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Systemic therapy for treating locoregional recurrence in women with breast cancer (Review)

Rauschecker HHF, Clarke MJ, Gatzemeier W, Recht A

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Systemic therapy for treating locoregional recurrence in women with breast cancer.
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TABLE OF CONTENTS

[Intervention Review]

Systemic therapy for treating locoregional recurrence in women with breast cancer

Helmut HF Rauschecker[1], Mike J Clarke[2], Wolfgang Gatzemeier[3], Abram Recht[4]

[1]German Breast Cancer Study Group (GBSG), University of Erlangen, Rosenheim, Germany. [2]Centre for Public Health, Queen's University Belfast, Belfast, UK. [3]European School of Oncology, Milan, Italy. [4]Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Contact: Helmut HF Rauschecker, rauschecker@t-online.de.

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ABSTRACT

Background

Between 10% and 35% of women with operable breast cancer will experience an isolated locoregional recurrence following their primary treatment. There is currently no good evidence that adjuvant systemic treatment is effective in this situation and there is no standard treatment for women who have such a recurrence.

Objectives

To investigate whether additional systemic treatment will improve the result of local therapy in regard to relapse-free and overall survival in women with potentially curatively resected locoregional recurrence following breast cancer and who have not had a previous or synchronous distant metastases.

Search methods

The specialised register of the Cochrane Breast Cancer Collaborative Review Group, *The Cochrane Library,* MEDLINE and EMBASE and records of the Early Breast Cancer Trialists´ Collaborative Group were searched for the initial review in 2001. A subsequent search of the Cochrane Breast Cancer Specialised Register was conducted (19th May 2008).

Selection criteria

Randomised controlled trials or trials in which women were allocated to active treatment or observation by a quasi-randomised process (such as alternation or date of birth) were eligible. Our aim was to consider separately women with a first incidence of isolated loco-regional recurrence in the treated breast, the chest wall or the regional lymphnode areas (except clavicular nodes) which can be resected without (R0) or with (R1) microscopically demonstrable residual disease. Women with previous or synchronous distant metastases were to be excluded from this part of the review. The second part of the review was to consider women with inoperable loco-regional recurrence and/or clavicular lymphnode involvement, regardless of previous or synchronous metastases.

Data collection and analysis

We identified three completed studies in which there were a total of four randomised comparisons of systemic therapy versus observation for women who have received radiotherapy for loco-regional recurrence of breast cancer. One trial from the 1960's assessed actinomycin-D and randomised 32 patients and another from the early 1980's randomised the same number of women to alpha-interferon versus observation. The Swiss SAKK trial assessed the use of tamoxifen for 'good risk' patients and combination chemotherapy (vincristine, doxorubicin and cyclophosphamide) for 'poor risk' patients by randomising 178 and 50 women respectively, from 1982-1991. Where possible, data on relapse-free and overall survival were extracted for these trials and analysed using RevMan. No attempt was made to

pool the results of the studies because of clinical heterogeneity and the small number of randomised patients. Three ongoing trials of chemotherapy versus observation have been identified.

Main results

The trial of 32 women who received either radiotherapy alone or in combination with systemic administration of actinomycin-D found that chemotherapy improved the local control rate but had no apparent effect on overall survival. The interferon trial, which also included a total of only 32 patients, showed that the addition of alpha-interferon to local treatment of locoregional recurrent breast cancer had no apparent effect on the further course of the disease. The Swiss SAKK trial of tamoxifen (178 women randomised) found an improvement in disease-free survival but not in overall survival. No results were available for the 50 women randomised into the concurrent trial of chemotherapy. The three ongoing trials of chemotherapy have a total target accrual of nearly 2000 patients.

Authors' conclusions

This systematic review of randomised trials provides insufficient evidence to support systemic treatment in women with loco-regional recurrence of breast cancer. Participation in randomised trials of systemic treatment versus observation is appropriate.

