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Follow-up strategies for women treated for early breast cancer (Review)

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 6
OBJECTIVES 7
METHODS 7
RESULTS 9
Figure 1. 10
Figure 2. 12
DISCUSSION 14
AUTHORS' CONCLUSIONS 15
ACKNOWLEDGEMENTS 15
REFERENCES 16
CHARACTERISTICS OF STUDIES 18
DATA AND ANALYSES 24
Analysis 1.1. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 1 Overall survival. 25
Analysis 1.2. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 2 Overall survival by age. 26
Analysis 1.3. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 3 Overall survival by tumour size. 26
Analysis 1.4. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 4 Overall survival by lymphonodal status. 27
Analysis 1.5. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 5 Overall survival 5 years. 27
Analysis 1.6. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 6 Disease-free survival. 28
Analysis 1.7. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 7 Disease-free survival by age. 28
Analysis 1.8. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 8 Disease-free survival by tumour size. 28
Analysis 1.9. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 9 Disease-free survival by lymphonodal status. 29
Analysis 1.10. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 10 number of metastasis detected in an asymptomatic way. 29
Analysis 2.1. Comparison 2 Centralised vs decentralised follow-up, Outcome 1 Overall survival. 30
Analysis 2.2. Comparison 2 Centralised vs decentralised follow-up, Outcome 2 Disease-free survival. 30
ADDITIONAL TABLES 30
APPENDICES 31
WHAT'S NEW 36
HISTORY 36
CONTRIBUTIONS OF AUTHORS 37
DECLARATIONS OF INTEREST 37
SOURCES OF SUPPORT 37
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 37
INDEX TERMS 37

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[Intervention Review]

Follow-up strategies for women treated for early breast cancer

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ABSTRACT

Background

Follow-up examinations are commonly performed after primary treatment for women with breast cancer. They are used to detect recurrences at an early (asymptomatic) stage. This is an update of a Cochrane review first published in 2000.

Objectives

To assess the effectiveness of different policies of follow-up for distant metastases on mortality, morbidity and quality of life in women treated for stage I, II or III breast cancer.

Search methods

For this 2014 review update, we searched the Cochrane Breast Cancer Group's Specialised Register (4 July 2014), MEDLINE (4 July 2014), Embase (4 July 2014), CENTRAL (2014, Issue 3), the World Health Organization (WHO) International Clinical Trials Registry Platform (4 July 2014) and ClinicalTrials.gov (4 July 2014). References from retrieved articles were also checked.

Selection criteria

All randomised controlled trials (RCTs) assessing the effectiveness of different policies of follow-up after primary treatment were reviewed for inclusion.

Data collection and analysis

Two review authors independently assessed trials for eligibility for inclusion in the review and risk of bias. Data were pooled in an individual patient data meta-analysis for the two RCTs testing the effectiveness of different follow-up schemes. Subgroup analyses were conducted by age, tumour size and lymph node status.

Main results

Since 2000, one new trial has been published; the updated review now includes five RCTs involving 4023 women with breast cancer (clinical stage I, II or III).

Two trials involving 2563 women compared follow-up based on clinical visits and mammography with a more intensive scheme including radiological and laboratory tests. After pooling the data, no significant differences in overall survival (hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.84 to 1.15, two studies, 2563 participants, *high-quality evidence*), or disease-free survival (HR 0.84, 95% CI 0.71 to 1.00, two studies, 2563 participants, *low-quality evidence*) emerged. No differences in overall survival and disease-free survival emerged in subgroup

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analyses according to patient age, tumour size and lymph node status before primary treatment. In 1999, 10-year follow-up data became available for one trial of these trials, and no significant differences in overall survival were found. No difference was noted in quality of life measures (one study, 639 participants, *high-quality evidence*).

The new included trial, together with a previously included trial involving 1264 women compared follow-up performed by a hospital-based specialist versus follow-up performed by general practitioners. No significant differences were noted in overall survival (HR 1.07, 95% CI 0.64 to 1.78, one study, 968 participants, *moderate-quality evidence*), time to detection of recurrence (HR 1.06, 95% CI 0.76 to 1.47, two studies, 1264 participants, *moderate-quality evidence*), and quality of life (one study, 356 participants, *high-quality evidence*). Patient satisfaction was greater among patients treated by general practitioners. One RCT involving 196 women compared regularly scheduled follow-up visits versus less frequent visits restricted to the time of mammography. No significant differences emerged in interim use of telephone and frequency of general practitioners's consultations.

Authors' conclusions

This updated review of RCTs conducted almost 20 years ago suggests that follow-up programs based on regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on regular performance of laboratory and instrumental tests in terms of timeliness of recurrence detection, overall survival and quality of life.

In two RCTs, follow-up care performed by trained and not trained general practitioners working in an organised practice setting had comparable effectiveness to that delivered by hospital-based specialists in terms of overall survival, recurrence detection, and quality of life.

PLAIN LANGUAGE SUMMARY

Different follow-up strategies for women after breast cancer treatment

Review question: Whether an intensive follow-up decreases the number of recurrences or deaths and affects health-related quality of life (HRQoL) compared with a less intensive follow-up and whether a follow-up offered by specialists is different from that performed by family physicians.

Background: Follow-up after breast cancer is performed in order to check whether breast cancer has returned to the breast or other part of the body and to monitor side effects related to treatment. Follow-up may be performed by specialists or family physicians, regularly or on demand, and may be based on routine clinical visits (physical examinations and yearly mammography), or on a more intensive surveillance (laboratory tests and imaging examinations). The first update of this Cochrane review published in 2004 has shown that having more tests does not improve the length or quality of life in breast cancer survivors and a comparable effectiveness of follow up by specialist to that by primary physician. Moreover, additional screening tests could increase anxiety related to false positive results, unnecessary radiation exposure and health-related costs.

Study Characteristics: A literature search up to July 2014 found five trials (involving 4023 women with a median follow-up variable from 16 to 120 months). Since the previous version of this Cochrane review in 2004, one new study has been published.

Key results: This review of trials found that follow-up programs based on a regular physical examination and a yearly mammogram appear to be as effective as the more intensive approaches and to have similar impact on HRQoL. No significant differences were found between follow-up performed by specialists or family physicians, regularly or on demand. These results should be interpreted with caution bearing in mind that these studies were conducted almost two decades ago; additional trials incorporating new biological knowledge and improved imaging technologies are needed.

