third RCT (309 women) compared four cycles of primary MM (mitoxantrone [mitozantrone], methotrexate) chemotherapy followed by surgery and four further cycles of MM versus surgery followed by eight cycles of adjuvant MM. [83] 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 four cycles of AC (adriamycin [doxorubicin], cyclophosphamide) as primary or adjuvant chemotherapy, found identical survival rates (67%) in the two groups at 60 months. [84] The fifth RCT (698 women) compared four cycles of fluorouracil, epirubicin, and cyclophosphamide, as primary or adjuvant chemotherapy. [85] It found no significant difference between primary and adjuvant chemotherapy in 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), or loco-regional 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. [84] [88] [89] 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 less than 0.005). [88] 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. [84] 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. [89]

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. [84] [88] [89] See harms of adjuvant combination chemotherapy, p 7 .

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. [84] [88] [89]

OPTION TOTAL NODAL RADIOTHERAPY

Treatment success

Radiotherapy after mastectomy (including total nodal irradiation) compared with mastectomy alone Radiotherapy (including total nodal irradiation) after mastectomy may be more effective at reducing the 5-year risk of isolated local recurrence in women with node-positive and node-negative disease (very low-quality evidence).

Mortality

Radiotherapy after mastectomy (including total nodal irradiation) compared with mastectomy alone We don't know whether radiotherapy (including total nodal irradiation) after mastectomy is more effective at reducing the 15-year risk of breast cancer mortality in women with node-positive and node-negative disease (very low-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits: We found one systematic review (search date not reported, 36 RCTs of postmastectomy radiotherapy), which included 26 RCTs of total nodal irradiation to the internal mammary chain, supraclavicular fossa, and axilla. [61] It found that postoperative radiotherapy reduced loco-regional 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 21 . 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 29 ; See harms of radiotherapy to the ipsilateral supraclavicular fossa, p 30 ; and See harms of axillary management, p 25 . Three RCTs included in the review found no increase in cardiac mortality because of radiotherapy. [66] [67] [68] [75]

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 remains unanswered. In terms of risk, the greatest risk of recurrence in most high-risk patients are 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, post-operative 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 four 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 undegoing 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 44 .

Benefits:

Axillary clearance versus axillary sampling:
We found no systematic review but found one RCT (466 women) in women having breast-conserving surgery. [90] The RCT compared complete axillary clearance (level I, II, and III dissection) versus four 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: 88.6% with axillary sampling *v* 82.1% 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). [43] 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. [43]

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 31 .

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. [90] It compared complete axillary clearance (level I, II, and III dissection) versus four 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, 25–50% 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). [90]

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 12–60%, with most studies suggesting that at least a third of women are affected. [91] 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 0–42%, with most studies reporting a rate of 20–30% 1 year after operation. [91] 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. [92] [93] One RCT found that a sample of four nodes provided sufficient information to categorise an axilla as histologically positive or negative. [94] 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. [92] [93]

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 progostic information against morbidity.

OPTION DIFFERENT PRIMARY CHEMOTHERAPY REGIMENS

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, adriamycin [doxorubicin], 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, adriamycin {doxorubicin}, vincristine, prednisolone]) at improving clinical response rates in women who have acheived complete or partial response to four cycles of CVAP (low-quality evidence). Primary treatment with docetaxel may be more effective than no primary treatment in women who have received four cycles of AC (adriamycin [doxorubicin], 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, adriamycin [doxorubicin], and 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 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 44 .

Benefits:

Standard versus dose intensified anthracycline based regimens:
We found no systematic review but found one RCT. [95] 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. [96] The RCT (174 women in the USA) compared conventional FAC (fluorouracil, adriamycin [doxorubicin], and 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. [97] 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. [98] [99] The first RCT (104 women who had achieved complete or partial clinical response to four cycles of CVAP [cyclophosphamide, adriamycin {doxorubicin}, vincristine, prednisolone]) compared a further four cycles of CVAP versus four cycles of docetaxel. [98] 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). [98] In the second RCT (2411 people), all women received four cycles of AC (adriamycin [doxorubicin], cyclophosphamide) and were then randomly allocated to three regimens: surgery alone, four cycles of docetaxel followed by surgery, or surgery followed by four cycles of docetaxel. [99] 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 less than 0.001). The final results, which will also examine the effects of adjuvant docetaxel, are awaited.