PLAIN LANGUAGE SUMMARY

It is not yet clear whether adding chemotherapy (anti-cancer drugs) to another treatment for a recurrence of breast cancer in the same area improves survival

Early breast cancer can be removed by surgery, and for most women the chance of the cancer returning (recurrence) is small. In some women however, the cancer returns in the same area. Chemotherapy (anti-cancer drugs) can be used together with other treatments, such as surgery or radiation therapy, to try to treat recurring cancer and improve survival. The review found that few trials have been performed to investigate its effectiveness. There is currently not enough evidence that adding chemotherapy to other treatments helps to treat the recurring cancer or to improve survival. However, chemotherapy may be an option, and further trials are underway.

BACKGROUND

In the western world, a woman's lifetime risk of developing breast cancer is approximately one in nine (Schleicher 1995). The majority of women with breast cancer have apparently operable disease. They are treated with surgery and, in many cases, with radiotherapy and/or some form of systemic therapy (such as chemotherapy or tamoxifen). However, depending on the stage of the disease and the treatment given, between 10% and 35% of women experience an isolated locoregional recurrence (LRR) (EBCTCG 1995; Fisher 1995; Veronesi 1993). About 80% of these recurrences happen during the first two years after primary treatment (Recht 1999). Various attempts have been made to identify a prognostic profile for patients at risk for LRR (Rauschecker 1998) but further work is still needed in this area.

Regardless of whether the primary treatment is mastectomy or breast preserving therapy, locoregional recurrence in breast cancer comprises any reappearance of the disease in the area of the primary (local) treatment and/or the regional lymph nodes (axillary, clavicular, parasternal, or internal mammary). Recurrence may be preceded or accompanied by distant metastases. Isolated LRR (that is no overt evidence of distant metastases) may be resectable without (categorised as R0), or with (R1), microscopical disease remaining in situ. In patients with isolated locoregional failures the biological significance of LRR is still not clear. There is an ongoing debate as to whether LRR is generally an indication for poor prognosis (Haffty 1996; Whelan 1994) or whether resectable LRR is a strictly locally confined reappearance of the disease (Veronesi 1995). If the latter is true, a complete removal of the LRR should, like a complete resection of the primary breast cancer, make a definitive cure a possibility. However, when women with resected breast cancer who have had a LRR are compared with women who have not had an LRR, an increased rate of further progress of the disease is found. The 10 year survival for women with LRR is less than 50% (Recht 1999). After a potentially curative resection of the primary cancer, adjuvant systemic treatment has been shown to prolong recurrence-free and overall survival (EBCTCG 1998a; EBCTCG 1998b). Consequently, it might seem advisable to also use systemic adjuvant therapy after 'potentially curative' resection of LRR. However, there is currently no good evidence that adjuvant systemic treatment is effective in this situation and there is no standard treatment for LRR of breast cancer.

This review updates the previous 2001 review.

OBJECTIVES

To investigate whether additional systemic treatment will improve the result of local therapy in regard to relapse-free and overall survival in women with potentially curatively-resected LRR following breast cancer and who have not had a previous or synchronous distant metastases. The effectiveness of chemotherapy, hormonal therapy and the combination of both were examined. The investigation also attempted to identify whether the type of primary therapy used influenced the outcome of subsequent LRR, whether any specific treatment regimen was especially beneficial, and whether certain categories of women were more or less likely to benefit. However, as expected, we found that there is insufficient evidence available to address these issues reliably.

For women with only partially resectable or inoperable LRR, the review investigated the additive effect of chemotherapy or hormonal therapy to local irradiation. This applied also to women with a recurrence in the supraclavicular lymphnode area which is regarded as a special type of LRR (classified as M1in the present UICC/AJCC breast cancer classification scheme).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials or trials in which women were allocated to different treatments using a quasi-randomised process (such as alternation or date of birth).