Quality of the evidence: Allocation concealment was adequate in all but one trial; two trials were judged to be at low risk of selection bias; the blinding of the outcome assessor was not described in two trials. For one trial it was not possible to judge risk of bias because it reported no methodological information.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: Non-intensive versus intensive follow-up for women treated for early breast cancer

Non-intensive versus intensive follow-up for women treated for early breast cancer

Patient or population: women treated for early breast cancer
Settings: outpatients
Intervention: non-intensive follow-up
Comparison: intensive follow-up

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intensive	Non-intensive				
Overall survival Follow-up: median 71 months	**Study population**		**HR 0.98** (0.84 to 1.15)	2563 (2 studies)	⊕⊕⊕⊕ **HIGH** [1]	
	26 per 100	**26 per 100** (23 to 30)				
Disease-free survival Follow-up: median 71 months	**Study population**		**HR 0.84** (0.71 to 1.00)	2563 (2 studies)	⊕⊕⊖⊖ **LOW** [2,3]	
	23 per 100	**19 per 100** (17 to 23)				
Quality of life [4]	See comment	See comment	Not estimable[4]	639 1 study	⊕⊕⊕⊕ **HIGH** [5]	

*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; **HR:** Hazard 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]Heterogeneity was considered low (I^2 = 28%) and we did not downgrade.
[2]Heterogeneity was considerable (I^2 = 52%) and we decided to downgrade once for inconsistency of results.

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[3]We downgraded once due to possible detection bias in both trials - it was not described whether the outcome assessor was blinded. In Rosselli Del Turco 1994, the random sequence generation was not described but we did not downgrade for this because taking into account the period in which RCT was done, it was possible that the authors simply did not report the details of how the random sequence was generated.

[4]The study provided nominal information on quality of life and it was not possible to extract useful data. The trial authors concluded that there were no difference in quality of life between the two types of follow-up.

[5]We did not downgrade the quality of evidence for this outcome (as suggested by the GRADE approach).

Summary of findings 2. Summary of findings: Decentralised versus centralised follow-up for women treated for early breast cancer

Decentralised versus centralised follow-up for women treated for early breast cancer

Patient or population: women treated for early breast cancer
Settings: outpatients
Intervention: decentralised follow-up
Comparison: centralised follow-up

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Centralised follow-up	Decentralised follow-up				
Overall survival Follow-up: median 42 months	**Study population**		**HR 1.07** (0.64 to 1.78)	968 (1 study)	⊕⊕⊕⊖ **MODERATE** [1,2]	
	6 per 100	**7 per 100** (4 to 11)				
Disease-free survival Follow-up: median 42 months	**Study population**		**HR 1.06** (0.76 to 1.47)	1264 (2 studies)	⊕⊕⊕⊖ **MODERATE** [1,2,3,4]	
	13 per 100	**13 per 100** (10 to 18)				
Quality of life [5]	See comment	See comment	Not estimable	356 (1 study)	⊕⊕⊕⊕ **HIGH**	

*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; **HR:** Hazard 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.

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

[1]The publication did not describe how many women were lost to follow-up and how the random sequence was generated. We downgraded once for the first reason.
[2]There was a low event rate so we decided not to downgrade for imprecision.
[3]We downgraded once for this outcome because follow-up schedules varied even within a study.
[4]General practitioners were assured that a "rapid re-referral" would have been possible if any problem developed. This would only be feasible in a clinical trial setting or well organised health systems.
[5]Trial authors concluded that there were no difference in quality of life between the two types of follow-up. As we were unable to judge the GRADE domains for this outcome due to a lack of information, we did not downgrade the quality of evidence for this outcome (as suggested by the GRADE approach).

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BACKGROUND

Description of the condition

Breast cancer is the second most common cancer in the world and the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) (Globocan 2012). In Europe, the estimated age-adjusted annual incidence of breast cancer was 94.2/100,000 and the mortality was 23.1/100,000 in 2012 (Ferlay 2013). In the USA, according to the SEER database (2006 to 2010), the age-adjusted annual incidence of breast cancer was 124.6/100,000 and the mortality was 22.2/100,000. The median age at breast cancer diagnosis is 61 years. About 10% of breast cancers occur among women aged younger than 45 years, while 40% occur among women aged 65 years or older (SEER database 2014). Overall, 60% of breast cancers are diagnosed at a localised stage, 32% at a regional stage and 5% at an advanced stage. The five-year relative survival rate for women diagnosed with localised breast cancer is 98.5%; survival declines to 84.6% for regional stage and 25% for distant stage. Due to both early detection through screening programs and the improvement in the available treatment strategies, the percentage of women surviving at least five years after diagnosis and treatment has shifted from 74.8% in the early 1970s to 90.3% in the late 1990s. In the last few years, the increase in the number of women diagnosed with breast cancer each year and the improvement in the survival rates, have led to a significant increase in the number of breast cancer survivors (SEER database 2014).

Description of the intervention

Follow-up (care after primary treatment) of women with breast cancer includes terms such as "routine testing", "follow-up" or "surveillance". These indicate the regular use of laboratory or instrumental tests in otherwise asymptomatic patients to detect distant metastases (that is, when the cancer has spread beyond the breast) earlier. The type of tests can vary by hospital or doctor or both and they typically include routine haematological tests, all biochemical first level test examinations, for example, liver function tests, kidney function test, C-reactive protein, erythrocyte sedimentation rate, tumour markers, chest X-rays, and bone and liver scans.

How the intervention might work

Follow-up care should have several aims. These include the provision of physical and psychosocial rehabilitation, monitoring of treatment effectiveness including short- and long-term toxicity, and detecting recurrence or new cancers.

Post-treatment survivors are at risk for physical and psychosocial sequelae. Women with breast cancer may experience early and late treatment-related side effects such as fatigue, arthralgia (joint pain), cardiotoxicity, reproductive system changes, osteoporosis and the development of second tumours. Other effects may include cognitive dysfunction and psychosocial issues such as anxiety and depression, disturbances in body image, and changes in sexual quality of life (Burstein 2000). So, the post-treatment follow-up is essential to ensure detection and management of late or long-term effects and to provide psychological and supportive care.

In actual practice, however, follow-up care is offered with the main objective of detecting local or distant recurrences earlier, so that treatment for any relapse can be started. Conceptually, follow-up care can be considered as a screening program - i.e. screening for early detection of metastases. As such, it is quite difficult to evaluate its efficacy retrospectively, because survival of asymptomatic patients who have relapses detected by these screening tests can only be compared with survival of symptomatic patients who have relapses. This kind of comparison can be severely biased by lead time (early detection simply increases the period during which a metastasis is observed), and length time (cases with a long pre-clinical phase and, therefore, presumably less aggressive relapses are more likely to be detected by a screening program) (Duffy 2008). A randomised design is thus the only valid way to get an unconfounded estimate of the effectiveness of different follow-up strategies. Despite the lack of convincing proof that this postoperative surveillance care improves outcomes in these patients, intensive follow-up is quite common in clinical practice and represents a significant workload for radiotherapy, surgical and oncologic departments (Grunfeld 2010; Loprinzi 1994).

Why it is important to do this review

In the previous update of this review in 2004 of randomised clinical trials (RCTs) evaluating the different strategies of follow-up for stage I, II or III breast cancer patients, we concluded that, according to the RCTs available at that time, a follow-up based on routine clinical visits (physical examinations and yearly mammography) had the same effectiveness as a more intensive surveillance (laboratory tests and imaging examinations) in terms of overall survival and quality of life. Furthermore, a centralised approach (follow-up performed by a specialist at a multidisciplinary breast clinic) showed the same effectiveness as the decentralised approach (surveillance performed by a general practitioner); finally, no differences were found among a regularly scheduled surveillance and a follow-up strategy “on demand”.

