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Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus) (Review)

Morgan J, Wyld L, Collins KA, Reed MW

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[Intervention Review]

Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

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ABSTRACT

Background

Several studies have evaluated the clinical effectiveness of endocrine therapy alone in women aged 70 years or over with operable breast cancer and who are fit for surgery.

Objectives

To systematically review the evidence for the clinical effectiveness of surgery (with or without adjuvant endocrine therapy) in comparison to primary endocrine therapy in the treatment of operable breast cancer in women aged 70 years and over, both in terms of local progression and mortality.

Search methods

We conducted an updated search of the Cochrane Breast Cancer Group's Specialised Register (27th March 2013) and new searches of the Cochrane Central Register of Controlled Trials (CENTRAL, 2013, Issue 3), MEDLINE, EMBASE, the World Health Organization's International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and www.clinicaltrials.gov, using the search terms 'early breast cancer', 'endocrine therapy', 'psychosocial' or 'surgery'.

Selection criteria

Randomised trials comparing surgery, with or without adjuvant endocrine therapy, to primary endocrine therapy in the management of women aged 70 years or over with early breast cancer and who were fit for surgery.

Data collection and analysis

We assessed studies for eligibility and quality, and two review authors independently extracted data from published trials. We derived hazard ratios for time-to-event outcomes, where possible, and used a fixed-effect model for meta-analysis. We extracted toxicity and quality-of-life data, where present. Where outcome data were not available, we contacted trialists and requested unpublished data.

Main results

We identified seven eligible trials, of which six had published time-to-event data and one was published only in abstract form with no usable data. The quality of the allocation concealment was adequate in three studies and unclear in the remainder. In each case the endocrine therapy used was tamoxifen.

Data, based on an estimated 1081 deaths in 1571 women, did not show a statistically significant difference in favour of either surgery or primary endocrine therapy in respect of overall survival. However, there was a statistically significant difference in terms of progression-free survival, which favoured surgery with (474 participants) or without endocrine therapy (164 participants).

The hazard ratios (HRs) for overall survival were: HR 0.98 (95% confidence interval (CI) 0.81 to 1.20, P = 0.85; 3 trials, 495 participants) for surgery alone versus primary endocrine therapy; HR 0.86 (95% CI 0.73 to 1.00, P = 0.06; 3 trials, 1076 participants) for surgery plus endocrine therapy versus primary endocrine therapy. The HRs for progression-free survival were: HR 0.55 (95% CI 0.39 to 0.77, P = 0.0006) for surgery alone versus primary endocrine therapy; HR 0.65 (95% CI 0.53 to 0.81, P = 0.0001) for surgery plus endocrine therapy versus primary endocrine therapy (each comparison based on only one trial). Tamoxifen-related adverse effects included hot flushes, skin rash, vaginal discharge, indigestion, breast pain, sleepiness, headache, vertigo, itching, hair loss, cystitis, acute thrombophlebitis, nausea, and indigestion. Surgery-related adverse effects included paraesthesia on the ipsilateral arm and lateral thoracic wall in those who had axillary clearance. One study suggested that those undergoing surgery suffered more psychosocial morbidity at three months post-surgery, although this difference had disappeared by two years.

Authors' conclusions

Primary endocrine therapy should only be offered to women with oestrogen receptor (ER)-positive tumours who are unfit for surgery, at increased risk of serious surgical or anaesthetic complications if subjected to surgery, or who refuse surgery. In a cohort of women with significant co-morbid disease and ER-positive tumours it is possible that primary endocrine therapy may be a superior option to surgery. Trials are needed to evaluate the clinical effectiveness of aromatase inhibitors as primary therapy for an infirm older population with ER-positive tumours.

PLAIN LANGUAGE SUMMARY

Surgery versus primary endocrine therapy for elderly women with operable primary breast cancer

While younger women with early-stage, oestrogen-sensitive breast cancer are almost invariably treated with surgery plus endocrine therapy, (which deprives the cancer of the hormonal stimulus that induces its growth), women over the age of 70 years are frequently offered endocrine therapy alone. This is known as primary endocrine therapy.

Primary endocrine therapy using tamoxifen (a drug which blocks oestrogen receptors on the cancer cell, inhibiting its growth) was first suggested as a treatment for older women in the 1980s. Tamoxifen was given without surgery, radiotherapy or chemotherapy on the basis that older women are more likely to have cancers with oestrogen receptors and will therefore respond well to treatment. In addition they were thought less suitable for major surgery because of other existing health issues. However, a tumour will often only respond to this treatment for between 18 and 24 months, and those women who relapse will have to consider additional hormone treatment or opt for surgery or radiotherapy at a greater age. The long-term data suggest that, at 12 years of follow-up, more elderly women treated by primary tamoxifen alone will suffer a progression of their cancer than those who have had surgery.

We undertook this review to assess the evidence for the clinical effectiveness of surgery (with or without endocrine therapy) compared with primary endocrine therapy in the treatment of operable breast cancer in women aged 70 years and over. Based on seven trials and an estimated 1081 deaths in 1571 women, the results of this review showed no benefit in respect to survival for either surgery or primary endocrine therapy. However, women who had surgery were less likely to relapse than women on primary endocrine therapy.

The authors conclude that surgery controls breast cancer better than tamoxifen alone in older women but does not extend survival. Both interventions were associated with adverse events. Tamoxifen-related adverse effects included hot flushes, skin rash, vaginal discharge, indigestion, breast pain, sleepiness, headache, vertigo, itching, hair loss, cystitis, acute thrombophlebitis, nausea, and indigestion. Surgery-related adverse effects included tingling or numbness on the arm on the side of the surgery, and psychosocial problems. On this basis, primary endocrine therapy should only be offered to women with oestrogen receptor (ER)-positive tumours who are unfit for, or who refuse surgery. We need further trials to evaluate the clinical effectiveness of other agents such as aromatase inhibitors for use as primary endocrine therapy for an infirm older population with ER-positive tumours.

Summary of findings for the main comparison. Surgery compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Surgery compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Patient or population: Women (70 years plus)with operable primary breast cancer
Settings: Hospital
Intervention: Surgery
Comparison: **P**rimary endocrine therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primary endocrine therapy	Surgery				
Survival - overall Follow-up: 0 - 28 years	**Study population**		**HR 0.98** (0.81 to 1.20)	495 (3 studies)	⊕⊕⊝⊝ **low** [1]	
	862 per 1000	**854 per 1000** (826 to 877)				
	Moderate					
	969 per 1000	**967 per 1000** (960 to 973)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Unselected Oestrogen receptor status. Variability of surgery undertaken. No co-morbidity assessment undertaken.

Summary of findings 2. Surgery plus endocrine therapy compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Surgery plus endocrine therapy compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Patient or population: Women (70 years plus) with operable primary breast cancer
Intervention: Surgery plus endocrine therapy
Comparison: Primary endocrine therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primary endocrine therapy	Surgery plus endocrine therapy				
Survival - overall Follow-up: 0 - 12 years	**Study population**		**HR 0.86** (0.73 to 1)	1076 (3 studies)	⊕⊕⊝⊝ **low** [1]	
	617 per 1000	**581 per 1000** (541 to 617)				
	Moderate					
	613 per 1000	**577 per 1000** (536 to 613)				
Local disease control Follow-up: 0 - 12 years	**Study population**		**HR 0.28** (0.23 to 0.35)	929 (2 studies)	⊕⊕⊕⊕ **high**	
	452 per 1000	**187 per 1000** (159 to 224)				
	Moderate					
	452 per 1000	**188 per 1000** (159 to 224)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.

Very low quality: We are very uncertain about the estimate.

[1] Unselected Oestrogen receptor status. Variability of surgery undertaken. No co-morbidity assessment undertaken.

BACKGROUND

Description of the condition

Invasive breast cancer occurs when uncontrolled, abnormal growth and division of cells in either the lobules or the ducts of the breast spread to the surrounding tissue. The Union Internationale Contre le Cancer (UICC) staging system for breast cancer reflects how, when left untreated, cancer cells can spread locally to the breast tissue and the lymph glands in the armpit (Stages 1 to 3) and through the bloodstream and lymphatic system to other parts of the body (Stage 4). UICC Stages 1 to 3 are known as 'early breast cancer' (UICC 2009).

Breast cancer is the most common type of cancer in women. In 2008, there were an estimated 1.38 million new cases and over 458,000 deaths (Globocan 2010). Up to 30% of all breast cancers are reported to occur in the over-70 years age-group and 48% in the over-65s (Sader 1999; Wanebo 1997). An ageing population in developed countries may see these percentages increase still further (Silliman 1993). However, owing to omission of the elderly from the majority of clinical trials (Bayer 2000; Bugeja 1997), there are few data defining the optimum treatment for breast cancer in the elderly.

