

Breast cancer (non-metastatic)

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

LIKELY TO BE BENEFICIAL

Radiotherapy (reduced recurrence)

Two RCTs identified by a systematic review found that radiotherapy after breast conserving surgery for ductal carcinoma *in situ* reduced local recurrence and invasive carcinoma compared with no radiotherapy after 4 and 8 years. However, they found no evidence of an effect on survival. One RCT in women having local excision found no significant difference between tamoxifen plus radiotherapy and radiotherapy alone in total invasive or ductal carcinoma *in situ* events after median follow up of 1 year.

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

One RCT found that adjuvant tamoxifen reduced breast cancer events in women who had undergone wide excision and radiotherapy after median follow up of 6 years, although subgroup analysis suggested that benefit may be limited to women with oestrogen receptor positive tumours. It found no evidence of an effect on survival. One RCT in women having local excision found no significant difference between tamoxifen plus radiotherapy and radiotherapy alone in invasive or ductal carcinoma *in situ* events after median follow up of 1 year.

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

BENEFICIAL

Adjuvant combination chemotherapy

One systematic review found that adjuvant combination chemotherapy reduced recurrence and improved survival at 10 years compared with no chemotherapy. The benefit seemed to be independent of nodal or menopausal status, although the absolute improvements were greater in women with node positive disease, and probably greater in younger women. 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.

Adjuvant tamoxifen (in women with oestrogen receptor positive tumours)

One systematic review found that adjuvant tamoxifen taken for up to 5 years reduced the risk of recurrence and death in women with oestrogen receptor positive tumours irrespective of age, menopausal status, nodal involvement, or the addition of chemotherapy. Five years of treatment was more effective than shorter durations, but available evidence did not find benefit associated with prolongation of treatment beyond 5 years. Tamoxifen slightly increased the risk of endometrial cancer and thrombotic complications, but we found no evidence of an overall adverse effect on non-breast cancer mortality.

Anthracycline regimens as adjuvant chemotherapy

One systematic review found that adjuvant regimens containing an anthracycline reduced recurrence, and improved survival compared with a standard multidrug ▶

chemotherapy (CMF) regimen at 5 years. Adverse effects of chemotherapy include nausea and vomiting, hair loss, bone marrow suppression, fatigue, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

Combined chemotherapy plus tamoxifen

One RCT found that adding chemotherapy to tamoxifen improved survival at 5 years in women with lymph node negative, oestrogen receptor positive early breast cancer. It found that adding combined chemotherapy to tamoxifen was associated with increased adverse effects such as nausea, neutropenia, alopecia, thromboembolism, and phlebitis.

Less extensive surgery (similar survival to more extensive surgery, and better cosmetic outcome)

Two systematic reviews and long term follow up of included RCTs found that more extensive surgery did not improve outcomes compared with less extensive surgery in women with early invasive breast cancer, providing that all local disease was excised. Cosmetic appearance is worse with more extensive surgery.

Ovarian ablation in premenopausal women

One systematic review found that in premenopausal women with early breast cancer, ovarian ablation improved survival compared with no ablation after 15 years follow up.

Radiotherapy after breast conserving surgery (reduced local recurrence and had similar survival rates to breast conserving surgery alone)

One systematic review and one subsequent RCT found that adding radiotherapy to breast conserving surgery reduced the risk of local recurrence compared with breast conserving surgery alone. They found no significant difference in survival between breast conserving surgery plus radiotherapy and breast conserving surgery alone. One systematic review and one additional RCT found no significant difference in survival and local recurrence with breast conserving surgery plus radiotherapy compared with mastectomy. One RCT found that radiotherapy (with or without tamoxifen) reduced ipsilateral breast cancer recurrence compared with tamoxifen alone after median follow up of 87 months. It found no significant difference in survival. Radiotherapy may be associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture.