Despite all the studies included in the systematic review concluding that new studies would have been necessary on this topic, only one new study has been published so far; moreover, to our knowledge, while cancer research is actively pushed in the field of anticancer treatments and drug development, no clinical trials evaluating the efficacy of the different follow-up strategies are ongoing in ClinicalTrials.gov (Clinical trial 2014) or the WHO ICTRP search portal (WHO 2014).

Updating this systematic review about follow-up strategies for women with breast cancer would allow us to understand better the state of the art on this clinically relevant topic, which could be the basis to focus future research in this field. In fact, due to the improvements in the understanding of the biology of breast cancer, the availability of advanced imaging technologies and the progress made in the treatment of breast cancer, new more personalised follow-up approaches should be studied. In particular, positron emission tomography (PET)-computed tomography (CT) showed to be more sensitive and specific in detecting distant metastatic lesion as compared to conventional imaging (Constantinidou 2011). Furthermore, new biomarkers such as circulating tumour cells are promising markers to detect microscopic residual disease after primary treatment (Lucci 2012). These new diagnostic tools should be studied for their ability to anticipate the clinical evidence of recurrence, and the subsequent impact on survival.

Breast cancer is no longer considered a single disease, but is classified into at least four different intrinsic molecular subtypes based on the immunohistochemical classification (Luminal A-like,

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Luminal B-like, HER2 positive, and triple negative (Goldhirsch 2013)). Nowadays, it is well-established that not only the stage at diagnosis, but also the biology of the disease influence the risk of breast cancer recurrence and death (Jatoi 2011). Moreover, a growing amount of evidence has shown that the different biological subtypes differ in terms of timing of disease recurrence (Jatoi 2011; Metzger-Filho 2013) and pattern of metastatic spread (particularly, site of first recurrence) (Kennecke 2010). These observation could lead to the hypothesis that different schedules and different intensity of follow-up strategies should vary according to the different breast cancer subtypes.

Moreover, thanks to the improvement of breast cancer management and the availability of new effective treatments, metastatic breast cancer, at least for a small percentage of women, should not be considered a fatal condition anymore (Hortobagyi 2002): particularly, women with oligometastatic disease treated with a multidisciplinary aggressive approach can still be cured (Kobayashi 2012). Based on this assumption, an early detection of metastatic disease could lead to the identification of patients with low burden of disease who can be still treated with curative intent.

Taking into account the improvement in the understanding of the biology of breast cancer, in the available imaging technologies and in the treatment of the disease, a better assessment of the state of the art about the follow-up strategies should be considered the basis for the design of new clinical trials in this setting towards a more “personalised follow-up approach”.

OBJECTIVES

To assess the effectiveness of different policies of routine follow-up testing on morbidity, survival and quality of life in women with breast cancer after primary treatment.

Specifically, the effectiveness of the following types of routine follow-up policies were explored.

- Follow-up based on routine clinical visits plus yearly mammogram compared to a more intensive surveillance where radiological and laboratory tests are regularly added to routine visits.
- Centralised compared to decentralised follow-up (i.e. surveillance offered by a specialist at a multidisciplinary breast clinic compared to that delivered by a general practitioner).
- Regular follow-up compared to surveillance on demand.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) comparing different approaches to follow-up after completion of primary treatment.

We extracted and reviewed additional information from prospective non-randomised studies but the data were not used for quantitative pooling.

Types of participants

Women who have had primary surgical treatment for breast cancer (clinical stage I, II or III), with no evidence of recurrence.

Types of interventions

- Follow-up based on routine clinical visits plus yearly mammogram compared to a more intensive surveillance including radiological and laboratory tests.
- Centralised versus decentralised follow-up (i.e. surveillance offered by a specialist at a multidisciplinary breast clinic compared to that delivered by a general practitioner).
- Regular follow-up compared to surveillance on demand.

Types of outcome measures

Primary outcomes

- Overall survival, as estimated from the date of randomisation to the date of last contact or death from any cause.
- Health-related quality of life (HRQoL), assessed using EORTC QLQ-C30, SF-36 and the "hospital anxiety and depression scale (HADS)"

Secondary outcomes

- Disease-free survival (expression of the time to detect a recurrence). It is used in this context to compare the power of different follow-up strategies to detect recurrence earlier, possibly in an asymptomatic stage.
- Occurrence of metastases detected in an asymptomatic status.

Search methods for identification of studies

Electronic searches

(a) The Cochrane Breast Cancer Group Specialised Register was searched on the 4 July 2014 (details of 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 http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Studies including the text words 'early breast cancer', 'locally advanced breast cancer', 'follow up', 'follow-up studies', 'follow-up care', 'centralised follow-up', 'decentralised follow-up', postoperative surveillance' and 'routine clinical visits' on the Specialised Register were retrieved for consideration.
(b) MEDLINE (via OvidSP) from 1950 until 4 July 2014. Appendix 1.
(c) Embase (via Embase.com) from 1966 until 4 July 2014. Appendix 2.
(d) CENTRAL, 2014, Issue 3. See Appendix 3.
(e) The WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials on the 4 July 2014. See Appendix 4.
(f) ClinicalTrials.gov (http://clinicaltrials.gov/ct2/home) was searched until 4 July 2014. See Appendix 5.

Searching other resources

No other sources were searched.

Data collection and analysis

Selection of studies

For this 2014 review update and the previous update two review authors (2014 update: Ivan Moschetti (IM), Michela Cinquini (MC); 2004 update: IM, Laura Coe (LC)) independently inspected the search hits by reading the titles and abstracts. The full-text article

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of each potentially relevant study identified in the search was obtained and assessed for inclusion independently by the same two authors. No disagreements regarding eligibility occurred. Both review authors read and assessed 15 PDF documents. The other papers retrieved by the search strategy were not considered because they were not RCTs, or they clearly referred to follow-up managed by nurses. For this reason a "Characteristics of excluded studies" table was not completed.

Data extraction and management

Two review authors independently extracted data (2014 update: IM, MC; 2004 update: IM, LC) using a standardised data collection form.

We extracted the following characteristics from each included study: participants, setting, interventions, comparators and outcomes, *see* "Characteristics of included studies" table. When a meta-analysis was performed (i.e. for the GIVIO and Rosselli Del Turco trials), we used individual patient data. We did not contact any trial authors for the 2004 and 2014 updates.

For studies with more than one publication, we extracted data from all publications. However, we considered the final or updated version of each trial as the primary reference.

Assessment of risk of bias in included studies

Two review authors (2014 review update: IM, MC) independently assessed the risk of bias in each trial using Cochrane's 'Risk of bias' tool. Any differences were resolved in a consensus meeting.

We classified the generation of allocation sequence, allocation concealment, blinding of outcome assessor, completeness of outcome data, and selective outcome reporting as low risk of bias, high risk of bias, or 'unclear' following the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1.0* (Higgins 2011).