Description of the intervention

The standard treatment for early-stage breast cancer in women of all ages was surgery until the late 1970s, with good results reported (Kesseler 1978). Primary endocrine therapy was first described in the early 1980s as an alternative to standard therapy for older women (Bradbeer 1983; Preece 1982). Treatment involved the sole use of a drug called tamoxifen, without surgery, radiotherapy or chemotherapy. Tamoxifen is an anti-oestrogen. It acts by blocking the oestrogen receptor (ER) in the nucleus of breast cancer cells. If oestrogen binds to these receptors, the breast cancer cells are stimulated to grow. Blocking of this receptor causes the cancer to stop growing and regress, in most cases. The majority (70%) of breast cancers have oestrogen receptors but the percentage does vary with age. Older women are much more likely to have cancers with oestrogen receptors (Diab 2000; McCarty 1983).

How the intervention might work

Older women who were started on tamoxifen primary endocrine therapy in these early studies responded relatively well to the treatment. The cancer in the breast would either shrink or fail to progress in 75% of women. The treatment was well-tolerated and enabled the avoidance of complications related to surgery. This treatment option was, therefore, enthusiastically adopted by both surgeons and their elderly patients. The treatment was refined by the use of oestrogen receptor status to select those likely to respond. A good response can be expected in between 79% and 83% of women who are moderately or strongly ER-positive, compared to a 90% to 100% progression rate in those with absent ER staining (Gaskell 1989; Gaskell 1992).

However, the mean duration of response to primary endocrine therapy is only 18 to 24 months. In consequence, women who relapse are then faced with the prospect of changing to second-line hormonal therapy, surgery or radiotherapy, at a greater age, and run the risk that the disease may become inoperable. Overall, when long-term data are studied, 81% of elderly women treated by primary tamoxifen will go on to develop progression after 12 years of follow-up compared with 38% following mastectomy alone (Kenny 1998). As yet, there is no clear consensus as to whether or not there is a survival advantage for tamoxifen or surgery in this age group. It would seem, on the basis of current evidence, that there is little to recommend the use of tamoxifen alone for the primary treatment of operable primary breast cancer in all but the very infirm.

The trend towards primary tamoxifen treatment was based on the premise that older women are less likely to be fit for surgery. The incidence of significant co-morbidity is greater in the elderly (Satariano 1994), which is thought to render general anaesthesia more hazardous. However, the majority of elderly women will be fit for surgery under general anaesthesia because mastectomy, even when combined with axillary clearance, has a low morbidity and mortality. The recent UK National Mastectomy and Reconstruction Audit has demonstrated that overall the mortality for breast surgery is 0.26% (NHSIC 2011). Review of articles reporting treatment specifically in the over-70 age group by wide local excision, either under local or general anaesthesia, reports only two deaths in 615 women undergoing surgery (0.3%) (Wyld 2003). The recent trend towards sentinel node biopsy rather than a full axillary clearance of all axillary nodes, a much less invasive operation, would further reduce the risks of surgery (Burak 2002). In addition, even a mastectomy can usually be performed under local anaesthesia (Oakley 1996), reducing risks still further. However, many older women may be keen to avoid surgery for diverse reasons when offered a choice of surgery or primary endocrine therapy, such as avoidance of hospitalisation, fear of mutilation, or desire to maintain independence (Husain 2008).

Why it is important to do this review

It is difficult to assess how widespread the use of primary endocrine therapy is worldwide. It is apparently not a treatment option in the USA (Diab 2000) and is rarely used in Australia (Craft 2000). In Europe, reports of primary endocrine therapy usage for the elderly vary greatly; from 3% in Italy (Crivellari 1991), 9% in France (Garbay 1998), 16% in the Netherlands (Van Dalsen 1995), 26% in Eire (Hooper 2002), up to 32% in Sweden (Bouchardy 2003). By contrast, audits of current UK practice have confirmed that the use of primary endocrine therapy is widespread, with 42% of all women over 70 being treated in this way (Wyld 2004) and 55% of women over the age of 80 (Monypenny 2003). In addition, in many of these cases there is no documentation of co-morbidity to justify its use (Wyld 2004). It is therefore important to establish whether this type of treatment is justifiable for older women with breast cancer and, if it is, under what circumstances.

OBJECTIVES

To systematically review the evidence for the clinical effectiveness of surgery (with or without endocrine therapy) in comparison to primary endocrine therapy in the treatment of operable breast cancer in women aged 70 years and over, both in terms of local progression and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women aged 70 years or over with clinically-defined operable primary breast cancer, that is, primary tumour not fixed to underlying structures (including the TNM classification T1 - T3 and T4b where there is only minor skin involvement and N0-1, mobile lymph nodes (UICC 2009). We planned the following age-based subgroup analyses: 70 to 79 years; 80 years and over.

Types of interventions

1. Surgery alone versus primary endocrine therapy.

With the following subgroups for the surgery arm:

- mastectomy alone with or without axillary surgery (where 'axillary surgery' includes axillary clearance or sampling);
- wide local excision alone, with or without axillary surgery, with the following further subgroups: margins unspecified; margins specified and adequate (histologically clear, as specified in Smitt 1995); margins specified but inadequate by modern standards;
- wide local excision and deep x-ray therapy or radiotherapy, with or without axillary surgery, with the following further subgroups: margins unspecified; margins specified and adequate (histologically clear); margins specified but inadequate by modern standards.

With the following subgroups for both arms:

- oestrogen receptor (ER) status: positive; negative or unknown;
- progesterone receptor (PR) status: positive; negative or unknown;
- clinical stage at diagnosis, to include size of primary tumour and whether nodes are palpable, or unknown.

2. Surgery plus adjuvant endocrine therapy versus primary endocrine therapy.

With the following subgroups for the surgery arm:

- mastectomy alone, with or without axillary surgery;
- wide local excision alone, with or without axillary surgery, with the following further subgroups: margins unspecified; margins specified and adequate (histologically clear); margins specified but inadequate by modern standards;
- wide local excision and deep x-ray therapy or radiotherapy, with or without axillary surgery, with the following further subgroups: margins unspecified; margins specified and adequate (histologically clear); margins specified but inadequate by modern standards.

With the following subgroups for the primary endocrine therapy arm:

- oestrogen receptor (ER) status: positive; negative or unknown;
- progesterone receptor (PR) status: positive; negative or unknown;
- clinical stage at diagnosis, to include size of primary tumour and whether nodes are palpable, or unknown.

Types of outcome measures

Primary outcomes

1. Overall survival (interval between start of treatment and participant's death; cause of death where available).
2. Progression-free survival (interval between start of treatment and need for second-line treatment/palliative treatment/recurrence/death from any cause).

Secondary outcomes

1. Adverse effects (number of surgical complications/primary endocrine therapy-related side effects, including hot flushes, nausea, vomiting, vaginal discharge, vaginal bleeding, thrombosis, endometrial carcinoma, visual problems, skin rashes).
2. Local disease control (interval between start of treatment and need for second-line treatment/palliative treatment/recurrence; specified whether local disease has recurred in the breast/mastectomy scar or axilla).
3. Distant metastasis-free interval (interval between start of treatment and the development of metastatic disease).
4. Quality of life (however measured).

Search methods for identification of studies

Electronic searches

For the 2013 review update, we undertook the following searches:

- The Cochrane Breast Cancer Group (CBCG) Specialised Register on the 27 March 2013 (details of the search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group's module at www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). We identified studies with the text words 'early breast cancer', 'endocrine therapy', 'psychosocial' or 'surgery' for consideration.
- Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* 2013, Issue 3 (Appendix 1).
- MEDLINE (via OvidSP) from 2008 until 27 March 2013. Appendix 2.
- EMBASE (via Embase.com) from 2008 until 27 March 2013. Appendix 3.
- The WHO International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials on the 27 March 2013. See Appendix 4.
- ClinicalTrials.gov (clinicaltrials.gov/ct2/home) until 27 March 2013. See Appendix 5.

Searching other resources

We checked the reference lists of identified trials and reviews to identify any additional eligible studies.

Data collection and analysis

Selection of studies

Assessing trials for eligibility

We applied the selection criteria, as defined above, to each trial.

1. We justified any exclusions of a potentially eligible trial in the final report.
2. We used trial publications to assess the trial's eligibility with the results section (and any other area where results may have appeared) masked.
3. If a trial had not been published, we obtained information from the trial protocol or next best available resource.
4. Where necessary, and possible, we sought additional information from the principal investigator of the trial concerned.

Quality control and peer review

1. We considered only evidence provided by randomised controlled trials.
2. Two reviewers, JM and LW, independently assessed each potentially eligible trial for inclusion in the updated review.
3. We assessed trial publications for eligibility with the results section (and any other area where results may appear) masked.
4. Where necessary, we sought additional information from the principal investigator of the trial concerned. We copied any additional information obtained from trial investigators to the Managing Editor of the CBCG for inclusion in the specialised register.

Data extraction and management

Two review authors (JM and LW) independently extracted data from the included studies using a paper data extraction form. JM entered and analysed data in Cochrane Review Manager 5 software (RevMan 2012).

Several studies had more than one publication. This 2013 review update found only new publications with updated results from already included studies. We extracted data from these recent publications and added them or replaced previously extracted data where appropriate. We considered the most recent publication containing the relevant outcome data to be the primary reference for each study. This is indicated by an asterisk in the Reference section.