Types of participants

Our aim was to consider separately women with a first incidence of isolated LRR in the treated breast, the chest wall or the regional lymphnode areas (except clavicular nodes) which could be resected without (R0) or with (R1) microscopically demonstrable residual disease. Women with previous or synchronous distant metastases were excluded from this part of the review. The second part of the review was to consider women with inoperable LRR and/or clavicular lymphnode involvement, regardless of previous or synchronous metastases.

Types of interventions

For the first part of the review, we expected that all women who had not received radiotherapy as part of their primary treatment would have received radiotherapy after local excision of LRR. The main analysis for the review was likely, therefore, to compare women receiving no systemic therapy versus those receiving some form of systemic treatment. This could be chemotherapy, hormonal therapy or both. Younger women with a high risk of another recurrence might have been given high dose chemotherapy in recent trials.

For the second part of the review, women with non-resectable but isolated LRR or supraclavicular metastases were considered as a separate category from those with inoperable LRR with preceding or simultaneous distant metastases. We intended that the analysis would compare women receiving radiotherapy alone versus those receiving radiotherapy plus chemotherapy, as well as women receiving radiotherapy alone versus those receiving radiotherapy plus hormonal therapy.

Types of outcome measures

If possible, the different therapies were assessed in regard to recurrence-free and overall survival during each year of follow-up. Quality of life in relation to the therapy given was to be investigated if sufficient data were available in the identified studies.

Search methods for identification of studies

Randomised controlled trials relevant to this question were difficult to identify. Electronic search strategies had low precision because terms such as locoregional recurrence appear as an outcome in nearly all reports of trials of the primary treatment of breast cancer. The initial search for this review was conducted in 2001; the Specialised Register of the Cochrane Breast Cancer Collaborative Review Group, *The Cochrane Library*, MEDLINE and EMBASE were

searched. In addition, the records of the Early Breast Cancer Trialists´ Collaborative Group were checked for any relevant trials, in case these had been mistakenly retrieved for that project. The citations in articles reviewing the treatment of locoregional recurrence of breast cancer were checked.

A subsequent search of The Cochrane Breast Cancer Specialised Register was conducted (18th August 2005).

Data collection and analysis

Articles identified as possibly relevant were checked by at least two review authors. Decisions as to which studies should be included were reached using simple agreement and there were no disagreements.

Methodological quality assessment was performed by one author (MC) to assess the quality of the allocation concealment prior to randomisation. The quality of allocation concealment was graded using the following codes
A: Adequate concealment.
B: Uncertain.
C: Clearly inadequate concealment.
Although our intention was to seek missing information from the investigators responsible for the relevant studies, it was clear that the collection of this missing information would not affect our conclusions because so little randomised evidence was identified.

The Cochrane review manager software (RevMan) was used to analyse data. If we had found studies that were sufficiently similar, these would have been pooled, dichotomous variables would have been combined using odds ratios and 95% confidence intervals, and heterogeneity of effect size between studies would have been tested. The sensitivity analyses proposed in the protocol (relating to the quality assessment described above to enable the presentation of results with and without the inclusion of any quasi-randomised trials) has not been undertaken because of the lack of a sufficient number of trials at this time.

It was not possible to present results separately for women with the different types of locoregional recurrence described in the 'Types of participants' section. Sufficient data were not available for any additional subgroup analyses: such as age above and below 50 years at randomisation for the treatment of LRR) and type of primary therapy.

RESULTS

Description of studies

Three studies were identified with a total of four randomised comparisons of systemic therapy versus observation for women who have received radiotherapy for loco-regional recurrence of breast cancer. One trial from the 1960's assessed actinomycin-D and randomised 32 patients (Olson 1977). Another early 1980's trial randomised the same number of women to interferon versus observation (Fentiman 1987). The Swiss SAKK trial assessed tamoxifen for 'good risk' patients (SAKK (TAM) 2003) and combination chemotherapy (vincristine, doxorubicin and cyclophosphamide) for 'poor risk' patients (SAKK (CT) 1994). Good risk was defined as estrogen receptor (ER+) positive recurrence, or in the case of an unknown receptor status, a disease free interval of greater than 12 months and three or less recurrent tumor nodules each 3cm or less in diameter. Poor risk was defined as being unsuitable for endocrine therapy. The SAKK trial randomised 178 and 50 women respectively to the two interventions from 1982 to1991. More details are given for these trials in the 'Characteristics of Included Studies' table.