Given the nature of the interventions under investigation, only blinding of outcome assessor (avoidance of performance bias and detection bias) was considered for subjective outcomes (e.g. quality of life, disease-free survival and occurrence of metastases).

No sensitivity analyses depending on 'Risk of bias' criteria were performed.

Measures of treatment effect

For each trial, the overall and disease-free survival hazard ratio (HR) was calculated using the log rank "O-E" and its variance (V). When the HR and the relative confidence interval (CI) were not reported in the article to permit a direct calculation of this two measures, we calculated them indirectly using the Mantel-Haenszel estimate of the HR and its CI reported in the paper, or we used the total number of events and the number of patients at risk in each arm. The individual HR estimates were combined into an overall HR using the Peto odds ratio method that allows for fixed-effect only.

We planned to report the occurrence of metastases detected in an asymptomatic state as risk ratio (RR) and its 95% CI.

Quality of life was considered as a continuous outcome and we planned to report the results as the mean difference (MD) and its standard error. However, none of the trials had information on health-related quality of life (HRQoL) that could be extracted and meta-analysed. These data have been described in a narrative way. For quality of life, we considered the "overall health perception", the "satisfaction of patients" and the "hospital anxiety and depression scale (HADS)".

Unit of analysis issues

The unit of analysis was the study participant.

Dealing with missing data

For this 2014 review update, we did not contact the authors of primary studies. All analyses were performed on an intention-to-treat basis.

Assessment of heterogeneity

A formal statistical test for heterogeneity was done using the Chi^2 test and I^2 statistic. A P value of 0.10 for heterogeneity was considered as statistically significant. We planned to use a fixed-effect model or a random-effects model, depending on the evidence of statistical heterogeneity.

Assessment of reporting biases

Publication bias was not evaluated given the type of intervention considered. We are confident that no relevant data on this type of intervention have been kept concealed.

Data synthesis

For time-to-event outcomes, we used a fixed-effect analysis (O-E and Variance).

Because a certain degree of heterogeneity was not expected among trials for dichotomous outcomes, we used a fixed-effect analysis (Mantel-Haenszel).

For continuous outcomes, we planned to use a fixed-effect analysis (inverse-variance method).

RevMan 5.3 software was used for all the analyses.

The overall quality of the evidence for all the outcome was judged using the GRADE system (GRADE 2004), which takes into account the 'Risk of bias' assessment, imprecision and directness of results. The 'Summary of findings' tables present the main findings of the review.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses by age, tumour size and lymph node status before primary treatment were conducted based on the hypothesis that these may influence the biological behaviour of the disease and therefore lead to different benefits for the different follow-up strategies (De Lena 1995; Greco 1998).

Sensitivity analysis

A sensitivity analysis was not carried out.

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RESULTS

Description of studies

Results of the search

In this 2014 review update, searching the Specialised Register, MEDLINE, Embase and CENTRAL yielded 1493 records while ClinicalTrials.gov and WHO ICTRP retrieved 669 ongoing trials. Two review authors (IM, MC) independently screened all records excluding 2102 of them by title and abstracts. For the remaining 15 records, after reading the full text, only one answered the review's question. No disagreement rose between review authors during the process of study selection.

This update includes information from one new report and provides the results of a study conducted in Ontario from 1997 to 2003 (Grunfeld 2006) comparing a follow-up structured in the cancer centre according to usual practice and a follow-up managed by family physicians (see Figure 1).

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Figure 1. Study flow diagram.

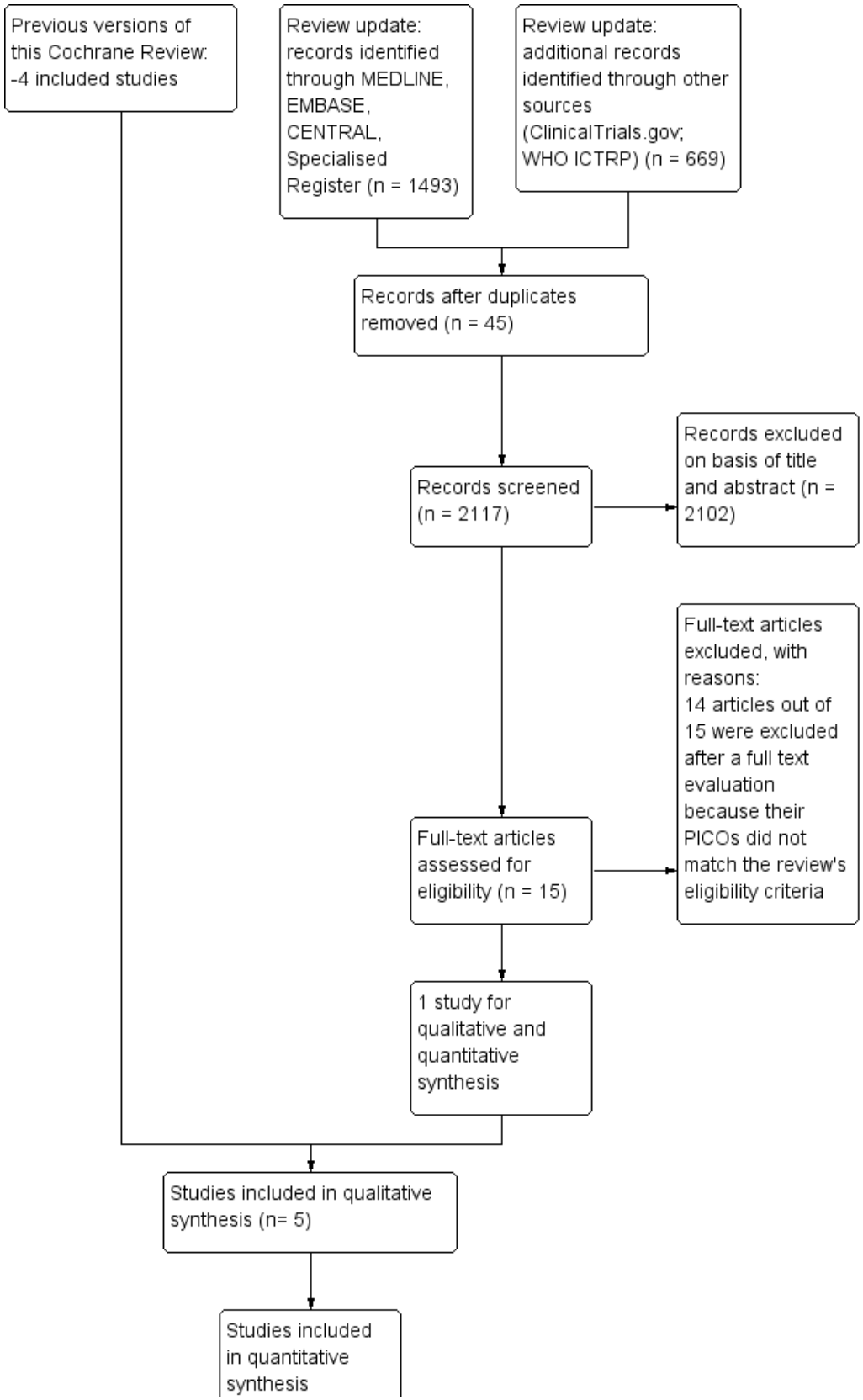

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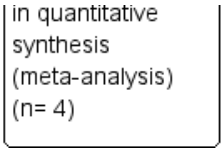
Figure 1. (Continued)



Included studies

Five studies met the inclusion criteria. All of the studies were multicentre randomised controlled trials (RCTs) comparing different types of follow-up in women with breast cancer. Overall, these studies included 4023 women (the number of patients ranged from 196 to 1320) with breast cancer (clinical stages I, II or III) with no evidence of recurrence after their primary surgical treatment. The median follow-up time available in the five trials varied from 16 to 120 months.