Assessment of risk of bias in included studies

See 'Risk of bias' tables in the Characteristics of included studies section.

The review authors independently evaluated the quality of the included trials, resolving discrepancies by consensus. We sought clarification from the trial author if the published data provided inadequate information for the review.

(1) Selection bias (Allocation concealment)

Allocation concealment is regarded as particularly important in protecting against bias. We assessed and graded the quality of the randomisation processed accordingly (Higgins 2011):

Low risk: Clearly adequate concealment.

Unclear risk: Possibly adequate, or insufficient information to judge.

High risk: Clearly inadequate concealment.

(2) Performance bias and Detection bias (blinding):

Owing to the nature of the interventions, it is not possible to blind either participants, care givers or outcome assessment to the type of intervention received.

(3) Attrition bias (intention-to-treat analysis):

We assessed and graded attrition bias as follows (Higgins 2011):

Low risk: We analysed all participants in the treatment group to which they were allocated, regardless of whether or not they received the allocated intervention.

Unclear risk: We could not determine if participants were analysed according to the intention-to-treat principle after contact with the authors.

High risk: Some participants are not analysed in the treatment group to which they were randomised because they did not receive the study intervention; they withdrew from the study; or because of protocol violation.

(4) Reporting bias:

Owing to the limited number of studies, it was not possible to adequately assess for reporting bias using funnel plot asymmetry assessment. We therefore reviewed each study according to the appropriateness of the outcomes reported.

Low risk: Data were fully reported on all relevant outcomes.

Unclear risk: Relevant outcomes were reported but usable data were not presented.

High risk: No relevant outcomes were reported.

Overall quality assessment:

From the quality assessment of the trials, we summarised the potential risk of bias into three categories as described by The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011):

Low risk of bias: plausible bias unlikely. All of the criteria met, therefore unlikely to seriously alter the results.

Moderate risk of bias: plausible bias. One or more criteria partly met, or one not met, which therefore raises some doubt about the results.

High risk of bias: plausible bias. Two or more criteria not met. Seriously weakens confidence in the results.

Measures of treatment effect

Two review authors (JM and LW) independently assembled the most complete dataset feasible.

1. We statistically synthesised results of eligible studies (meta-analysis).

2. We conducted all analyses on an intention-to-treat basis.

3. We conducted time-to-event analyses for time to death (survival) and time to disease progression (progression-free survival). We synthesised (meta-analysed) trial outcome data, if appropriate (i.e., there was more than one trial with similar populations,

interventions and outcomes) and possible (i.e. there were adequate data). In the absence of published summary statistics (i.e., hazard ratios (HRs) and confidence intervals (CIs)), we sought these relevant summary statistics or individual patient data from the trialists. All analyses were on an intention-to-treat principle. For time-to-event analyses, we calculated combined hazard ratios and 95% confidence intervals using the O-E and variance methods in The Cochrane Collaboration Review Manager 5 software (RevMan 2012). This uses the log hazard ratio and its variance from the relevant outcome of each trial. These, in turn, we calculated using a Microsoft Excel spreadsheet authored by Matt Sydes of the MRC Clinical Trials Unit, which incorporates Parmar's methods for extracting summary statistics to perform meta-analyses of the published literature for survival endpoints (Parmar 1998).

We estimated the log hazard ratio and its variance by two of Parmar's hierarchy of methods depending on the availability of summary statistics. Where possible, we used the methods described in subsection 4 of Parmar 1998, which estimates the variance of the log hazard ratio indirectly from the hazard ratio and its 95% confidence interval. If the study did not report the HR or CI, we employed the methods described in subsection 5 (Parmar 1998), which estimates the log hazard ratio and its variance from survival curves. Where event numbers were not published, we reported the 'effective number of deaths' for each arm, as calculated in the MRC spreadsheet, in the Review Manager forest plots. These estimates in no way affect the calculation of the hazard ratio and its variance and should be considered illustrative. Additional Table 1 ('Source data for comparisons') records the summary statistics used for this purpose.

We reported ratios of treatment effects, so that HRs less than 1.0 favour surgery or surgery plus endocrine therapy, and values greater than 1.0 favour primary endocrine therapy.

4. We made a decision regarding whether and how to combine quality-of-life outcomes depending on whether and how each trial collected this information.

Unit of analysis issues

There were no unit of analysis issues.

Dealing with missing data

Several trials did not report relevant survival data, and we therefore contacted the original investigators (performed by JM and authors of the original review: DH, LW, MR).

In the 2013 update, there were no missing data issues and we obtained anonymised individual patient data wherever possible.

Assessment of heterogeneity

We assessed heterogeneity between trial results using the Chi^2 test and the I^2 measurement. The Chi^2 test assesses the amount of variation in a set of trials. Small P values suggest that there is more heterogeneity present than would be expected by chance. Chi^2 is not a particularly sensitive test: a cut-off P value less than 0.10 is often used to indicate significance, but lack of statistical significance does not mean there is no heterogeneity. I^2 is the proportion of variation that is due to heterogeneity rather than chance (Higgins 2003). Large values of I^2 suggest heterogeneity. I^2 values of 25%, 50%, and 75% could be interpreted as representing low, moderate, and high heterogeneity.

Assessment of reporting biases

Owing to the small number of included studies, it was not possible to use funnel plot asymmetry to assess for the presence of reporting bias as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0. (Higgins 2011).

Data synthesis

For the primary outcomes of overall and progression-free survival (i.e. time-to-event analyses), we calculated combined hazard ratios and 95% confidence intervals using Exp [(O-E)/V] methods in The Cochrane Collaboration software Review Manager 5 (RevMan 2012), using a fixed-effect model (Peto method - Yusuf 1985, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We analysed data according to those trials randomising to surgery alone versus primary endocrine therapy, and those trials randomising to surgery plus endocrine therapy versus primary endocrine therapy. We had planned to conduct subgroup analyses; however owing to the small number of trials with limited data, this was not possible.

Sensitivity analysis

We were unable to conduct the proposed sensitivity analysis (based on trial quality), because of the small number of trials.

RESULTS

Description of studies

Results of the search

For this 2013 review update, we reviewed 1761 references. Of these, 1760 could be excluded based on information in the title or abstract. We retrieved one full-text article for further examination and identified one further publication through handsearching. Both of these publications pertained to studies already included in the previous review (Nottingham 1; St Georges). The searches identified no new studies.

For the previous version of this review, on 13th November 2007, the Cochrane Breast Cancer Group Specialised Register contained 838 references coded to studies of 'EARLY BREAST CANCER', 'ENDOCRINE THERAPY', 'PSYCHOSOCIAL' or 'SURGERY'. Of these, we excluded 810 based on information in the title or abstract. The remaining 28 references reported on seven potentially eligible studies for the review. We excluded none of these studies. We retrieved five additional papers relating to the same trials through handsearching.

Included studies

We include seven studies in total.

We identified three eligible trials addressing surgery versus primary endocrine therapy, all of which reported data. In each case the endocrine therapy used was tamoxifen.

We identified four eligible trials addressing surgery plus endocrine therapy versus primary endocrine therapy, of which three have reported data; there are currently no data from one (Naples) in a

form that can be meta-analysed. In each case the endocrine therapy used was tamoxifen.

Not all trials identified provided information on all outcomes.