Radiotherapy after mastectomy in women at high risk of local recurrence

One systematic review found that radiotherapy to the chest wall after mastectomy reduced the risk of local recurrence by about two thirds compared with no postoperative radiotherapy. It found that radiotherapy did not reduce all cause mortality and breast cancer mortality after mastectomy alone or mastectomy plus axillary clearance. However, radiotherapy did reduce all cause mortality and breast cancer mortality after mastectomy plus axillary sampling. Radiotherapy may be associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture.

LIKELY TO BE BENEFICIAL

Neoadjuvant chemotherapy (reduced mastectomy rates and had similar survival rates to adjuvant chemotherapy)

Five RCTs found no significant difference in survival with neoadjuvant chemotherapy compared with adjuvant chemotherapy. Three RCTs found that neoadjuvant chemotherapy reduced mastectomy rate compared with adjuvant chemotherapy. 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.

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Total nodal radiotherapy

One systematic review found that postmastectomy radiotherapy, including total nodal irradiation, reduced locoregional recurrence. It found that postmastectomy radiotherapy improved survival in women receiving mastectomy plus axillary sampling, but not in women receiving mastectomy alone or mastectomy plus axillary clearance.

TRADE OFF BETWEEN BENEFITS AND HARMS

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

One systematic review found that radiotherapy to the chest wall after mastectomy reduced the risk of local recurrence by about two thirds compared with no postoperative radiotherapy. It found that radiotherapy did not reduce all cause mortality or breast cancer mortality after mastectomy alone or mastectomy plus axillary clearance. However, radiotherapy did reduce all cause mortality and breast cancer mortality after mastectomy plus axillary sampling. Radiotherapy may be associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture. There is, therefore, a trade off between absolute benefits and harms in women not at high risk of local recurrence.

Axillary clearance

There is consensus that axillary clearance reduces regional recurrence compared with no axillary management. RCTs found no significant difference in survival at 5–10 years between axillary clearance and axillary sampling (followed by axillary radiotherapy in women found to be node positive) or axillary radiotherapy (regardless of axillary nodal status). One systematic review found that axillary radiotherapy reduced isolated local recurrence compared with axillary clearance, but this difference was not significant. One systematic review of mainly poor quality evidence found that the risk of arm lymphoedema was highest with axillary clearance plus radiotherapy, lower with axillary sampling plus radiotherapy, and lowest with sampling alone.

Axillary radiotherapy

One systematic review found that axillary radiotherapy reduced isolated local recurrence compared with axillary clearance, but this difference was not significant. The review found no significant difference in survival at 10 years between axillary radiotherapy and axillary clearance. One systematic review of mainly poor quality evidence found that the risk of arm lymphoedema was highest with axillary clearance plus radiotherapy, lower with axillary sampling plus radiotherapy, and lowest with sampling alone.

Axillary sampling

One RCT found no significant difference in survival at 5 years between axillary clearance and axillary sampling (followed by axillary radiotherapy in women found to be node positive). One systematic review of mainly poor quality evidence found that the risk of arm lymphoedema was highest with axillary clearance plus radiotherapy, lower with axillary sampling plus radiotherapy, and lowest with sampling alone.

UNKNOWN EFFECTIVENESS

Different neoadjuvant chemotherapy regimens (insufficient evidence regarding which regimen is most effective)

We found insufficient evidence of any difference between the common neoadjuvant chemotherapy regimens in survival, recurrence, or quality of life.

Radiotherapy to the internal mammary chain

One RCT found no significant difference in relapse or survival at 2–3 years between radiotherapy and no radiotherapy to the internal mammary chain. Treatment may increase radiation induced cardiac morbidity.

Radiotherapy to the ipsilateral supraclavicular fossa

We found insufficient evidence about the effects of irradiation of the ipsilateral supraclavicular fossa on survival. RCTs have found that radiotherapy to the chest wall and lymph nodes is associated with reduced risk of locoregional recurrence, including supraclavicular fossa nodal recurrence. Morbidity associated with irradiation of the supraclavicular fossa is rare and, where it occurs, is mild and temporary.