Data on overall and disease-free survival were available for four trials (GIVIO; Grunfeld 1996; Grunfeld 2006; Rosselli Del Turco 1994). None of the trials had information on health-related quality of life (HRQoL) that could be extracted and meta-analysed. These data have been described in a narrative way. Only one trial (GIVIO) reported information about metastases.

The trials included in this review explored three different follow-up strategies.

- Two trials (GIVIO and Rosselli Del Turco 1994) compared follow-up based on clinical visits and mammography alone, with a more intensive surveillance scheme including radiological and laboratory tests. Combined, they included 2563 women. Their outcomes were overall survival, disease-free survival and, in one trial (GIVIO), HRQoL.
- Two trials (Grunfeld 1996 and Grunfeld 2006) compared follow-up offered by a specialist at the hospital with follow-up offered by a general practitioner. The first trial included 296 women. Its outcomes were time to detection of recurrence and HRQoL. The second trial enrolled 968 women and evaluated overall survival, disease-free survival and quality of life.
- One trial (Gulliford 1997) compared conventionally scheduled follow-up with follow-up limited to the time of mammography, but with telephone and GP consultation available on demand. It included 196 women and was a pilot study to evaluate feasibility of women's acceptance of symptom-driven follow-up. Outcomes included acceptability of less frequent follow-up, use of telephone and GP consultations and satisfaction with allocation to a particular follow-up strategy.

Excluded studies

There are no excluded studies.

Risk of bias in included studies

An iconographic summary of the risk of bias is illustrated in Figure 2. The Gulliford 1997 trial was judged as having an unclear risk of bias on all domains because it reported no methodological information.

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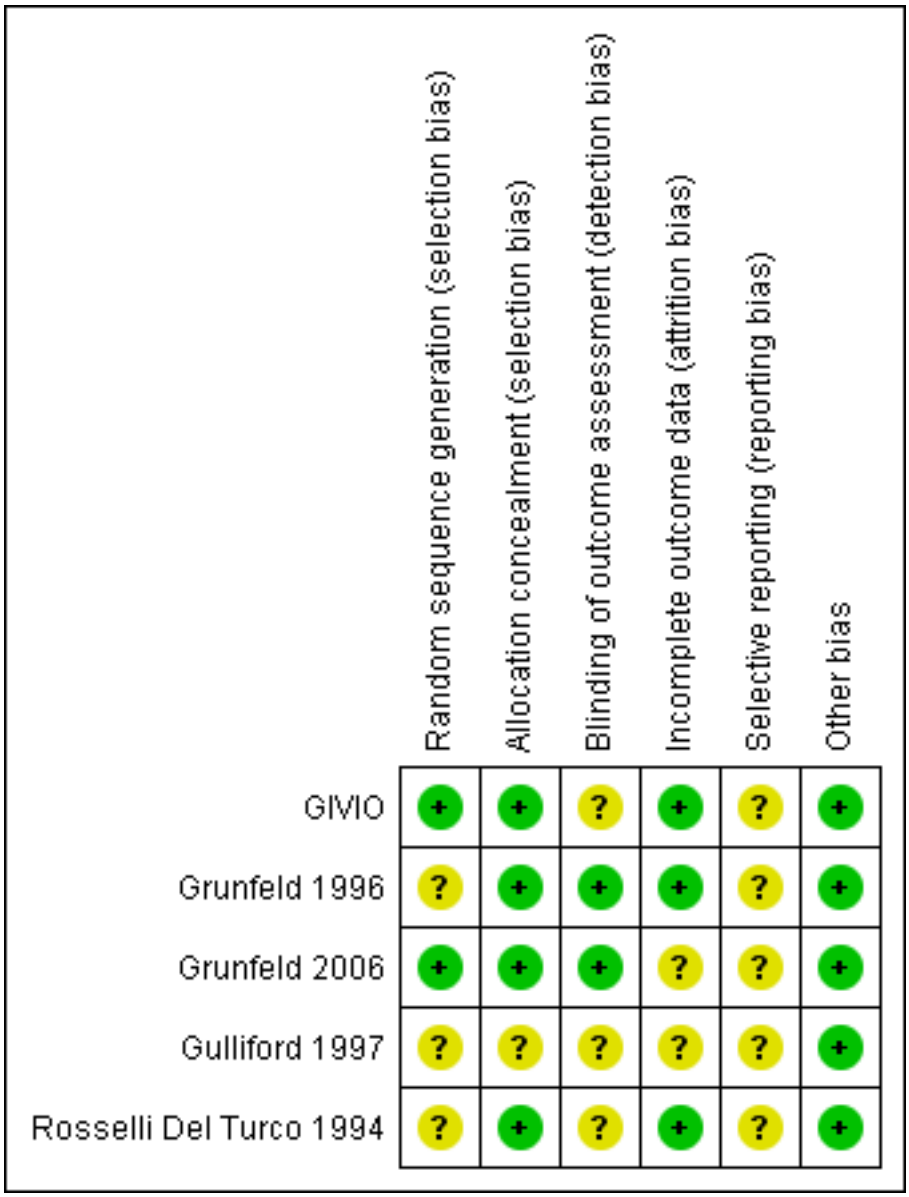
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

In the Gulliford 1997, Grunfeld 1996 and Rosselli Del Turco 1994 trials the method for generating the random sequence was not reported; in Grunfeld 1996, the trial authors stated only that "random allocation was in blocks of eight". GIVIO and Grunfeld 2006 had an adequate random sequence generation using a computer-generated list.

Allocation concealment

Allocation concealment was adequate in all trials, except for Gulliford 1997.

Blinding

Double-blinding was not considered as adequate for this kind of study, so only the blinding of the outcome assessor was judged.

Blinding of outcome assessors

In the GIVIO, Gulliford 1997 and Rosselli Del Turco 1994 trials, it was not described whether or not the outcome assessor was blinded. This can lead to a potential detection bias for disease-free survival. In Grunfeld 1996, blinding of the outcome assessors was judged as adequate as they assessed recurrence independently even though the trial authors stated that "in some cases, the allocation group could have been deduced from the course of clinical events". A blinded committee adjudicated all events in Grunfeld 2006.