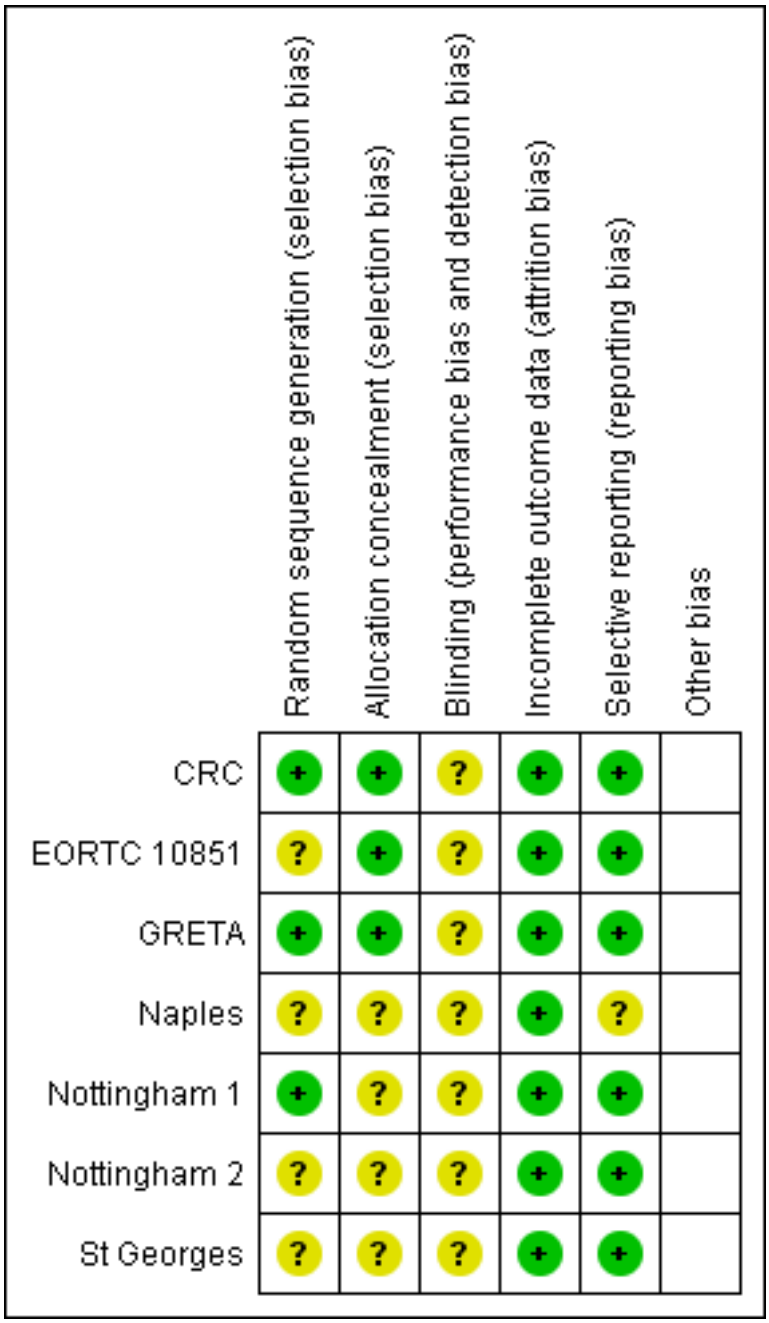
Excluded studies

We excluded none of the potentially eligible studies identified by the search.

Risk of bias in included studies

It was not possible to accurately assess the quality of all studies owing to lack of information in the published articles. Please see Characteristics of included studies and Figure 1 for more details.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence Generation:

Three trials provided adequate information on the generation of the allocation sequence and we graded these as being low risk of bias (CRC; Nottingham 1; GRETA), with the rest being graded as unclear risk of bias (EORTC 10851; Naples; Nottingham 2; St Georges).

Allocation Concealment:

Three trials provided adequate information to be graded as being low risk of bias (CRC; EORTC 10851; GRETA), with the rest being graded as unclear risk of bias (Naples; Nottingham 1; Nottingham 2; St Georges).

Blinding

Owing to the nature of the interventions, neither participants, clinicians nor outcome assessors could be blinded in these studies. In a comparison between a surgical treatment and a medication, it will be clear to both participants and clinicians which treatment a participant has been assigned to, and blinding was therefore considered to be at unclear risk of bias. We made no further assessment.

Incomplete outcome data

All studies reported on the relevant outcomes.

Selective reporting

All studies reported on our primary outcome, overall survival, although not all could be included in the meta-analysis owing to non-comparable presentation of data. All studies were deemed at low risk of bias except Naples, which was graded as unclear risk due to lack of published information.

Other potential sources of bias

We did not note other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Surgery compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus); **Summary of findings 2** Surgery plus endocrine therapy compared to primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Results for the two comparisons (surgery versus primary endocrine therapy; surgery plus endocrine therapy versus primary endocrine therapy) are considered separately.

1. Surgery versus primary endocrine therapy

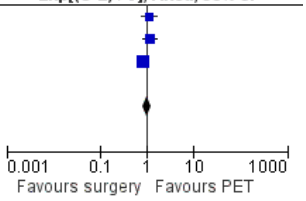
Survival - overall

The first primary analysis of overall effect using hazard ratios derived from published survival curves (EORTC 10851; Nottingham 1; St Georges) involved three trials (495 women). The calculated hazard ratio showed no significant difference between the two treatment arms for this outcome (HR 0.98 , 95% CI 0.81 to 1.20, P = 0.85; Analysis 1.1; Figure 2). There was only minor heterogeneity (Chi^2 = 2.67, df = 2, P = 0.26; I^2 = 25%).

Figure 2. Forest plot of comparison: 1 Surgery versus primary endocrine therapy, outcome: 1.1 Survival - overall.

Study or Subgroup	Surgery Events	Surgery Total	Primary endocrine therapy Events	Primary endocrine therapy Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
EORTC 10851	60	82	50	82	2.59	24.52	24.9%	1.11 [0.75, 1.65]
Nottingham 1	66	66	63	65	4.33	32.25	32.7%	1.14 [0.81, 1.62]
St Georges	100	100	100	100	-8.8	41.8	42.4%	0.81 [0.60, 1.10]
Total (95% CI)		**248**		**247**			**100.0%**	**0.98 [0.81, 1.20]**
Total events	226		213					

Heterogeneity: Chi^2 = 2.67, df = 2 (P = 0.26); I^2 = 25%
Test for overall effect: Z = 0.19 (P = 0.85)



There were insufficient data to justify any quantitative analysis of prospectively identified subsets.

Progression-free survival

Only one trial, EORTC 10851, reported data related to this outcome. We calculated a hazard ratio from published summary statistics using the method described by Parmar 1998, which favoured surgery (HR 0.55, 95% CI 0.39 to 0.77; P = 0.0006; 164 participants).

Adverse effects

There were insufficient data to justify any quantitative analysis of this outcome. Neither EORTC 10851 nor Nottingham 1 reported on side effects. In the St Georges trial no participant discontinued treatment with primary endocrine therapy. Eight participants had a total of 10 side effects, including hot flushes, skin rash, vaginal discharge, indigestion, breast pain and sleepiness.

Local disease control

Estimates of effect were available from published survival curves (EORTC 10851; Nottingham 1) and from anonymised individual patient data (St Georges) for three trials. In one trial (St Georges), surgical margins were inadequate by modern standards; this trial had also introduced informative censoring. All three trials had substantial competing risks, in some cases as high as 50%. In our original review, the Cochrane Breast Cancer Group's statisticians recommended that the potential for bias was considerable, and we present neither a meta-analysis, nor individual results from these trials. We discuss competing risks, heterogeneity of interventions and informative censoring below.

Distant metastasis-free interval

Estimates of effect were available from one published survival curve (EORTC 10851) and from anonymised individual patient data (St Georges) for two trials. Because of heterogeneity between

the two trials and competing risks within each analysis, the Cochrane Breast Cancer Group's statisticians recommended that the potential for bias was considerable, and we do not present a meta-analysis. Distant failure was reported as a first event in 15/82 (surgery) and 7/82 (primary endocrine therapy) women in Table 2 (Fentiman 2003, page 314); however 16/82 (surgery) and 19/82 (primary endocrine therapy) observed events were reported beneath the Kaplan-Meier curve in Figure 4 (Fentiman 2003, page 313). Therefore, this hazard ratio reported above incorporates distant metastases recorded both as a first event, and following or simultaneously with a local progression. Despite the competing risk and the issue of multiple events, the Cochrane Breast Cancer Group's statisticians did not oppose calculation of a hazard ratio for EORTC 10851 (HR 0.77, 95% CI 0.37 to 1.58, P = 0.47, 164 women) from published summary statistics using the method described by Parmar 1998. We do not present a hazard ratio for the St Georges trial because it reports only first events, since surgical margins were inadequate by modern standards, and because of informative censoring. We discuss competing risks, heterogeneity of outcome measurement and informative censoring below.

Quality of life

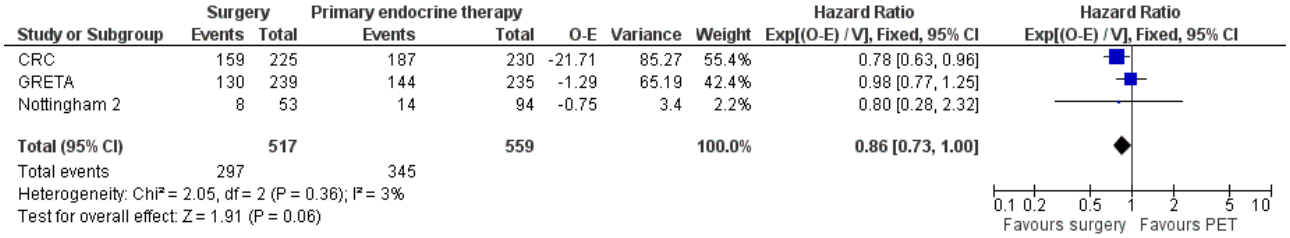
None of the trials reported any data pertinent to this outcome.

2. Surgery plus endocrine therapy versus primary endocrine therapy

Survival - overall

The first primary analysis of overall effect using hazard ratios derived from published survival curves (Nottingham 2) or directly from trialists (CRC; GRETA) involved three trials (1076 women). There was a non-significant trend in favour of surgery plus endocrine therapy (HR 0.86, 95% CI 0.73 to 1.00; P = 0.06; Analysis 2.1; Figure 3). There was no significant heterogeneity across trials (Chi^2 2.05, df 2, P = 0.36, I^2 = 3%).

Figure 3. Forest plot of comparison: 2 Surgery plus endocrine therapy versus primary endocrine therapy, outcome: 2.1 Survival - overall.