We have also identified three ongoing randomised trials, which are described in the 'Characteristics of Ongoing Studies' table. There were no excluded studies.

Risk of bias in included studies

There was insufficient information provided in the trial publications to determine the method of randomisation for two of the trials (Fentiman 1987; Olson 1977). In light of the relatively few women randomised and the likelihood that additional information would not be useful at this time we have not sought to clarify this. The other trial used centralised computer randomisation, which was obtained by a telephone call to the coordinating office (SAKK (CT) 1994; SAKK (TAM) 2003).

Effects of interventions

Data could not be extracted on all relevant outcomes for all the randomised comparisons identified. However, because the total amount of randomised evidence identified was insufficient to provide reliable information we have not sought further data. The results of each trial are summarised.

Olson's trial of 32 women who received either radiotherapy alone or in combination with systemic administration of actinomycin-D found that chemotherapy improved the local control rate but had no apparent effect on overall survival (Olson 1977). The trial reported by Fentiman, also comprising a total of only 32 patients, showed that the addition of alpha-interferon to local treatment of locoregional recurrent breast cancer had no apparent effect on the further course of the disease (Fentiman 1987).

The Swiss SAKK trial of tamoxifen (178 women randomised) found an improvement in disease-free survival in patients after local treatment for isolated locoregional recurrence but not in overall survival. The last reported analysis of this trial (SAKK (TAM) 2003) included a median follow-up time for surviving patients of 11.6 years. This trial reported a median disease-free survival (DFS) of 6.5 years with tamoxifen and 2.7 years with observation (P value 0.053). In postmenopausal patients, tamoxifen led to an increase of DFS from 33% to 61% (P value 0.006). In premenopausal women, 5-year DFS was 60%, independent of tamoxifen medication. For the whole study population, the median post-recurrence overall survival (OS) was 11.2 and 11.5 years in the observation and the tamoxifen group, respectively; premenopausal patients experienced a 5-year OS of 90% for observation compared with 67% for tamoxifen (P value 0.175), while the respective figure for postmenopausal patients was 75% for both.

No results were available for the 50 women randomised into the concurrent trial of chemotherapy (SAKK (CT) 1994) .

None of these trials reported effects of the systematic treatment on the patient's quality of life.

DISCUSSION

Despite a thorough search for relevant clinical trials, insufficient randomised evidence has been identified to assess reliably the

effects of systemic therapy after local therapy of a loco-regional recurrence for women with breast cancer. As mentioned above, if loco-regional recurrence is mainly a marker of bad prognosis for a woman with breast cancer the addition of systemic therapy to potentially curative local treatment is likely to have only moderate effects, perhaps of a similar size to those seen in the primary adjuvant setting (EBCTCG 1998a; EBCTCG 1998b). If, on the other hand, additional systemic therapy has no effect on relapse or death, it would be better not to use such treatments given the known toxicity, the likelihood that the treatment will adversely affect the patient's quality of life, and the costs assosciated with such treatment. Hopefully, the currently ongoing randomised trials will gather sufficient randomised evidence to show the effect of these treatments.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of randomised trials provides insufficient evidence to do other than conclude that the most appropriate form of practice might be participation in randomised trials of systemic treatment versus observation. There are three such trials ongoing at the moment. However, studies like these will probably find that the number of eligible women in each individual institution taking part is rather low and a large number of participating institutions will be needed to ensure that the trials recruit a sufficiently large number of patients. Therefore, clinicians and institutions that take care of patients with locally recurrent breast cancer should consider participating in these or similar randomised trials. If there is no possibility for a particular patient to take part in a randomised trial, she and her doctor should discuss the use of systemic therapy in light of their preferences for such treatments and their experience of the treatment used when the women was first diagnosed with breast cancer.