Navelbine based regimens:
We found no systematic reviews 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. [100] 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 less than 0.05); however, this was not associated with a survival benefit. [100]

Harms:

Standard versus dose intensified anthracycline based regimens:
There were similar numbers of serious adverse events requiring hospitalisation in the groups (60 events with CEF *v* 68 events with ECFi; P value not reported). The dose intensified ECFi regimen increased nausea and vomiting, and induced more grade 3 and 4 anaemia, but there were fewer febrile neutropenic episodes compared with CEF (AR for nausea: 11.8% with CEF *v* 22.3% with ECFi; vomiting: 10.9% with CEF *v* 18.8% with ECFi; anaemia: 16.3% with CEF *v* 50.9% with ECFi; febrile neutropenia: 14% with CEF *v* 8.4% with ECFi; no P values reported for comparisons).

FAC versus paclitaxel:
In the RCT comparing FAC versus paclitaxel, rates of septic neutropenia (53% with paclitaxel *v* 21% with FAC) and granulocyte colony stimulating factor usage (56% with paclitaxel *v* 25% with FAC) were higher in women taking paclitaxel. [96]

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. [95] 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, 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. [101] Clinical trials are currently underway addressing different regimens in the primary setting, including the use of taxane-platinum regimens which may be associated with lower long-term toxicities, including leukaemia and cardiac failure when compared to anthracyclines.

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 (moderate-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).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits: We found one systematic review, [102] one additional RCT, [103] [104] and one subsequent RCT [105] of less than whole-breast radiotherapy after breast-conserving surgery. The review (search date 2002) compared intraoperative radiotherapy versus standard postoperative radiotherapy in women receiving breast-conserving surgery, and found no fully published RCTs (see comment). [102] The 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). [103] [104] 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). [103] [104] The subsequent RCT found no significant difference in local recurrence, distant recurrence, or survival between tumour bed radiotherapy and whole-breast radiotherapy at 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). [105] The RCT aimed to recruit 400 women, but it closed early because of problems with recruitment; therefore, the RCT may have been underpowered to detect a clinically important difference. [105]

Harms: The additional 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). [103] [104] The differences may be related to radiation fractionation, rather than the target field area. The subsequent RCT gave no information on adverse effects. [105]

Comment: The review found one RCT, which was published in abstract form only, making it difficult to assess study quality. [102] The abstract reported similar levels of "good to excellent" cosmetic result with intraoperative 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. 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 intraoperative technique is used, it may be possible to place radiotherapy dose more accurately within the excision area. [106] There are several techniques under consideration for less than whole-breast radiotherapy: intraoperative brachytherapy; delayed brachytherapy, intraoperative external beam techniques (electrons, low energy x rays), and delayed external beam techniques. We found only two fully published RCTs, [103] [104] [105] 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 intraoperative 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. [106]

Clinical guide: Studies are currently attempting to address the question as to whether partial breast irradiation may be sufficient treatment for some sub-groups of breast cancer. Until those studies are complete, and the follow-up data 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 44 .

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. [107] 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 17 . Radiotherapy to the internal mammary chain is more likely to affect the heart compared with other types of radiotherapy. [108]

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. [109] [110] The risk of internal mammary chain recurrence is low, and after modified radical mastectomy alone is 2%. [111] 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. [43] [112] [113] Recent 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. [66] [67] [75] Another RCT of internal mammary chain irradiation has started recently (sponsored by the European Organisation for Research and Treatment of Cancer [EORTC]).

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 loco-regional recurrence: see benefits of radiotherapy after breast-conserving surgery, p 17 ; radiotherapy after mastectomy, p 21 ; and radiotherapy to the internal mammary chain, p 29 . [61] 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 [1.3%] with radiotherapy *v* 37/686 [5.4%] with no radiotherapy; CI not reported). [75]

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. [65] [114] 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 3 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, 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 44 .