Survival - by oestrogen receptor status

Limited data for subgroup analysis by oestrogen receptor status were available. In the one trial where oestrogen receptor status was positive for all participants (Nottingham 2: 147 women), there was no significant difference between the interventions (HR 0.80, 95% CI 0.28 to 2.32; P = 0.68). In the remaining two trials (CRC; GRETA: total 929 women) the oestrogen receptor status of participants was unknown. Here there was no significant difference between interventions (HR 0.86, 95% CI 0.73 to 1.00; P = 0.06). There was no significant heterogeneity across trials (Chi^2 2.04, df 1, P = 0.15, I^2 = 50.9%).

Survival - by age

Age-related subgroup analysis was not possible on the basis of published data. In a conference abstract (Mustacchi 1998), trialists from GRETA and CRC reported analyses of combined individual patient data from both trials. They reported that participant age was the most important determinant of survival in later years (75 years plus). In those aged between 70 and 75 years, initial surgery (rather than primary endocrine therapy) determined survival.

Survival - breast cancer-specific

We obtained unpublished hazard ratios for breast cancer-specific survival data from two trials (CRC; GRETA), but were unable to conduct a subgroup meta-analysis as there were no data on the risk of a non-breast cancer-related death. A published meta-analysis of individual patient data from the CRC and GRETA studies found a significant trend in favour of surgery plus endocrine therapy (HR 0.70, 95% CI 0.51 to 0.95) (Mustacchi 1998).

Progression-free survival

Only one trial (GRETA), reported data related to this outcome. We calculated a hazard ratio from published summary statistics using the method described by Parmar 1998: this favoured surgery plus endocrine therapy (HR 0.65, 95% CI 0.53 to 0.81, P = 0.0001; 474 participants).

Adverse effects

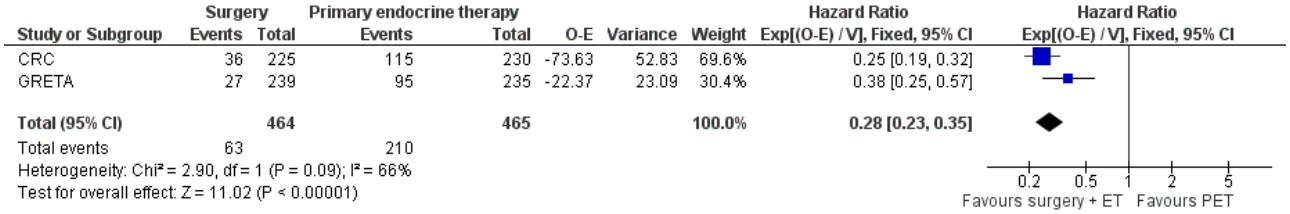
There were insufficient data to justify any quantitative analysis of this outcome. The CRC trial did not quantify adverse events, only reporting that one woman from the primary endocrine therapy arm had to drop out of the trial because of endocrine therapy-related adverse effects. Nottingham 2 did not report adverse events. In the GRETA trial, all participants in the surgery plus primary endocrine therapy arm who had axillary clearance had paraesthesia on the ipsilateral arm and lateral thoracic wall. Tamoxifen-related toxicity was similar between the two groups and included headache, vertigo, itching, hair loss, cystitis, vaginal bleeding, acute thrombophlebitis, nausea, and indigestion.

Local disease control

We conducted an analysis of overall effect, using hazard ratios derived from one unpublished (CRC) and one published (GRETA) survival curve involving two trials (929 women). This showed a significant difference in favour of surgery plus endocrine therapy (HR 0.28, 95% CI 0.23 to 0.35, P < 0.00001; Analysis 2.2; Figure 4). There was significant heterogeneity across trials (Chi^2 2.90, df 1, P = 0.09, I^2 = 66%), which is discussed below. We did not include

data from Nottingham 2 in this analysis, as reported results were immature compared to the other two trials.

Figure 4. Forest plot of comparison: 2 Surgery plus endocrine therapy versus primary endocrine therapy, outcome: 2.2 Local disease control.



There were insufficient data to justify any quantitative analysis of prospectively identified subsets. However, one trial (Nottingham 2), which recruited only women with ER-positive tumours reported better local control in the surgery plus endocrine arm. Another trial (CRC) reported this outcome by type of surgery, comparing both mastectomy (52 of 225 women) and breast-conserving surgery (159 of 225) against the same population of primary endocrine therapy (230 women). The trialists reported better local disease control for both mastectomy and breast-conserving surgery than for primary endocrine therapy. Note that 14 participants in the surgery arm did not receive their planned surgery and were excluded from this subgroup analysis.

Distant metastasis-free interval

We obtained summary data from one trialist (GRETA); however, Cochrane Breast Cancer Group statisticians advised that the confidence interval was too narrow to be reliable, and that until we were able to clarify the quality of these data we should not report the outcome.

Quality of life

There were insufficient data to justify any quantitative analysis of this outcome. However, the CRC group used the General Health Questionnaire 28 (GHQ-28: Goldberg 1970), which detects psychological morbidity, and a socio-demographic questionnaire, which investigated levels of domestic support and social isolation. At three months after start of treatment, the surgery group had more psychosocial morbidity (P = 0.03). However, there was no difference between the surgery and primary endocrine therapy groups at two years (Fallowfield 1994).

DISCUSSION

Summary of main results

This study has demonstrated that primary endocrine therapy is inferior to surgery with endocrine therapy for the local control of breast cancer in ER-unselected, medically fit older women. It is also independent of the type of surgery, with both mastectomy and wide excision (without adjuvant radiotherapy) achieving superior local control. However, surgical treatment does not result in significantly better overall survival.

Overall completeness and applicability of evidence

The results of this review need to be read bearing in mind that they are derived from a small number of individually underpowered studies. Additionally, there are four areas where treatment regimens in the trials do not necessarily coincide with modern clinical practice. Therefore, the appropriateness of the following should be questioned: (1) endocrine therapy for women with ER-negative tumours; (2) surgery without adjuvant endocrine therapy; (3) primary endocrine therapy where the individual is fit for and agreeable to surgery; (4) new endocrine therapies.

(1) Oestrogen receptor status

Most of the included trials recruited women regardless of oestrogen receptor status. However, only 85% to 90% of women in this age group have ER-positive tumours (Diab 2000). For those with ER-negative tumours, endocrine therapy was not an active intervention and such treatment is not in line with modern clinical practice.

Their inclusion may also have biased the results of the meta-analysis, although the extent is difficult to assess. Had women with ER-negative tumours been excluded from the studies (which would have been a fairer comparison), the primary endocrine therapy arm might have performed better against the surgery plus endocrine therapy arm, although it is unlikely that the considerable local control advantage conferred by surgery would be overcome. Only Nottingham 2, a trial comparing surgery with adjuvant endocrine therapy against endocrine therapy alone, recruited exclusively participants with ER-positive tumours. Local control was inferior in the primary endocrine therapy group despite this.

(2) Surgery without adjuvant endocrine therapy

Three of the trials included in this study (EORTC 10851; Nottingham 1; St Georges) did not include adjuvant endocrine therapy after surgery. However, it is considered best practice today for women with ER-positive tumours to receive adjuvant endocrine therapy in addition to surgery (NICE 2002). The results of this study showed no difference in overall survival where surgery alone was compared with primary endocrine therapy (HR 0.98, 95% CI 0.81 to 1.20, P = 0.85). Where surgery and adjuvant endocrine therapy were compared to primary endocrine therapy, the direction of effect favoured surgery; however, this was only of borderline significance (HR 0.86, 95% CI 0.73 to 1.00, P = 0.06). As discussed above, it is possible that selection of ER-positive women might improve the relative effectiveness of primary endocrine therapy.

(3) Co-morbidity

Primary endocrine therapy for the treatment of operable breast cancer in older women is still in widespread use in the UK (BCCOM 2007; Monypenny 2003; Wyld 2004); however, the populations

represented in the included studies may not be typical of those who receive such treatment today. The women recruited to these studies were, by definition, fit for surgery and therefore their life expectancy would have been good (Exterman 2000) and the surgical risks low. The reality of current practice in many units in the UK is to restrict primary endocrine therapy to those women in whom the risks of surgery are high or who would be expected to have a reduced life expectancy because of co-morbid diseases (Wyld 2004).

It is worth noting that none of the included studies controlled for participant co-morbidity, which has a significant influence on survival in this age group (Satariano 1994). Thus we see that breast cancer-specific survival is improved in those randomised to surgery plus endocrine therapy compared to those on primary endocrine therapy (HR 0.70, 95% CI 0.51 to 0.95: Mustacchi 1998). As already noted, difference in overall survival still favours the surgery arm but is only of borderline significance. This serves to emphasise that, even among those fit for surgery in this age group, a significant proportion of participants still die of co-morbid diseases, so reducing the relative advantages of any breast cancer therapies (Satariano 1994).