Implications for research

The optimisation of treatment is one of the main goals of clinical research in breast cancer. As long as research into new areas, such as genetics, does not provide keys to controlling breast cancer, randomised trials of interventions remain the only way to identify which treatments will improve outcome for patients. Given the current lack of high quality evidence on the effects of systemic treatments for women who have had a loco-regional recurrence of breast cancer, research should focus on randomised trials of systemic treatment versus observation. There are three relevant trials ongoing at the moment and patients and doctors should be encouraged to take part in these or similar studies.

ACKNOWLEDGEMENTS

We are grateful to Libby Weir and Sam James for their help in the identification of potentially eligible trials and to Davina Ghersi for her encouragement to complete the full review.

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References to ongoing studies

GBSG-GABG 6 *{published data only}*

GABG-6.. Ongoing study. October 1998.. Contact author for more information.

IBCSG *{published data only}*

IBCSG.. Ongoing study. 2001. Contact author for more information.

PACS-03 *{published data only}*

PACS-03.. Ongoing study. February 2001.. Contact author for more information.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Fentiman 1987

Study characteristics		
Methods	Randomised, but no information on method of randomisation.	
Participants	Women with breast cancer recurrence in chest wall or regional lymph nodes.	
Interventions	All women received radiotherapy. Randomised interventions: 1. observation; 2. alpha interferon (for 1 year).	
Outcomes	Relapse. Survival. Side effects of interferon.	
Notes	1982 to 1985. 32 women were randomised. Results available for 20 month disease free survival and for 20 month survival.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Olson 1977

Study characteristics	
Methods	Randomised, but no information on method of randomisation.
Participants	Women with breast cancer recurrence in chest wall or regional lymph nodes.
Interventions	All women received radiotherapy. Randomised interventions: 1. control; 2. actinomycin-D.
Outcomes	Local control. Median survival.
Notes	1962 to 1971. 32 women were randomised. Results not available on relapses or deaths.
Risk of bias	

Olson 1977 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

SAKK (CT) 1994

Study characteristics	
Methods	Randomised. Randomisation was done by telephone to a central office, after surgery.
Participants	Poor risk (defined as being unsuitable for endocrine therapy). Women with loco-regional recurrence after prior treatment for breast cancer.
Interventions	All women received radical excision of the recurrence followed by local radiotherapy (2 Gy per fraction, 5 times per week, for a total dose of 50Gy). Randomised interventions: 1. observation; 2. vincristine + doxorubicin + cyclophosphamide.
Outcomes	Disease free survival. Overall survival. Relapse at any site. Second malignancy.
Notes	1982 to1991. 50 women were randomised. Results not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

SAKK (TAM) 2003

Study characteristics	
Methods	Randomised. Randomisation was done by telephone to a central office, after surgery. Stratified according to menopausal status, adjuvant chemotherapy and axillary node involvement at diagnosis.
Participants	'Good risk' women with loco-regional recurrence after prior treatment for breast cancer. Good risk was defined as estrogen receptor (ER+) positive recurrence, or in the case of an unknown receptor status, a disease free interval of greater than 12 months and 3 or less recurrent tumor nodules each 3cm or less in diameter.
Interventions	All women received radical excision of the recurrence followed by local radiotherapy (2 Gy per fraction, 5 times per week, for a total dose of 50Gy). Randomised interventions:

SAKK (TAM) 2003 *(Continued)*

	1. observation; 2. tamoxifen (20mg/d until progression).
Outcomes	Disease free survival - calculated from the day of randomisation to the first event Overall survival. Relapse at any site. Second malignancy.
Notes	1982 to 1991. 178 women were randomised. Follow up 11.6 years for surviving patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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

GBSG-GABG 6

Study name	GABG-6.
Methods	
Participants	Women aged 18 to 75 with histologically confirmed first isolated (that is non- metastasised) resectable (R0, R1) local and/or regional recurrence of invasive breast cancer, following mastectomy or breast -conserving therapy.
Interventions	All women receive local radiotherapy if required. Randomised interventions: 1. control; 2. doxorubicin (50 mg/m2) + docetaxel (75 mg/m2) every 3 weeks x 4.
Outcomes	Disease free survival. Overall survival. Quality of life.
Starting date	October 1998.
Contact information	Dr. H.F. Rauschecker Westermayerstr. 18, D-83022 Rosenheim Germany Phone: +49-8031- 219990 Fax: +49-8031-381367 Email: rauschecker@t-online.de
Notes	Randomisation by telephone. Target accrual: 500.