Benefits:

Sentinel node biopsy versus axillary procedures (sampling or clearance):
We found two 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). [115] [116] In the first RCT, both groups received radiation therapy after surgery for 8 weeks. It found that sentinel node biopsy improved postoperative pain and arm mobility versus 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 with sentinel node biopsy *v* 61/100 with axillary dissection, P value not reported; 80–100% arm mobility: 100/100 with sentinel node biopsy *v* 79/100 with axillary dissection, P value not reported; breast cancer events: 13/259 with sentinel node biopsy *v* 21/257 with axillary dissection, P = 0.13; see comment below). [115] It found no significant difference in overall survival between treatments (P = 0.15). [115] The second RCT found that sentinel node biopsy significantly reduced postoperative arm swelling (298 people with early breast cancer; OR for subjective arm swelling 0.30, 95% CI 0.18 to 0.68; P = 0.004) and loss of sensation (AR of no loss of sensation: 34% with sentinel node biopsy *v* 16% with axillary dissection; OR 2.7, 95% CI 1.5 to 5.0) compared with axillary dissection. 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: 14% with sentinel node biopsy *v* 21% with axillary dissection, OR 0.60, 95% CI 0.33 to 1.11; risk of seroma formation in node-negative women: 11% with sentinel node biopsy *v* 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. [116]

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 toward fewer allergic reactions with smaller volumes of blue dye, although this was not significant. [117]

Sentinel node biopsy versus axillary procedures:
Neither RCT reported on harms specific to sentinel node biopsy. [115] [116]

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. [118] The guidelines also point out that the clinical significance of isolated cancer cells detected by detailed pathological examination of sentinel nodes is unknown.

Assessment of performance of sentinel node biopsy test:
We found one systematic review (search date not stated, 69 studies, 8059 people), which included studies assessing the diagnostic performance of sentinel node biopsy. [119] 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 less than 0.01) and studies with fewer successfully mapped nodes (P = 0.009). [119]

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 due to positive sentinel node status. These women were included in the analysis for the sentinel node group. [115] We found three preliminary publications of two RCTs comparing sentinel node biopsy versus axillary procedures. [120] [121] [122] 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. [120] 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. 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 less than 0.0001 for both outcomes). [121] The RCT found no significant difference between treatments in shoulder flexion and abduction, and internal and external rotation of the shoulder. [121] Results of the validation phase of this RCT suggest that indiscriminate removal of axillary nodes may worsen the morbidity of sentinel node biopsy. [121]

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

Mortality
Compared with conventional chemotherapy High-dose chemotherapy plus autologous stem cell transplantation seems to be equally effective as conventional chemotherapy at prolonging 3- 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 44 .

Benefits: We found one systematic review (search date 2004, 13 RCTs, 5064 women with early, poor prognosis breast cancer, multiple positive axillary lymph nodes, and no distant metastasis), which compared high-dose chemotherapy plus bone marrow or peripheral blood stem cell autograft versus conventional chemotherapy (see comment below). [123] 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 versus 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). [123] .

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 v 4/2529 [0.2%] with conventional chemotherapy; RR 8.58, 95% CI 4.13 to 17.80). [123]

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. [123] 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.

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

OPTION POSTOPERATIVE RADIOTHERAPY (IN WOMEN ALSO RECEIVING POSTOPERATIVE SYSTEMIC TREATMENT)

Treatment success

Post operative radiotherapy in women also receiving postoperative systemic treatment compared with no radiotherapy Postoperative radiotherapy may be more effective at reducing recurrences or at improving disease-free survival at 10 years in women who also receive chemotherapy or hormone therapy following mastectomy (very low-quality evidence).

Mortality

Post operative radiotherapy in women also receiving postoperative systemic treatment 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 44 .

Benefits:

We found no systematic review but found four RCTs. [67] [75] [124] [125] The first RCT (184 women, including some with stage III B disease, receiving premastectomy and postmastectomy chemoendocrine treatment) compared postmastectomy radiotherapy to the chest wall and regional lymphatics (45–50 Gy in 5 weeks) versus no radiotherapy. [124] However, 43% of the 184 women were excluded and there were more exclusions in the radiotherapy group, and it is impossible to ascertain what percentage of women were stage III B. 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 less than 0.05). [124] Due to 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) [125] 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). [125] Radiotherapy reduced loco-regional sites as first recurrence by 9%. The third RCT (1708 premenopausal women who had undergone mastectomy for stage II or III breast cancer) compared eight cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) chemotherapy plus radiotherapy to the chest wall and regional lymph nodes versus chemotherapy alone. [67] It found that addition of postoperative radiotherapy to adjuvant chemotherapy after surgery significantly reduced loco-regional 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). [67] The fourth RCT (1375 postmenopausal women, all with high-risk breast cancer, receiving adjuvant tamoxifen) found that postoperative radiotherapy significantly reduced loco-regional 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 less than 0.001; disease-free survival: 36% with radiotherapy *v* 24% without radiotherapy, P less than 0.001). [75] 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). [75] 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 provided; 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 17 . However, in stage III B 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 addressing directly stage III B 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. 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 SURGERY

Treatment success

Surgery 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 III B) rendered operable by prior chemotherapy (moderate-quality evidence).