(4) Different endocrine therapies

In each included study the endocrine therapy used was tamoxifen, an oestrogen-receptor antagonist. Since these studies were designed, new endocrine therapies for the treatment of ER-positive breast cancer have become available. These are the aromatase inhibitors anastrozole, letrozole and exemestane. Letrozole has been shown to be superior to tamoxifen in the neoadjuvant setting (Eiermann 2001; Ellis 2011) and in the metastatic setting (Mouridsen 2003). Anastrazole is superior to tamoxifen in the adjuvant setting (ATAC 2005). It is possible that primary endocrine therapy using these newer agents may be even more attractive for older women who are unfit for surgery. This hypothesis should be tested in a randomised controlled trial (RCT), although a recent attempt to run a multicentre UK RCT comparing surgery plus an adjuvant aromatase inhibitor versus primary endocrine therapy with an aromatase inhibitor failed to recruit, due to women refusing randomisation and preferring to make their own choice of treatment (Reed 2009).

Quality of the evidence

In some cases, the internal validity of the included trials was affected by competing risks and informative censoring. Heterogeneity between trials, in terms of interventions and outcome assessment, also made the review team's assessment of some outcomes difficult.

(1) Competing risks

The calculation of the Kaplan-Meier (KM) probabilities assumes that failure from local recurrence is still possible beyond the time of censoring. For those participants who failed from other causes (e.g., death without failing) this is called the 'competing risk'. Censoring participants who fail from competing risks is not appropriate as it gives an underestimate of the probability of local failure by treating those cases who have not failed locally and are alive the same as those who have not failed locally but have died. This approach is clearly undesirable.

Despite the fact that none of the trials adjusted for competing risks when calculating local disease control, Cochrane Breast Cancer Group statisticians advised us that the Kaplan-Meier plots and estimates of the hazard ratio would be more likely to be valid if the following conditions were met:
(a) the rate of deaths without breast cancer recurrence (not necessarily the same as non-breast cancer-related death) was similar and accounted for a small percentage of the deaths in both arms (maybe less than 10%); and,
(b) the duration over which deaths without recurrence were happening was roughly the same (the competing risk of deaths is uniform over the two arms across the follow-up period).
In none of the trials can we be sure that these conditions are met. Therefore, the results in the trial reports for this outcome must be read with caution. Not only should these trials not be meta-analysed but Cochrane Breast Cancer Group statisticians advise us it would be inappropriate to further disseminate their results for this particular outcome, as it represents a potentially misleading estimate of effect. The same issue arises with distant metastasis-free interval for the surgery alone versus primary endocrine therapy comparison.

(2) Informative censoring

The Kaplan-Meier methods used to calculate time to local or distant recurrence assume that censoring is non-informative, i.e., that the fact that a person is censored at a given time is independent of their potential outcome. In the St Georges trial, participants are censored at the time of the last clinical examination. If we assume that those who have progressed are more likely to attend follow-up clinics and that those who are disease- or metastases-free are less likely to attend clinics, the latter group will be censored earlier, and will stop contributing information to the study. Thus the censoring is potentially dependent on the likelihood of disease progression (i.e., related to the outcome). This is another source of potential bias, as the rate of censoring does not leave a representative sample of those at risk. Therefore Cochrane Breast Cancer Group statisticians advised us that the censoring is likely to be informative and the assumption of non-informative censoring required for the KM method is likely to be violated.

(3) Heterogeneity of interventions

For the surgery alone versus primary endocrine therapy comparison, there was heterogeneity between trials in terms of interventions. One study (St Georges) included larger (T3 and T4) tumours in the surgical arm, which would result in an increased local recurrence rate. The other two trials included only participants with T1 - T2 (Nottingham 1) and T1 - T3a (EORTC 10851) tumours respectively. The St Georges study treated 64 women with wide local excision and 36 with mastectomy; in the Nottingham 1 and EORTC 10851 trials all women were treated with mastectomy. It is arguable, therefore, that St Georges is different enough in terms of its populations and interventions to make statistical synthesis with the other two studies inappropriate. Nevertheless, both the populations and interventions of all included studies are in conformity with the inclusion criteria for this review.

(4) Heterogeneity of outcome assessments

For the surgery-alone versus primary endocrine therapy comparison, there was a difference between the definitions of distant metastasis-free interval between the two trials: in EORTC 10851 they have counted some distant events which occurred after

local events; in St Georges they have only counted first events. This made it inappropriate to combine the outcomes from the two trials. For the surgery plus endocrine therapy versus primary endocrine therapy comparison, evidence of heterogeneity between trials was identified for local disease control; funnel plots were not practical, with only two included trials, and the reasons must remain speculative. It is possible that here too there is a difference between each trial's outcome definitions in terms of whether only first events were counted.

Potential biases in the review process

An overview of the bias assessment is summarised in Figure 1.

Agreements and disagreements with other studies or reviews

This is the only published meta-analysis of randomised controlled trials comparing surgery (with or without adjuvant endocrine therapy) with primary endocrine therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Primary endocrine therapy should only be offered to women with ER-positive tumours who are unfit or borderline-fit for surgery, or who refuse it. In a cohort of women with reduced life expectancy, due to significant co-morbid disease, and ER-positive tumours, primary endocrine therapy may be an appropriate treatment choice.

Implications for research

Trials are needed to evaluate the clinical effectiveness of aromatase inhibitors as primary therapy for an infirm older population with ER-positive tumours. The Bridging the Age Gap study - a national UK cohort study - may provide more clinically relevant answers to this question.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CRC

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery plus tamoxifen (40 mg/d) versus tamoxifen alone
Outcomes	Survival - overall; Disease-free survival; Local disease control; Distant metastasis-free survival; Quality of life
Notes	Comparability between groups at the baseline: stated as "good"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis - 16 protocol violators (full explanations) analysed as randomised (intention-to-treat)
Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes.

EORTC 10851

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery versus tamoxifen (20 mg/d)
Outcomes	Survival - overall; Disease-free survival; Local disease control; Distant metastasis free survival
Notes	Comparability between groups at the baseline: stated as "well-balanced"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated (but stated that it was randomised).
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis: analysis based on intention-to-treat. 13 found ineligible after randomisation and excluded from analysis. 1 participant allocated tamoxifen opted for surgery.
Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes.

GRETA

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery plus tamoxifen (20 mg/d) versus tamoxifen alone
Outcomes	Survival - overall; Disease-free survival; Local disease control; Distant metastasis free survival
Notes	Comparability between groups at the baseline: good

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias)	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed

GRETA *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes

Naples

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery plus tamoxifen (20 mg/d) versus tamoxifen alone
Outcomes	Survival - overall; Disease-free survival
Notes	No data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in results presented.
Selective reporting (reporting bias)	Unclear risk	Adequate outcomes reported on but insufficient data presented for meta-analysis

Nottingham 1

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery versus tamoxifen (40 mg/d)
Outcomes	Survival - overall; Disease-free survival; Local disease control; Distant metastasis-free survival

Nottingham 1 *(Continued)*

Notes	Comparability between groups at the baseline: appears similar by age, tumour volume and tumour site. Little else specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random card allocation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis: analysis based on intention-to-treat. 2 incorrect randomisations in each group. 122/135 followed up. Other 13 participants assessed by GP at time of analysis as too frail to attend clinic
Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes

Nottingham 2

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery plus tamoxifen versus tamoxifen (20 mg/d)
Outcomes	Survival - overall; Disease-free survival
Notes	Comparability between groups at the baseline: stated as "similarly matched for age" (no other characteristics reported)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis: analysed as randomised (intention-to-treat)

Nottingham 2 *(Continued)*

Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes

St Georges

Methods	Randomised controlled trial
Participants	Women (aged 70+) with operable breast cancer
Interventions	Surgery versus tamoxifen (20 mg/d)
Outcomes	Survival - overall; Disease-free survival; Local disease control; Distant metastasis free survival
Notes	Comparability between groups at the baseline: More T4 tumours in primary endocrine therapy group (n = 14/100 versus n = 7/100 in the surgery group) but, with small numbers in each arm, this may not be significant. Ages were similar. No other characteristics were reported

Risk of bias

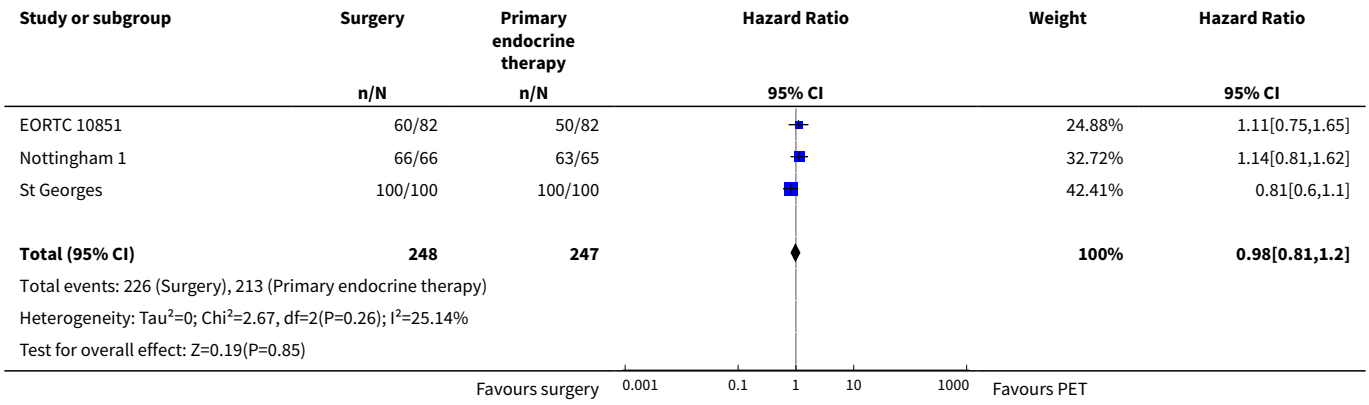
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of these studies was not possible due to interventions used, therefore this has not been assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of all randomised participants in the analysis: no errors or exclusions were reported
Selective reporting (reporting bias)	Low risk	Sufficient data reported on all relevant outcomes

