Surgery vs. tamoxifen for operable primary breast cancer in older women: Cochrane review

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THE COCHRANE COLLABORATION

CITATION

D Hind, L Wyld, CB Beverley, MW Reed. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). The Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004272.pub2. DOI: 10.1002/14651858.CD004272.pub2.

ABSTRACT

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

Objectives: To identify and review the evidence from randomised trials comparing primary endocrine therapy (endocrine therapy alone) to surgery, with or without adjuvant endocrine therapy, in the management of women aged 70 years or over with operable breast cancer.

Search strategy: The Cochrane Breast Cancer Group Specialised Register was searched on 21st August 2003 using the codes for "early breast cancer", "endocrine therapy", "psychosocial" or "surgery". Details of the search strategy applied to create the register and the procedure used to code references are described in the Cochrane Breast Cancer Group module on The Cochrane Library.

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

Data collection and analysis: Studies were assessed for eligibility and quality, and data from published trials were extracted by two independent reviewers. Hazard ratios were derived for time-to-event outcomes, where possible, and a fixed-effect model was used for meta-analysis. Toxicity and quality-of-life data were extracted, where present. Where outcome data were not available, trialists were contacted and unpublished data requested.

Main results: Seven eligible trials were identified 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 869 deaths in 1571 women, were unable to 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 or without endocrine therapy.

The hazard ratios (HR) for overall survival were: 0.98 (95% confidence interval (CI) 0.74 to 1.30, p=0.9) for surgery alone versus primary endocrine therapy; 0.86 (95% CI 0.73 to 1.00, p=0.06) for surgery plus endocrine therapy versus primary endocrine therapy. The HRs for progression-free survival were: 0.55 (95% CI 0.39 to 0.77, p=0.0006) for surgery alone versus primary endocrine therapy; 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 paresthesia 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 postsurgery, 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 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.

INTRODUCTION

The standard treatment for early-stage breast cancer in women of all ages was surgery until the late 1970s.[1] Primary endocrine therapy was first described in the early 1980s as an alternative for older women.[2] Treatment involved the sole use of tamoxifen an oestrogen-receptor antagonist, without surgery, radiotherapy or chemotherapy. Tamoxifen controls cancer in around 80% of women with moderately or strongly ER positive tumours,[3] but for less time than surgery.[4]

In the UK, the trend towards treating women aged 70 and over with tamoxifen alone has been based on the premise that they are less likely to be fit for surgery because of co-morbidity.[5] However, both mastectomy[6] and wide local excision[7] have low morbidity and mortality rates. Primary endocrine therapy is not a treatment option in the USA[8] and is rarely used in Australia.[9] In the UK, its use is widespread, with up to 42% of all women over 70 being treated in this way, regardless of whether co-morbidity is documented.[10]

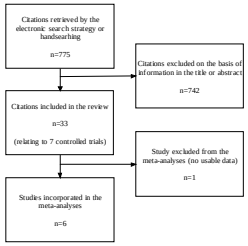
To establish whether primary endocrine therapy is justifiable for women who are fit for surgery, we identified and reviewed the evidence from randomised trials comparing it to surgery, with or without adjuvant endocrine therapy, in the management of women aged 70 years or over with operable breast cancer.

METHODS

Full details of the methods employed are published elsewhere.[11] We searched the Cochrane Breast Cancer Group Specialised Register for citations coded as "EARLY BREAST CANCER", "ENDOCRINE THERAPY", "PSYCHOSOCIAL" or "SURGERY". Only controlled trials with the following characteristics were included. Participants were women aged 70 years or over with clinically-defined operable primary breast cancer, that is, primary tumour not fixed to underlying structures (TNM T1-3 and T4b where there was only minor skin involvement, N0-1, mobile lymph nodes[12]). Studies had to compare either: (1) surgery alone versus primary endocrine therapy; or, (2) surgery plus adjuvant endocrine therapy versus primary endocrine therapy. Primary outcomes were overall survival and progression-free survival (interval between start of treatment and need for second-line or palliative treatment, recurrence or death from any cause). Secondary outcomes were adverse effects (surgical complications or tamoxifen side effects), local disease control, distant metastasis-free interval and quality of life. Two reviewers independently assessed each potentially eligible trial for inclusion in the review with the results section masked and reviewed the quality of each study. The most complete dataset feasible was assembled from the published literature. Where necessary, we sought additional information from the principal investigator of the trial concerned. HRs and 95% CIs from eligible published studies were statistically synthesised (meta-analysis), using Parmar's methods.[13] Heterogeneity between trial results was tested using the chi^2 test and the I^2 measurement.[14] Absolute risk reductions and numbers needed to treat were calculated using Altman and Andersen's method.[15]