Mortality

Surgery 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 III B) rendered operable by prior chemotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits:

Surgery alone versus radiotherapy alone:

We found no systematic reviews but found two RCTs, which compared surgery alone with radiotherapy alone as local treatment. [126] [127] In the first RCT (113 women with stage III breast cancer, 67% stage III B), women were given chemotherapy and 81% became operable; then 87 women were randomised to surgery or radiotherapy. [126] 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. [126] In the second RCT (132 women, 91% stage III B, 9% stage III A), all women received chemotherapy before randomisation to either surgery or radiotherapy. [127] 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). [127]

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 17 . However, in stage III B 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, [126] [127] 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

Mortality

Surgery compared with radiotherapy We don' t know whether surgery as sole local treatment is more effective at prolonging overall survival in women with locally advanced disease (stage III B) rendered operable by prior chemotherapy (moderate-quality evidence).

For GRADE evaluation of interventions for breast cancer (non-metastatic), see table, p 44 .

Benefits:

Radiotherapy alone versus surgery alone:

See benefits of surgery alone versus radiotherapy alone, p 34 .

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 17 . However, in stage III B 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 addressing directly stage III B 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, [126] [127] 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 LOW-DOSE RADIOTHERAPY

Mortality
Low-dose radiotherapy compared with tamoxifen We don't know whether low-dose 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 44 .

Benefits: **Low-dose radiotherapy versus tamoxifen:**
We found no systematic review but found one small RCT. [128] The RCT (143 women with locally advanced breast cancer) compared low-dose 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). [128]

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 17 . However, in stage III B 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 addressing directly stage III B 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, [126] [127] 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 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 loco-regional 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 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 44 .

Benefits:

Systemic treatment plus radiotherapy versus radiotherapy alone:
We found no systematic review but found three RCTs, [129] [130] [131] which compared radiotherapy versus radiotherapy plus systemic treatment (hormone treatment, chemotherapy, or both). The first RCT (410 women, most stage III B) [129] compared four treatments in a factorial design: radiotherapy; radiotherapy plus chemotherapy (CMF [cyclophosphamide, methotrexate, and fluorouracil] for 12 cycles); radiotherapy plus hormone treatment (ovarian irradiation for premenopausal women, tamoxifen for postmenopausal women); and radiotherapy plus chemotherapy plus hormone treatment. [129] Adding chemotherapy (P = 0.0002) or hormone treatment (P = 0.0007) to radiotherapy significantly delayed loco-regional recurrence, and adding both chemotherapy and hormone treatment had the greatest effect on delaying loco-regional recurrence (P = 0.0001). Adding chemotherapy or hormone treatment to radiotherapy reduced loco-regional 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 III B breast cancer) [130] compared three treatments: radiotherapy; radiotherapy plus chemotherapy (CMF for 12 cycles) plus tamoxifen; and chemotherapy (CMF alternating with adriamycin [doxorubicin] 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). [130] The third RCT (52 women with T4 breast cancer) compared an anthracycline chemotherapy regimen before radiotherapy versus similar radiotherapy alone. [131] Chemotherapy plus radiotherapy significantly increased initial loco-regional 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: 78.6% with chemotherapy plus radiotherapy *v* 45.8% with radiotherapy alone; P = 0.03). However, the proportion of women free of loco-regional 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 7).

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 III B) 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 loco-regional control in stage III B 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 due to small sample sizes in RCTs.

OPTION MULTIMODAL TREATMENT

Recurrence

Multimodal treatment compared with hormone treatment Multimodal treatment (primary chemotherapy, surgery, radiotherapy, and tamoxifen) seems to be 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 44 .