DATA AND ANALYSES

Comparison 1. Surgery versus primary endocrine therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival - overall	3	495	Hazard Ratio (95% CI)	0.98 [0.81, 1.20]

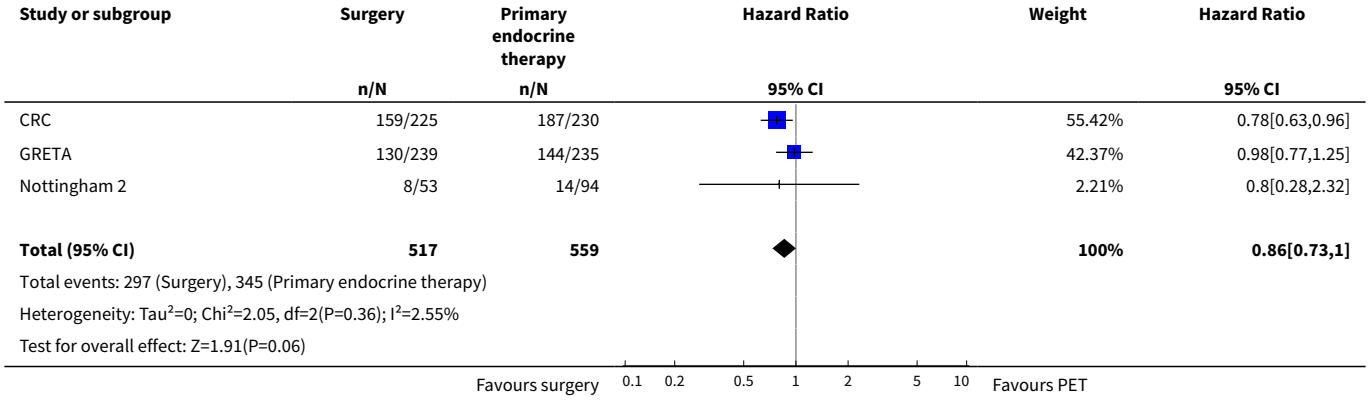
Analysis 1.1. Comparison 1 Surgery versus primary endocrine therapy, Outcome 1 Survival - overall.



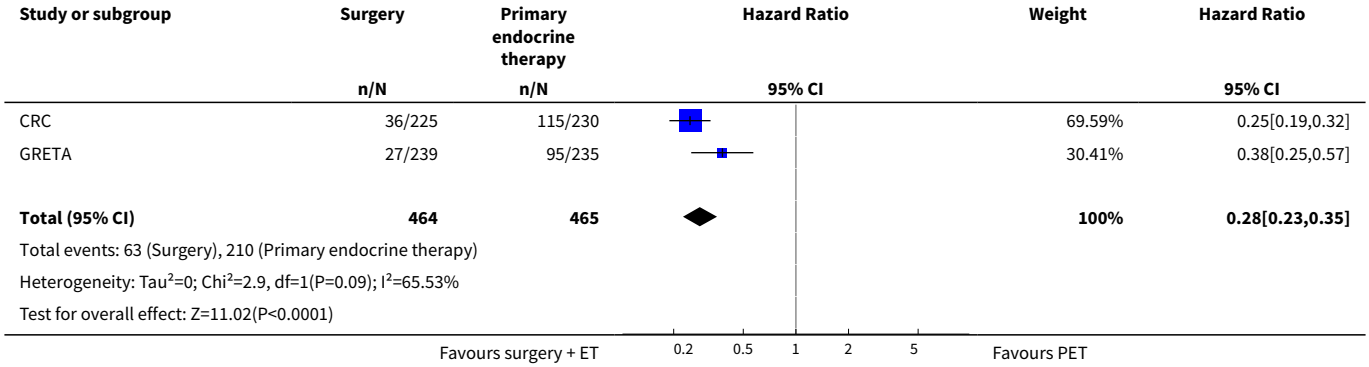
Comparison 2. Surgery plus endocrine therapy versus primary endocrine therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival - overall	3	1076	Hazard Ratio (95% CI)	0.86 [0.73, 1.00]
2 Local disease control	2	929	Hazard Ratio (95% CI)	0.28 [0.23, 0.35]

Analysis 2.1. Comparison 2 Surgery plus endocrine therapy versus primary endocrine therapy, Outcome 1 Survival - overall.



Analysis 2.2. Comparison 2 Surgery plus endocrine therapy versus primary endocrine therapy, Outcome 2 Local disease control.



ADDITIONAL TABLES

Table 1. Source data for comparisons

Comparison	Outcome	Trial	Follow-up	Summary statistics	Observed events (n)	Subsection of Parmar 1998
Surgery versus primary endocrine therapy	Survival - overall	EORTC 10851	Approximately 10 years. Surgery: median 11.7 years (95% CI: 11.2 to 12.8; range: 0 - 14.3). Primary endocrine therapy: 10.2 years (95% CI: 10.3 to 11.2; range: 0 - 14.9)	Fentiman 2003: Kaplan-Meier Curves; Fmin and Fmax stated in paper.	Fentiman 2003; Table 2, "Total deceased".	Subsection 5
Surgery versus primary endocrine therapy	Survival - overall	Nottingham 1	Median 73 and 74 months. Maximum follow-up 20 years	Chakrabarti 2011: Kaplan-Meier Curves.Fmin taken as first event; Fmax stated in paper.	Chakrabarti 2011. Table 1.	Subsection 5
Surgery versus primary endocrine therapy	Survival - overall	St Georges	Range: 0 - 28 years	Gazet 2011: Kaplan-Meier Curves	Gazet and Sutcliffe 2011: Table 1	Subsection 5
Surgery versus primary endocrine therapy	Progression-free survival	EORTC 10851	Approximately 10 years. Surgery: median 11.7 years (95% CI: 11.2 to 12.8; range: 0 - 14.3). Primary endocrine therapy: 10.2 years (95% CI: 10.3 to 11.2; range: 0 - 14.9)	Fentiman 2003, Table 3 (p 314): number of events and number randomised for each arm; P value	Fentiman 2003; Table 3, 'Progression-free survival: number of events'	Subsection 5

Table 1. Source data for comparisons *(Continued)*

Surgery versus primary endocrine therapy	Local disease control	EORTC 10851	Approximately 10 years. Surgery: median 11.7 years (95% CI: 11.2 to 12.8; range: 0 - 14.3). Primary endocrine therapy: 10.2 years (95% CI: 10.3 to 11.2; range: 0 - 14.9).	Fentiman 2003: Kaplan-Meier Curves; Fmin and Fmax stated in paper	Fentiman 2003; Table 3, 'Time to loco-regional progression'	Subsection 5
Surgery versus primary endocrine therapy	Local disease control	Nottingham 1	Median 145 months (range: 116 - 180 months)	Kenny 1998: Life tables	Kenny 1998; Figure 1, 'Local control by primary treatment	Subsection 5
Surgery versus primary endocrine therapy	Local disease control	St Georges	Median 6 years (range 3 - 11 years)	Martin Bland personal communication: Anonymised IPD from which hazard ratios and 95% confidence intervals were derived.	Gazet 1994; p 208	Subsection 4
Surgery versus primary endocrine therapy	Distant metastasis-free survival	EORTC 10851	Approximately 10 years. Surgery: median 11.7 years (95% CI: 11.2 - 12.8; range: 0 - 14.3). Primary endocrine therapy: 10.2 years (95% CI: 10.3 to 11.2; range: 0 - 14.9)	Fentiman 2003: Kaplan-Meier Curves; Fmin and Fmax stated in paper	Fentiman 2003; Table 2, added figures for, 'Distant [relapse]" and "Local and distant'	Subsection 5
Surgery versus primary endocrine therapy	Distant metastasis-free survival	St Georges	Median 6 years (range 3 - 11 years)	Martin Bland personal communication: Anonymised IPD from which hazard ratios and 95% confidence intervals were derived (Bland 2005 [pers comm])	Gazet 1994; p 210	Subsection 4
Surgery plus endocrine therapy versus primary endocrine therapy	Survival - overall	CRC	Median 12.7 years	Fennessey 2004 p 702: Hazard ratios and 95% confidence intervals	Fennessey 2004, Table 4	Subsection 4
Surgery plus endocrine therapy versus primary endocrine therapy	Survival - overall	GRETA	80 months.	Mustacchi personal communication: Hazard ratios and 95% confidence intervals (Mustacchi 2005 [pers comm])	Mustacchi 2003; Table 4.	Subsection 4
Surgery plus endocrine therapy versus primary endocrine therapy	Survival - overall	Nottingham 2	60 months.	Willsher 1997: Life Table reporting grouped data; Fmin assumed the same as Nottingham 1 (same trial-	Used 'effective number of deaths in t'	Subsection 5