RESULTS

The Cochrane Breast Cancer Group Specialised Register was searched on 29th June 2005 and the search strategy retrieved 770 citations. The study selection process is illustrated to the right, in accordance with the QUOROM statement.[16] Three eligible trials addressing surgery versus primary tamoxifen therapy were identified.[4;17;18] Four eligible trials addressing surgery plus endocrine therapy versus primary endocrine therapy were identified: three reported survival data;[19-22] one did not.[21] The quality of three trials was graded as A[17;19;20] with the rest being graded as B.[4;18;21;22]



SURGERY ALONE VERSUS TAMOXIFEN ALONE

Analysis of overall survival, based on three trials (495 women),[4;17;18] showed no significant difference between interventions (HR 0.98, 95% CI 0.74 to 1.30, p=0.9). One trial (164 women)[17] reported adequate summary data to show a significant difference in progression-free survival, favouring surgery (HR 0.55, 95% CI 0.39 to 0.77, p=0.0006). An extra 7% of participants receiving surgery benefited from the treatment: for every death or progression prevented over 120 months, 14 women would have to be treated using surgery. Methodological issues prohibited meta-analysis of data on local disease control or the distant metastasis-free interval. One trial (200 women)[18] reported adverse events (no one discontinued treatment. Eight patients had a total of ten side effects, including hot flushes, skin rash, vaginal discharge, indigestion, breast pain and sleepiness. No trial reported quality of life data.

SURGERY PLUS ADJUVANT TAMOXIFEN VERSUS TAMOXIFEN ALONE (1)

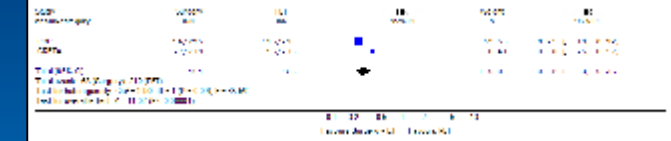
Three trials (1,076 women)[19;20;22] reported data on overall survival which could be meta-analysed. There was a non-significant trend in favour of surgery plus endocrine therapy (HR 0.86, 95% CI 0.73 to 1.00, p=0.06). Only one trial (474 women), 20 reported adequate data on progression-free survival to calculate a significant difference favouring surgery plus endocrine therapy (HR 0.65, 95% CI 0.53 to 0.81, p=0.0001). An extra 21% of participants receiving surgery benefited from the treatment: for every death or progression prevented over 80 months, five women would have to be treated using surgery.

Overall Survival

SURGERY PLUS ADJUVANT TAMOXIFEN VERSUS TAMOXIFEN ALONE (2)

Analysis of two trials (929 women)[19;20] showed a significant difference in local disease control in favour of surgery plus endocrine therapy (HR 0.28, 95% CI 0.23 to 0.35, p< 0.00001). There was significant heterogeneity between the two studies (chi^2 2.90, p<0.09, I^2 65.6%), which is discussed below, although each individually showed a statistically significant difference in treatment effect favouring the surgery arm. Data from one trial[22] were not included in this analysis as reported results were immature compared to the other two studies. Adequate data were not available to evaluate the difference in distant metastasis-free interval. One study reported that both mastectomy and wide local excision significantly improved local control compared to primary endocrine therapy.[19]

Local Control



One trial did not quantify adverse events.[19] In another, all patients in the surgery arm who had axillary clearance had paraesthesia on the ipsilateral arm and lateral thoracic wall. Tamoxifen-related toxicity was similar between the two arms.[20] The other two studies did not report adverse events.[21;22] The only trial to evaluate differences in quality of life used the General Health Questionnaire [28,23] which detects psychiatric morbidity. 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 PET groups at two years.[24]

DISCUSSION

The results of this review are based on a limited number of small trials of variable quality. In some cases, the validity of the primary studies was affected by competing risks and informative censoring, which violate the assumptions underlying the Kaplan-Meier survival analysis method. Heterogeneity between trials, in terms of interventions and outcome assessment, also made assessment of some outcomes problematic. In one trial, surgical margins were inadequate by modern standards.[18]

Most trials recruited women regardless of oestrogen receptor status. Only 85 to 90% of women in this age group have ER-positive tumours.[8] For the remainder, tamoxifen is not an active intervention its use not in line with modern clinical practice. Had such women been excluded from trials, the primary endocrine therapy arms may have performed better against surgery arm plus endocrine therapy in the meta-analysis. However, the one trial to recruit exclusively patients with ER-positive tumours found local control to be superior with surgery and adjuvant endocrine therapy.[22] None of the included studies controlled for patient co-morbidity and, even amongst those fit for surgery in this age group, a significant proportion of patients still die of co-morbid diseases, so reducing the relative advantages of any breast cancer therapies.[5]

Primary endocrine therapy should only be offered to women with ER-positive tumours who are unfit for, or who refuse, surgery. 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. Since these studies were designed, endocrine therapies other than tamoxifen have become available. Aromatase inhibitors have been shown to be superior to tamoxifen in the adjuvant setting and may by attractive as primary endocrine therapy for older women who are unfit for surgery. The ESTEEM trial will begin recruiting women in January 2007 in order to test this hypothesis.

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