Benefits:

Multimodal treatment versus hormone treatment:
We found no systematic review but found one RCT (two publications). [132] [133] The RCT (108 women) compared multimodal treatment (primary chemotherapy, surgery, radiotherapy, and tamoxifen) with initial hormone treatment plus subsequent salvage treatments upon tumour progression. [132] [133] 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). [132] 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). [133]

Harms: In many RCTs, harms of treatment were not reported (see harms of adjuvant combination chemotherapy, p 7).

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 44 .

Benefits: **Adjuvant chemotherapy versus primary plus adjuvant chemotherapy:**
We found no systematic review but found one RCT. [134] The RCT (101 women with operable T4bN0–2 breast cancer) compared six cycles of adjuvant CEF (cyclophosphamide, epirubicin, 5-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. [134] 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). [134]

Harms: In many RCTs, harms of treatment were not reported (see harms of adjuvant combination chemotherapy, p 7).

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.
Combination chemotherapy Two or more cytotoxic drugs given intravenously every 3–4 weeks for 4–6 months.
FAC Chemotherapy regimen containing fluorouracil, adriamycin (doxorubicin), and cyclophosphamide.
Lumpectomy Removal of tumour with a 1 cm margin (macroscopically) around the palpable cancer.
Milan regimen A sequential regimen of single agent anthracycline followed by CMF.
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.
Ovarian ablation Surgical, medical, or radiation induced suppression of ovarian function in premenopausal women.
Quadrantectomy Tumour excised with greater-than or equal to 2 cm of normal surrounding breast tissue and with a segment of breast tissue from the periphery of the breast to the nipple.
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.
Systemic therapy Use of oral or intravenous treatments which affect the whole body.
TNM staging system See “staging of breast cancer”, above.
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).
Disease-free survival Means being alive with no local or distant recurrence or contralateral disease.
Early invasive breast cancer (stage I or II) is M0 with T1 or T2 (tumour diameter less-than or equal to 5 cm, 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 III A) is T3 (tumours more than 5 cm) and N1 (non-matted involved axillary nodes). Locally advanced breast cancer (stage III B) 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 IV) 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.
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.
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 (more than 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 loco-regional treatment (surgery and or radiotherapy) to the breast to downstage large primary cancers which would require mastectomy to improve chances of survival.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adjuvant taxanes (under question on treatments for primary operable breast cancer) New option added. Six RCTs included. [37] [38] [39] [40] [41] [42] Adjuvant taxanes categorised as Likely to be beneficial.
Adjuvant aromatase inhibitors (under question on treatments for primary operable breast cancer) Two further follow-up reports of a previously included RCT added; [20] [22] benefits and harms data enhanced, categorisation unchanged (Beneficial).
High-dose chemotherapy (under question on treatments for primary operable breast cancer) One previously included systematic review updated; [123] benefits and harms data enhanced, categorisation of 'high-dose chemotherapy plus autologous stem cell transplantation' unchanged (Likely to be ineffective or harmful).
Radiotherapy (under question on interventions after breast-conserving surgery for ductal carcinoma *in situ*) One RCT added [10] and one extended 10-year follow-up of a previously included RCT added; [9] benefits and harms data enhanced, categorisation of radiotherapy (reduced recurrence) unchanged (Likely to be beneficial).
Radiotherapy after breast-conserving surgery (under question on treatments for primary operable breast cancer) One extended follow-up of a previously included RCT added; [62] benefits data enhanced, categorisation of "radiotherapy after breast-conserving surgery (reduced local recurrence and breast cancer mortality compared with breast-conserving surgery alone)" as Beneficial and "radiotherapy plus tamoxifen after breast-conserving surgery (reduced local recurrence rates)" as Likely to be beneficial unchanged.
Radiotherapy after mastectomy (under question on treatments for primary operable breast cancer) One report of 2 RCTs added; [74] benefits and harms data enhanced, categorisation of 'radiotherapy after mastectomy in women at high risk of local recurrence' as Beneficial and 'radiotherapy after mastectomy in women not at high risk of local recurrence' as Trade off between benefits and harms unchanged.

Tamoxifen plus radiotherapy (under question on interventions 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.