Table 1. Source data for comparisons *(Continued)*

				ists, same protocol); Fmax 60 months - from life table		
Surgery plus endocrine therapy versus primary endocrine therapy	Progression-free survival	GRETA	80 months.	Mustacchi 2003; observed events for research and control; numbers randomised to research and control; P value	Mustacchi 2003; Table 4; 'Total events.	Subsection 5
Surgery plus endocrine therapy versus primary endocrine therapy	Local disease control	GRETA	80 months.	Mustacchi 2003; Figure 1: Kaplan-Meier Curve	Mustacchi 2003; Table 4; 'First local progression'	Subsection 5
Surgery plus endocrine therapy versus primary endocrine therapy	Local disease control	CRC	Median 12.7 years.	Hazard Ratios from Fennessey 2004 p 701; Fmin from Table 1, Fmax from last entry on curve.	Fennessey 2004, Table 2, 'Local' + 'Axillary'	Subsection 4

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees

#2 early breast cancer* or early breast neoplas* or early breast tumour* or early breast tumor*

#3 locally advanced breast cancer* or locally advanced breast neoplas* or locally advanced breast tumour* or locally advanced breast tumor*

#4 #2 or #3

#5 #1 and #4

#6 MeSH descriptor: [Mastectomy] explode all trees

#7 mastecom* or surger* or wide local excision or axillary surger*

#8 #6 or #7

#9 endocrine therap*

#10 primary endocrine therapy or tamoxifen

#11 MeSH descriptor: [Tamoxifen] explode all trees

#12 #10 or #11

#13 #5 and #8

#14 #5 and #8 and #9

#15 #5 and #8 and #12

#16 #13 or #14 or #15

Appendix 2. MEDLINE

# ▲	Searches
1	randomised controlled trial.pt.
2	randomized controlled trial.pt.
3	controlled clinical trial.pt.
4	randomized.ab.
5	randomised.ab.
6	placebo.ab.
7	randomly.ab.
8	trial.ab.
9	groups.ab.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	early breast cancer.mp.
12	early breast carcinoma.mp.
13	early breast tumor.mp.
14	early breast tumour.mp.
15	early breast neoplasm.mp.
16	locally advanced breast cancer.mp.
17	locally advanced breast carcinoma.mp.
18	locally advanced breast neoplasm.mp.
19	locally advanced tumor.mp.
20	locally advanced tumour.mp.
21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	exp Mastectomy/
23	mastectom$.mp.
24	surger$.mp.
25	wide local excision.mp.
26	axillary surger$.mp.
27	22 or 23 or 24 or 25 or 26

(Continued)

28	endocrine therapy.mp.
29	primary endocrine therapy.mp.
30	exp Tamoxifen/
31	tamoxifen.mp.
32	29 or 30 or 31
33	10 and 21 and 27
34	10 and 21 and 27 and 28
35	10 and 21 and 32
36	33 or 34 or 35
37	**limit 36 to (humans and yr="2008 -Current")**

Appendix 3. EMBASE

#41

#40 AND [humans]/lim AND [embase]/lim AND [2008-2013]/py

#40

#37 OR **#38** OR **#39**

#39

#9 AND **#27** AND **#36**

#38

#9 AND **#27** AND **#32** AND **#33**

#37

#9 AND **#27** AND **#32**

#36

#34 OR **#35**

#35

'tamoxifen'/exp OR **tamoxifen**

#34

'primary endocrine therapy'

#33

'endocrine therapy'/exp OR **'endocrine therapy'**

#32

#28 OR **#29** OR **#30** OR **#31**

#31

'axillary surgery'

#30

'wide local excision'/exp OR **'wide local excision'**

#29

'surgery'/exp OR **surgery**

#28

'mastectomy'/exp OR **mastectomy**

#27

#15 AND **#26**

#26

#16 OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25**

#25

'locally advanced breast tumor'

#24

'locally advanced breast tumour'

#23

'locally advanced breast carcinoma'

#22

'locally advanced breast neoplasm'

#21

'locally advanced breast cancer'

#20

'early breast tumor'

#19

'early breast tumour'

#18

'early breast carcinoma'

#17

'early breast cancer'

#16

'early breast neoplasm'

#15

#10 OR **#11** OR **#12** OR **#13** OR **#14**

#14

'breast tumor'/exp OR **'breast tumor'**

#13

'breast tumour'

#12

'breast carcinoma'/exp OR **'breast carcinoma'**

#11

'breast cancer'/exp OR **'breast cancer'**

#10

'breast neoplasm'

#9

#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8**

#8

groups:ab

#7

trial:ab

#6

randomly:ab

#5

placebo:ab

#4

randomi*ed:ab

#3

controlled AND **clinical** AND **trial**

#2

randomized AND **controlled** AND **trial**

#1

randomised AND **controlled** AND **trial**

Appendix 4. WHO ICTRP

Basic Searches:

1. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

2. (Surgery AND endocrine therapy) AND breast cancer

3. (mastectomy AND endocrine therapy) AND breast cancer

4. Primary endocrine therapy AND breast cancer

Advanced Searches:

1. Title: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Recruitment: All

2. Condition: early breast cancer

Intervention: surgery AND endocrine therapy

Recruitment Status: All

3. Condition: locally advanced breast cancer

Intervention: surgery AND endocrine therapy

Recruitment Status: All

4. Condition: early breast cancer

Intervention: surgery OR endocrine therapy

Recruitment Status: All

5. Condition: locally advanced breast cancer

Intervention: surgery OR endocrine therapy

Recruitment Status: All

6. Condition: early breast cancer

Intervention: primary endocrine therapy OR Tamoxifen

Recruitment Status: All

7. Condition: locally advanced breast cancer

Intervention: primary endocrine therapy OR Tamoxifen

Recruitment Status: All

Appendix 5. ClinicalTrials.gov

Basic Searches:

1. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

2. (Surgery AND endocrine therapy) AND breast cancer

3. (mastectomy AND endocrine therapy) AND breast cancer

4. Primary endocrine therapy AND breast cancer

Advanced Searches:

1. Title Acornym/Titles: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

2. Condition: early breast cancer OR locally advanced breast cancer

Intervention: surgery AND endocrine therapy

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

3. Condition: early breast cancer OR locally advanced breast cancer

Intervention: surgery OR endocrine therapy

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

4. Condition: early breast cancer OR locally advanced breast cancer

Intervention: primary endocrine therapy OR Tamoxifen

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

WHAT'S NEW

Date	Event	Description
19 May 2014	Review declared as stable	As clinical practice and consumer preference have started to change in recent years, it is unlikely that new trials will compare surgery versus primary endocrine therapy. The authors therefore do not expect to update this review in the future

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 1, 2006

Date	Event	Description
27 March 2013	New search has been performed	Performed search for new studies on 27 March 2013. No new studies included. Data has been updated for two already-included studies (Nottingham 1; St Georges)
27 March 2013	New citation required but conclusions have not changed	This review update includes an accumulation of changes. These are: changes in authorship, the inclusion of updated data from two studies, full risk of bias tables and 'Summary of findings' tables
9 May 2008	Amended	Converted to new review format.
13 November 2007	New search has been performed	Review updated - no new citation. new search, no new trials to add
16 November 2005	New search has been performed	First review publication

Date	Event	Description
27 May 2003	Amended	Protocol first published

CONTRIBUTIONS OF AUTHORS

For the 2013 review update:
JM screened the search results
JM organised the retrieval of papers
JM and LW screened retrieved papers against inclusion criteria
JM entered data into Review Manager 5

JM, LW, KC and MR analysed and interpreted the data
JM, LW, KC and MR wrote and edited the update

DECLARATIONS OF INTEREST

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SOURCES OF SUPPORT

Internal sources

- North Trent Cancer Research Network, UK.

External sources

- No sources of support supplied

NOTES

1. Types of outcome measures - We have made an amendment to the second primary outcome to make clear that the event numbers for the outcome progression-free survival include both cancer progression and death events from any cause.

The protocol originally read:
"disease-free survival (interval between start of treatment and need for second line treatment/palliative treatment/recurrence)"

It now reads:
"progression-free survival (interval between start of treatment and need for second line treatment/palliative treatment/ recurrence/death from any cause)"

This has been modified to allay confusion between trials which record disease-free survival (which counts death as an event) and disease-free interval (which does not). The outcome we had originally defined (the text in brackets) was 'disease-free interval'. We had created the potential for confusion by then calling the outcome disease-free survival as they are different outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents, Hormonal [*therapeutic use]; Breast Neoplasms [*drug therapy] [*surgery]; Combined Modality Therapy; Randomized Controlled Trials as Topic; Tamoxifen [*therapeutic use]

MeSH check words

Aged; Aged, 80 and over; Female; Humans