UNLIKELY TO BE BENEFICIAL**Enhanced dose regimens of adjuvant combination chemotherapy**

RCTs did not find additional survival advantage from enhanced dose regimens of adjuvant combination chemotherapy. Adverse effects of chemotherapy include nausea and vomiting, hair loss, bone marrow suppression, fatigue, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

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

One systematic review found no additional survival benefit from prolonging adjuvant chemotherapy from 4–6 to 8–12 months. Adverse effects of chemotherapy include nausea and vomiting, hair loss, bone marrow suppression, fatigue, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function.

LIKELY TO BE INEFFECTIVE OR HARMFUL**High dose chemotherapy**

One systematic review found no significant difference between high dose chemotherapy plus autograft and conventional chemotherapy in 5 year survival for women with early, poor prognosis breast cancer. The review found that high dose chemotherapy plus autograft increased treatment related and non-cancer related deaths compared with conventional chemotherapy.

What are the effects of interventions in locally advanced breast cancer (stage III B)?**LIKELY TO BE BENEFICIAL****Hormonal treatment plus radiotherapy (improves survival compared with radiotherapy alone)**

One RCT found that hormonal treatment (tamoxifen or ovarian ablation) plus radiotherapy delayed locoregional recurrence and improved survival at 8 years in locally advanced breast cancer compared with radiotherapy alone.

Radiotherapy

Two small RCTs including women with locally advanced disease (stage III B) found that radiotherapy or surgery as sole local treatments have similar effects on response rates, duration of response, and overall survival for locally advanced breast cancer that is rendered operable by prior chemotherapy. Local skin toxicity (acute and late) after radiotherapy is greater in locally advanced breast cancer than after treatment for less advanced disease, because of the need for a higher radiation dose to skin.

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Radiotherapy after attempted curative surgery

One RCT found limited evidence that radiotherapy after attempted curative surgery reduced local and regional recurrence compared with no further local treatment, but did not improve time to relapse or overall survival. Local skin toxicity (acute and late) after radiotherapy is greater in locally advanced breast cancer than after treatment for less advanced disease, because of the need for a higher radiation dose to skin.

Surgery

Two small RCTs including women with locally advanced disease (stage III B) found that surgery or radiotherapy as sole local treatments have similar effects on response rates, duration of response, and overall survival for locally advanced breast cancer that is rendered operable by prior chemotherapy.

UNLIKELY TO BE BENEFICIAL

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

RCTs found insufficient evidence that radiotherapy plus cytotoxic chemotherapy using cyclophosphamide plus methotrexate plus fluorouracil, or an anthracycline based multidrug regimen improved survival, disease free survival, or long term locoregional control compared with radiotherapy alone in locally advanced breast cancer.

DEFINITION This chapter 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** can be separated into three main groups: early invasive breast cancer, locally advanced breast cancer, and metastatic breast cancer (see breast cancer [metastatic], p 506). **Operable breast cancer** is apparently restricted to the breast and sometimes to local lymph nodes and can be removed surgically. Although these 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 with multifocal cancers that are usually treated by mastectomy, and those with tumours less than 4 cm with unifocal cancers that can be treated by breast conserving surgery. **Locally advanced breast cancer** is defined according to the TNM staging system of the UICC¹ as stage III B (includes T4 a–d; N2 disease, but absence of metastases). It is a disease presentation with evidence (clinical or histopathological) of skin, or chest wall involvement, or axillary nodes matted together by tumour extension, or a combination of these features. **Metastatic breast cancer** is presented in a separate chapter (see breast cancer [metastatic], p 506).

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 15 000 new cases of breast cancer a year in the UK, 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 hormone replacement therapy, and 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

◀ **PROGNOSIS** **Primary 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 70% 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. Those with node positive disease have a 50–60% chance of recurrence within 5 years, compared with 30–35% for node negative disease. Recurrence at 10 years, according to one large systematic review,⁴ is 60–70% compared with 25–30% of node negative women. The prognosis for a disease free survival at 5 years is worse for stage III B (33%) than that for stage III A (71%). Five year overall survival is 44% for stage III B and 84% for stage III A.⁵ Poor survival and high rates of local recurrence characterise locally advanced breast cancer.

Please refer to the Clinical Evidence website for full text and references.