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TABLE 1 **Staging of breast cancer (the individual terms are explained in the glossary) (see text).** [1]

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

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 7).** [85]

	Control (%)	Chemotherapy (%)	Absolute benefit (%)	SD (%)	Significance (two sided)
Age under 50 years					
Node +ve	41.4	53.8	+12.4	2.4	P less than 0.0001
Node –ve	71.9	77.6	+5.7	2.1	P = 0.01
Age 50–69 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 11).** [86]

	Control (%)	Tamoxifen (%)	Absolute benefit (%)	SD (%)	Significance (two sided)
Node +ve	50.5	61.4	+10.9	2.5	P less than 0.00001
Node –ve	73.3	78.9	+5.6	1.3	P less than 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*?									
3, 1 paper (2862) [7] [8] [9] [10]	Treatment success	Radiotherapy *v* no radiotherapy	4	0	0	0	0	High	
3, 1 paper (2862) [7] [8] [9] [10]	Mortality	Radiotherapy *v* no radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1, 1 paper (1804) [12] [13]	Treatment success	Tamoxifen plus radiotherapy *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1, 1 paper (1804) [12] [13]	Mortality	Tamoxifen plus radiotherapy *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (523) [14]	Treatment success	Tamoxifen plus radiotherapy *v* radiothera py	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 [15]	Mortality	Adjuvant aromatase inhibitors *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2, 2 papers (14068) [16] [17] [18] [19]	Treatment success	Adjuvant aromatase inhibitors *v* tamoxifen	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2, 2 papers (14068) [16] [17] [18] [19]	Mortality	Adjuvant aromatase inhibitors *v* tamoxifen	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
47 (18000) [24]	Treatment success	Adjuvant combination chemotherapy *v* no chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
47 (18000) [24]	Mortality	Adjuvant combination chemotherapy *v* no chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
not reported (3454) [24]	Treatment success	Different treatment durations compared with each other (prolonged adjuvant combination chemotherapy)	4	0	0	0	0	High	
not reported (3454) [24]	Mortality	Different treatment durations compared with each other (prolonged adjuvant combination chemotherapy)	4	0	0	0	0	High	
2 (3877) [26] [27]	Treatment success	Different doses compared with each other (enhancedose regimens of adjuvant combination chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3877) [26] [27]	Mortality	Different doses compared with each other (enhancedose regimens of adjuvant combination chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (5942) [24]	Treatment success	Anthracycline regimens compared with 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
11 (5942) [24]	Mortality	Anthracycline regimens compared with standard CMF regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
55 (37000) [28]	Treatment success	Adjuvant tamoxifen *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
55 (37000) [28]	Mortality	Adjuvant tamoxifen *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3887) [29]	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) [29]	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) [34]	Treatment success	Trastuzumab *v* observation (after chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3387) [34]	Mortality	Trastuzumab *v* observation (after chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3351) [35]	Treatment success	Trastuzumab *v* observation (during chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3351) [35]	Mortality	Trastuzumab *v* observation (during chemotherapy)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (at least 3490 women) [37] [38] [39] [40] [41] [42]	Treatment success	Adjuvant taxoid regimens *v* standard anthracycline based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (at least 3490 women) [37] [38] [39] [40] [41] [42]	Mortality	Adjuvant taxoid regimens *v* standard anthracycline based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (2090) [43]	Mortality	Supraradical, radical, and total mastectomy compared with each other	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (1296) [43]	Mortality	Radical/total mastectomy *v* simple mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1079) [44]	Mortality	Radical mastectomy v total mastectomy with or without axillary radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (3107) [43]	Treatment success	Mastectomy *v* breast conservation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (4438) [43] [45]	Mortality	Mastectomy *v* breast conservation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (701) [46]	Mortality	Radical mastectomy *v* quandrantectomy plus radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1851) [47]	Mortality	Lumpectomy with or without radiotherapy *v* total mastectomy	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 (237) [48]	Mortality	Modified radical mastectomy *v* lumpectomy plus axillary dissection plus radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (705) [49]	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) [60]	Treatment success	Ovarian ablation *v* no ablation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
12 (2102) [60]	Mortality	Ovarian ablation *v* no ablation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
10 (7311) [61] [62]	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
10 (7311) [61]	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
8 (3531) [43] [63] [48]	Treatment success	Breast-conserving surgery plus radiotherapy *v* mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (3294) [43] [63]	Mortality	Breast-conserving surgery plus radiotherapy *v* mastectomy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (2073) [64] [69] [70]	Treatment success	Breast-conserving surgery plus radiotherapy v breast-conserving surgery plus tamoxifen	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (2071) [64] [69] [70]	Mortality	Radiotherapy plus tamoxifen *v* tamoxifen alone (after breast-conserving surgery)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
36 (10982) [61]	Treatment success	Radiotherapy after mastectomy v mastectomy alone (in women at high risk of local recurrence)	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs
36 (10982) [61]	Mortality	Radiotherapy after mastectomy *v* mastectomy alone (in women at high risk of local recurrence)	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs
36 (5195) [61]	Treatment success	Radiotherapy after mastectomy *v* mastectomy alone (in women not at high risk of local recurrence)	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs
36 (5195) [61]	Mortality	Radiotherapy after mastectomy *v* mastectomy alone (in women not at high risk of local recurrence)	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs
4 (2802) [84] [88] [89] [85]	Treatment success	Primary chemotherapy *v* adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (3216) [81] [82] [83] [84] [85]	Mortality	Primary chemotherapy *v* adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
26 (not reported) [61]	Treatment success	Radiotherapy after mastectomy *v* mastectomy alone in women at high risk of local recurrence	4	−2	−1	0	0	Very low	Quality points deducted for incomplete reporting of results and for inclusion of RCTs without total nodal radiation. Consistency point deducted for heterogeneity between RCTs