Incomplete outcome data

The GIVIO study lost 8% of its randomised patients, who could not be traced and were not included in the analyses. The overall loss to follow-up in Rosselli Del Turco 1994 was 0.8%. In both trials (GIVIO and Rosselli Del Turco 1994), approximately 10% of the patients discontinued follow-up care, with a similar distribution between intensive and clinical groups. Survival data were available for those

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lost to follow-up and were included in the analyses (intention-to-treat analysis). In Grunfeld 1996, only one patient per group was lost to follow-up. Grunfeld 2006 did not report any information.

Selective reporting

Grunfeld 1996 and Gulliford 1997 were not designed to assess overall survival. Their outcomes (quality of life, time to diagnosis of recurrence, interim use of telephone and GP consultations and patient satisfaction) were assessed to investigate differences within the first two years. For additional details see Characteristics of included studies.

As all the studies have been conducted before protocol registration was mandatory, we did not search for additional information.

Other potential sources of bias

No other sources of bias identified.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: Non-intensive versus intensive follow-up for women treated for early breast cancer; **Summary of findings 2** Summary of findings: Decentralised versus centralised follow-up for women treated for early breast cancer

See Summary of findings for the main comparison and Summary of findings 2.

Follow-up based on routine clinical visits (experimental group) compared to a more intensive surveillance (i.e. with radiological/laboratory tests) (control group)

Overall survival

The meta-analysis for overall survival of the GIVIO and Rosselli Del Turco 1994 trials found no significant survival advantage in the intensive surveillance group; hazard ratio (HR) 0.98 (95% confidence interval (CI) 0.84 to 1.15; two studies, 2563 participants; high-quality evidence; Analysis 1.1). We found no significant differences in overall survival between the strategies in respect to the subgroup analyses by age (Analysis 1.2), tumour size (Analysis 1.3), nodal status (Analysis 1.4), or at five years (Analysis 1.5).

Health-related quality of life (HRQoL)

Data regarding quality of life were available just for the GIVIO trial. Questionnaires used were the Functional Living Index-Cancer Scale, the Sickness Impact Profile, the Profile of Mood States, and the Cancer Inventory of Problem Situation. The HRQoL scores were assessed at baseline, six,12, 24, and 60 months, and administered four times between six and 60 months with an average response rate of 73.5%; overall, no significant difference was found between the two follow-up strategies. The evidence was graded as high quality.

Disease-free survival

The HR was 0.84 (95% CI 0.71 to 1.00; two studies, 2563 participants; low-quality evidence; Analysis 1.6) for disease-free survival after five years of follow-up. For this outcome, the pooled effect did not confirm the statistically significant effect found in diagnostic anticipation in the Rosselli Del Turco 1994 trial. We did not observe any advantage either in the subgroup analysis for age (Analysis 1.7), or for tumour size (Analysis 1.8), or for lymphonodal status (Analysis 1.9).

Occurrence of metastases detected in an asymptomatic status

Data regarding asymptomatic detection of metastases were available only from the GIVIO trial: 31% of cases of metastases in the intensive group and 21% in the clinical group were detected in an asymptomatic phase (Analysis 1.10). This information was not available in other studies where only the proportion of distant metastases has been reported. However, it is consistent with results of several prospective non-randomised studies (Hannisdal 1993; Hietanen 1986; Logarer 1990; Mahoney 1986; Pandya 1983; Rutgers 1989; Vestergaard 1989; Wickerhan 1986).

Centralised versus decentralised follow-up (i.e. surveillance offered by a specialist at a multidisciplinary breast clinic compared to that delivered by a general practitioner)

Overall survival

Overall survival was available only for Grunfeld 2006: HR 1.07 (95% CI 0.64 to 1.78; one study, 968 participants; moderate-quality evidence; Analysis 2.1).

Health-related quality of life (HRQoL)

Quality of life shows an expected small deterioration for both groups during the Grunfeld 1996 trial (British version of the SF-36; European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30); Hospital anxiety and depression scale. The HRQL scores were assessed at baseline, mid trial and at the end of the trial). The hospital group had a statistically significant increase in symptom scores for fatigue, dyspnoea and appetite loss. There was no difference in overall health, social and emotional functioning and levels of anxiety and depression.

This study also collected data on the patients who were asked about the trial but did not participate (149/445, 33.5%). These women were older than trial participants and had a lower education level, but there were no important differences in clinical characteristics or in baseline quality of life scores.

The Grunfeld 1996 data were used in a new publication that analysed patient satisfaction with care by general practitioners versus hospital specialists over an 18-month period (see Grunfeld 1999). Questionnaires completed by 93% of patients indicated that they were more satisfied with service delivery, consultation and the continuity of care provided by their general practitioner than by a specialist.

As stated by the authors in Grunfeld 2006, no statistically significant differences were detected between groups over time for any of the scores (Medical Outcomes Study Short Form 36-Item General Health Survey (SF-36) 48 and Hospital Anxiety and Depression Scale (HADS) 49). The HRQL scores were assessed at baseline and during the subsequent seven follow-ups at six, 12, 18, 24, 36, 48, and 60 months. Overall, SF-36 PCS declined over time (0.4 units per year; $P < 0.001$), SF-36 MCS increased slightly (0.2 units per year; $P = 0.08$), HADS anxiety declined (0.08 per year; $P = 0.01$), and HADS depression increased slightly (0.04 per year; $P = 0.12$). The evidence was graded as high quality.

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Disease-free survival

The two Grunfeld trials (Grunfeld 1996; Grunfeld 2006), comparing follow-up offered by a hospital-based specialist with follow-up offered by a general practitioner, showed no differences in time to recurrence between groups. The HR was 1.06 (95% CI 0.76 to 1.47; two studies, 1264 participants; moderate-quality evidence; Analysis 2.2).

Occurrence of metastases detected in an asymptomatic status

No information about occurrence of metastases was available in Grunfeld 1996 and Grunfeld 2006.

Regular follow-up versus surveillance on demand

The Gulliford 1997 trial comparing conventionally scheduled follow-up and less frequent follow-up (restricted to the time of mammography) showed that 7% of eligible patients refused to enter the study. The characteristics of these patients may suggest that younger women with more aggressive primary disease are not willing to reduce the frequency of follow-up visits. Unfortunately, no assessments were available for these patients in relation to their quality of life.

No significant differences were found between the groups with regards to the use of telephone and visits to general practitioners during the trial. Approximately one-third of the patients in both groups expressed a preference for a less frequent schedule of follow-up visits, but only 56 women answered this question on the questionnaire.

Overall survival

No information reported on this outcome.

Health-related quality of life (HRQoL)

No information presented on this outcome.

Disease-free survival

No information presented on this outcome.

Occurrence of metastases detected in an asymptomatic status

No information presented on this outcome.