IBCSG

Study name	IBCSG.

IBCSG *(Continued)*

Methods	
Participants	Women with histologically proven first isolated (i.e. non metastasised) resectable (R0, R1) loco-regional recurrence of invasive breast cancer, following either mastectomy or breast- conserving treatment.
Interventions	All women receive local radiotherapy. Randomised interventions: 1. control. 2. chemotherapy (at the discretion of the participating centre).
Outcomes	Disease free survival. Overall survival. Treatment toxicity. Quality of life.
Starting date	2001
Contact information	Dr. S. Aebi Inselspital CH- 3010 Bern, Germany
Notes	Randomisation by telephone. Target accrual: 1000.

PACS-03

Study name	PACS-03.
Methods	
Participants	Women aged 18 to 65 with histologically proven totally resected invasive intra-mammary relapse of breast cancer at least 6 months after primary breast- conserving treatment. No distant metastases.
Interventions	Randomised interventions: 1. control. 2. FEC 100 (every 21 days x3) then docetaxel (100 mg/m2 every 21 days x3).
Outcomes	Overall survival. Treatment safety.
Starting date	February 2001.
Contact information	Dr. G. Romieu Centre Val d'Aurelle- Paul Lamarque, 326 rue des Apothicaires F- 34298 Montpellier Cedex 05 France. Tel: +33-04-67613151 Fax: +33-04-67613157
Notes	Randomisation by telephone. Target accrual: 370.

WHAT'S NEW

Date	Event	Description
26 January 2018	Review declared as stable	As only one RCT (called the CALOR trial) has been published since 2001, we do not intend to update this review and direct readers to the results of this trial (Lancet Oncology 2014, 15(2): 156-63).

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 4, 2001

Date	Event	Description
19 May 2008	New search has been performed	New search conducted and citations reviewed for inclusion/exclusions. No new trials included
15 May 2008	Amended	Converted to new review format.
23 July 2001	New citation required and conclusions have changed	First review publication
30 May 2000	Amended	First protocol publication

CONTRIBUTIONS OF AUTHORS

All authors contributed to the design of the review, the writing of the protocol and the search for relevant studies. MC extracted data from the identified trials in consultation with HR. MC drafted the full review and all authors were involved in its revision and approval for publication.

DECLARATIONS OF INTEREST

Helmut Rauschecker is coordinator of the ongoing trial GBSG-GABG Study 6.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

NOTES

A search was last conducted for this review 18/08/2005.

One new reference has been added for Issue 1, 2006 - Waeber et al' Annals of Oncology 2003; 14(8):1215-21. This is an update of the randomised trial conducted by SAKK 2003 of the use of tamoxifen or not in individuals treated with radiation therapy for a local-regional recurrence following mastectomy. This publication includes an extended median follow up of surviving patients of 11.6 years and Disease Free Survival of 6.5yrs where previously these had been 3 and 5 years respectively. This has not changed the conclusions of the review.

The review for Issue 1, 2006 also includes full copyediting by Wiley copyedit support

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Breast Neoplasms [*drug therapy] [*radiotherapy]; Combined Modality Therapy; Dactinomycin [therapeutic use]; Interferon-alpha [therapeutic use]; Neoplasm Recurrence, Local [*drug therapy] [*radiotherapy]; Randomized Controlled Trials as Topic; Tamoxifen [therapeutic use]

MeSH check words

Female; Humans