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
26 (not reported) [61]	Mortality	Radiotherapy after mastectomy *v* mastectomy alone in women at high risk of local recurrence	4	−2	−2	0	0	Very low	Quality points deducted for incomplete reporting of results and for inclusion of RCTs without total nodal radiation. Consistency point deducted for conflicting results and for heterogeneity between RCTs
1 (466) [90]	Mortality	Axillary clearance *v* axillary sampling	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (4370) [43]	Treatment success	Axillary clearance *v* axillary radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (4370) [43]	Mortality	Axillary clearance *v* axillary radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (448) [95]	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) [95]	Mortality	Standard *v* dose intensified anthracycline based regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (174) [96]	Treatment success	FAC regimen (fluorouracil, adriamycin [doxorubicin], 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) [96]	Mortality	FAC regimen (fluorouracil, adriamycin [doxorubicin], 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) [97]	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) [98] [99]	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) [100]	Treatment success	Intra-arterial *v* intravenous administration	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (876) [103] [104] [105]	Treatment success	Less than whole-breast radiotherapy *v* whole breast radiotherapy	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
1 (168) [105]	Mortality	Less than whole-breast radiotherapy *v* whole breast radiotherapy	4	−1	−1	0	0	Moderate	Quality point deducted for sparse data and conflicting results
1 (270) [107]	Treatment success	Radiotherapy to the internal mammary chain *v* nointernal mammary chain irradiation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (270) [107]	Mortality	Radiotherapy to the internal mammary chain *v* nointernal mammary chain irradiation	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1375) [75]	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

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (498) [115] [116]	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) [115]	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 6 RCTs (at least 3015 women) [123]	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
13 (5064) [123]	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 greater than 5
What are the effects of interventions in locally advanced breast cancer (stage III B)?									
4 (3599) [67] [75] [124] [125]	Treatment success	Post-operative radiotherapy (in women also receiving postoperative systemic treatment) *v* no radiotherapy	4	−2	0	−1	0	Low	Quality poinst deducted for incomplete reporting of results and for weak methods. Directness points deducted for inclusion of women with different disease severities
4 (3599) [67] [75] [124] [125]	Mortality	Post-operative radiotherapy (in women also receiving postoperative systemic treatment) *v* no radiotherapy	4	−2	0	−1	0	Low	Quality poinst deducted for incomplete reporting of results and for weak methods. Directness points deducted for inclusion of women with different disease severities
2 (219) [126] [127]	Treatment success	Surgery alone *v* radiotherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (219) [126] [127]	Mortality	Surgery *v* radiotherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (143) [128]	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) [129] [130] [131]	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 points deducted for inclusion of women with less locally advanced breast cancer
3 (580) [129] [130] [131]	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 points deducted for inclusion of women with less locally advanced breast cancer
1, 1 publication (107) [132] [133]	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 2–5
1 (101) [134]	Mortality	Adjuvant chemotherapy *v* primary plus adjuvant chemotherapy	4	−1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Treatment success, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
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									