DISCUSSION

Summary of main results

It is important to remember that in the context of this review the terms "routine testing", "follow-up" as well as "surveillance" refer to the regular use of laboratory or instrumental tests in otherwise asymptomatic patients. These are done with the aim of earlier detection of distant metastases. For this reason, this review does not explore other, important, aspects of a follow-up program such as the provision of social and psychological support. Similarly, the review focuses on comprehensive follow-up packages and does not consider individual components of follow-up programs such as tumour markers or other diagnostic procedures. We chose to look only at this comparison (i.e. only clinical versus a package of tests) for pragmatic reasons as it would have been impossible to look at all possible contrasts among various types of intensive versus clinical follow-up.

Concerning the first intervention assessed (follow-up based on routine testing added to a regular visit and yearly mammogram compared to follow-up based on visits and mammography alone), the results of this systematic review confirm that doing more tests in asymptomatic patients does not add a survival advantage nor anticipate diagnosis of recurrences. These data have been endorsed by major international practice guidelines (ASCO 2013; ESMO 2013; NCCN 2014): though with some variation in terms of frequency of visits and mammography, all endorse a less intensive clinical follow-up (Table 1). Also, these last documents are similar to the previous in terms of frequency of visits and mammography and all three suggest a less intensive follow-up regimen for women treated for early breast cancer.

This review also allowed us to explore an organisational question, as well as the one about the intensity of follow-up. Despite some limitations in the evidence from Grunfeld 1996, the results suggest that decentralised follow-up (i.e. surveillance offered by a general practitioner) has the same effect on detection of recurrence as centralised follow-up. This is the result of special training given to general practitioners and this should be taken into consideration when planning to either transfer this experience or further investigate this topic.

In this updated review we added a new trial (Grunfeld 2006), conducted in Canada including 968 women. This trial was similar to Grunfeld 1996 in that no difference was found between surveillance offered by a general practitioner versus surveillance done by specialist clinic about primary (rate of recurrence-related serious clinical events) and secondary outcomes (HRQoL). Moreover, this trial was pragmatic because family physicians were provided with only one page of instruction based on published clinical guidelines without any specific training and using the usual procedures when referring patients with recurrence back to the cancer centre (no special procedures were put in place). In this trial, the 45% of approached patients chose not to participate. The authors gave no reason for this finding, but obviously this proportion could be change among different national/regional health systems.

Only one study compared the conventionally scheduled follow-up with a surveillance on demand to evaluate the feasibility of women's acceptance of symptom-driven follow-up. A reduced frequency of routine follow-up showed to be popular among women at standard risk, but younger patients with aggressive primary disease seemed to refuse a less intensive approach. However, further data and a multicentre experience are needed to draw more solid conclusions about the effectiveness of a more personalised follow-up with respect to disease outcomes.

Overall completeness and applicability of evidence

However, despite the evidence and consensus that intensive follow-up schemes provided no benefit on survival, surveys throughout the late 1990s found this message had not been completely transferred into clinical practice (Tomiak 1998; Harries 1996, Stark 1996) and that women still seemed to prefer a frequent schedule of tests in order to be reassured about their health status. In this update, we searched for new information on current clinician behaviour but did not find any new studies on the topic. It would be worthwhile to evaluate whether a good strategy of sharing information between the doctor and the patient would help women to be equally reassured when a less intensive follow-up is offered.

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Compared to other areas in medicine, it is worth noting that three of the five RCTs in this review did include quality of life as an outcome. However, different quality of life indicators (stress, anxiety and depression) were mostly used to rule out differences and thus it may well be that small differences may have gone undetected. Besides, authors of these trials noted that choosing the best time and frame for the measurement of quality of life is problematic and far from being totally agreed upon.

Results coming from these different studies have been produced in a very specific socio-cultural and geographical setting. Thus generalisability and direct application of the strategies here recommended should be carefully evaluated.

Finally, we did not find any eligible study that had evaluated the diagnostic value of using mammography as part of a follow-up strategy to monitor ipsilateral recurrences and new cancers in the contralateral breast. We have only found two prospective studies (Carlotti 1993; Holli 1998) investigating the difficulties in the interpretation of mammograms on an irradiated breast after surgery.

Quality of the evidence

Overall, we are confident that all the included studies in the quantitative analyses have a low risk of selection bias (even though some information on the random sequence generation was missing - see Grunfeld 1996 and Rosselli Del Turco 1994). Intention-to-treat analysis was performed in all trials and losses to follow-up were absent or in a low percentage in all trials. It resulted at low risk for two trials out of five (GIVIO and Rosselli Del Turco 1994). Grunfeld 1996 was judged at low risk of selective reporting even if it did not take into account overall survival.

Potential biases in the review process

This review is based on RCTs that were initiated in the late 1980s. One must consider that now, more than two decades later, knowledge, technology and treatment for breast cancer have improved, which may justify new RCTs.

Agreements and disagreements with other studies or reviews

Since the first Cochrane review was published we have not found RCTs or reviews showing new evidence in disagreement with the direction of the results discussed in this update. Again, we highlight that the translation of the results in to practice “toute coure” should be done with caution particularly for the risk of indirectness due to old trials on which this review is based.

AUTHORS' CONCLUSIONS

Implications for practice

In light of the evidence presented here, less intensive follow-up strategies based on periodical clinical exam and annual mammography seem as effective as more intense surveillance schemes. Further laboratory and radiological examinations may add useful information where women are symptomatic or the clinical visit suggests the need for further investigations.

A general practitioner's participation in the delivery of follow-up care appears feasible and appropriate but, to guarantee the directness of these results, the care should be organised in such a way that access to hospital care is easy when required.

Implications for research

The evidence from randomised controlled trials (RCTs) summarised here must, however, be interpreted with caution bearing in mind that the studies were conducted almost two decades ago when a more limited understanding of breast cancer biology and less advanced imaging technologies were available. For this reason, the applicability of the results of these "old" trials to the current clinical practice is controversial. Moreover, among clinicians a substantial variation in adherence to guidelines is observed (Chopra 2014; Grandjean 2012). Many physicians perform a more intensive surveillance approach, under the assumption that early detection and treatment of recurrences results in better outcome (Margenthaler 2012; Puglisi 2014). For these reasons, additional trials, targeted at high-risk patients and incorporating new biological knowledge and diagnostic modalities, are needed. These studies would provide new evidence of the impact of intensive follow-up on diagnostic anticipation of distant metastases and survival in women with early-stage breast cancer. A better understanding of this issue would lead to more personalised and cost-effective follow-up approaches in the case of positive results, and to the reduction of the actual non evidence-based prescriptions of diagnostic examinations in the case of negative results.

Further investigation may be warranted on the effects of less frequent schedules of follow-up and to identify the adequate frequency of mammography.

Further research should also focus on evaluating effects on long-term outcomes such as overall survival and morbidity of follow-up by a specialist compared to follow-up in primary care.

In addition, it would be interesting to evaluate current physician behaviour compared to guideline recommendations to determine to what extent the evidence has been transferred into practice.

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Rojas MPMP, Telaro E, Moschetti I, Coe L, Fossati R, Liberati A, et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD001768.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

GIVIO

Methods	Multicentre randomised controlled trial. 26 general hospitals, Italy. Randomisation by telephone, stratified by institution and pathological axillary nodal status. Inclusion within 6 weeks of surgery. Calculation of sample size reported. Intention-to-treat analysis. Protocols for adjuvant therapy and treatment of metastatic disease. Median follow-up of 71 months.
Participants	1320 women younger than 70. Histologically-confirmed, non-inflammatory, unilateral, breast carcinoma. Stage T1 to T3 (any size tumour without direct extension to chest wall or skin), N0 to N1 (no regional lymphonodal metastases or metastases to movable ipsilateral axillary lymph nodes), and M0 (no distant metastases).
Interventions	Intensive group (N = 655): -Physical exam every 3 months for 2 years and then every 6 months for 3 years. -Blood test every visit (alkaline phosphatase, gamma-glutamyl transpeptidase)

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GIVIO *(Continued)*

	-Chest roentgenography every 6 months. -Annual radionuclide bone scan. -Annual liver ecography. -Annual contralateral mammography. Control group (N = 665): -Physical exam every 3 months for 2 years and then every 6 months for 3 years. -Annual contralateral mammography.
Outcomes	Overall survival. Disease-free survival. HRQoL (quality of life perception, overall health perception, body image, emotional well-being, social functioning, symptoms and satisfaction with care). Instruments used included the Functional Living Index-Cancer Scale, the Sickness Impact Profile, the Profile of Mood States and the Cancer Inventory of Problem Situation. Time to detection of recurrence. Symptomatic status at diagnosis of metastases.
Notes	Ipsilateral breast assessment only by physical examination. 123 patients (9.3%) discontinued or were lost before relapsing, and were included in the analysis (similar distribution between experimental and control group). Additional 8% of randomised patients lost to follow-up not included in the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list, stratified by institution and pathologic axillary nodal status
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally via telephone
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not declared if assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall compliance was greater than 80% in both groups for every procedure. 91% of patients adhered to protocol recommendations.
Selective reporting (reporting bias)	Unclear risk	Study conducted before the registration of the protocol was mandatory
Other bias	Low risk	No other bias

Grunfeld 1996

Methods	Randomised controlled trial. 2 district general hospitals, England. Eligible patients were invited by letter to participate. 296/445 agreed to participate. Randomisation by telephone in blocks of eight. Calculation of sample size reported, N = 300. Follow-up 18 months Time to diagnosis assessed blinded by masking allocation information on clinical records.

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Grunfeld 1996 *(Continued)*

Participants	296 women: -initial stage I, II or III breast cancer (no distant metastases), -primary treatment completed at least 3 months previously, -attending outpatient clinic for routine follow-up, -no evidence of disease at last follow-up visit.
Interventions	Hospital group (N = 148): Routine follow-up with clinical visits and mammography, other exams only if clinically indicated. Frequency of visits in one hospital was every 3 months for 1 year and every 6 months from second to fifth years: in the other hospital was every 3, 4 and 6 months for first, second and third years and every year thereafter. General Practice group (N = 148): Follow-up with the same schedule of the reference hospital but made by the GP. GPs were sent a letter providing the patient's breast cancer history, a description of follow-up routine recommended, and assuring that rapid referral to specialist care was possible. An educational handbook on breast cancer follow-up care was provided.
Outcomes	Time to detection of recurrence. HRQoL assessed by 3 self-administered instruments: - British version of the SF-36 -European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) -Hospital anxiety and depression scale.
Notes	Characteristics of non participants are included. Random allocation not stratified by clinical stage. Educative intervention with GPs. Overall loss to follow-up 0.7%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described - Authors reported :"random allocation was in blocks of eight"
Allocation concealment (selection bias)	Low risk	Follow-up groups were assigned by a telephone call to the trial co-ordination centre in Oxford
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All clinical information on patients with suspected recurrence (record of visit forms, hospital notes, test results, doctors' correspondence) was assessed independently by three of the authors and any discrepancies or difficulties discussed. The information was masked as far as possible with respect to allocation group so that “time to diagnosis” was assessed in a blinded fashion. In some cases, however, the allocation group could have been deduced from the course of clinical events.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One (0.7%) participant in each group moved out of the district and was lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Study conducted before the registration of the protocol was mandatory.
Other bias	Low risk	No other bias.

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Grunfeld 2006

Methods	Multicentre, randomised, controlled trial; Six of the nine regional cancer centres in Ontario, Canada. Tertiary-care. The institutional review board of each participating institution approved the study protocol. All analyses were performed according to the intention-to-treat principle. Follow-up (maximum of 5 years 31.9% patients). Median follow-up was 3.5 years from randomisation (4.5 years from diagnosis) The calculated sample size of 1045 women was based on the assumption that the SCE proportion would be 4 % in both arms, with an upper level of tolerance of 5.5% in the FP arm (i.e. a non-inferiority margin of 1.5%). 968 women were enrolled. 483 allocated to the family physician (FP) group and 485 to the usual practice (CC) group.
Participants	Routine follow-up care after patients completed adjuvant therapy for early-stage breast cancer. Patients were enrolled between January 1997 and June 2001, and were observed until June 2003. Women who had completed adjuvant chemotherapy, radiotherapy, or both at least 3 months previously; who were disease-free; and who were between 9 and 15 months after diagnosis were targeted. Patients may have continued receiving adjuvant hormonal therapy.
Interventions	Patients were allocated in a 1:1 ratio to receive follow-up either in the cancer centre according to usual practice (CC group) or from their own family physician (FP group). Family physicians were provided with a one-page guideline on follow-up that recommended the following: physical examination and medical history every 3 to 6 months for 3 years, every 6 months for 2 years, and then yearly indefinitely; mammograms yearly; diagnostic tests to investigate signs or symptoms suggestive of recurrent or new primary cancer, but such tests were not to be performed routinely. For women taking tamoxifen, the guideline recommended that a history of vaginal bleeding be taken at each visit and a pelvic examination be performed annually. Family physicians were instructed to refer patients back to the cancer centre if a recurrence or new primary breast cancer developed. For patients in the FP group, if a surgeon had been involved in the patient's follow-up care, that follow-up was also transferred to the FP.
Outcomes	**Primary outcome**: recurrence-related serious clinical event (SCE) defined as any one of spinal cord compression, pathologic fracture, hypercalcaemia, uncontrolled local recurrence, brachial plexopathy, or poor functional status (Karnofsky performance score [KPS]70)47 at the time of diagnosis of recurrence. **Secondary outcome:** HRQoL: assessed using the Medical Outcomes Study Short Form 36-Item General Health Survey (SF-36) 48 and the Hospital Anxiety and Depression Scale (HADS) 49 while patients were recurrence-free. The SF-36 is scored to yield two summary scales: the Physical Component Summary (PCS) scale measuring physical health and the Mental Component Summary (MCS) scale measuring mental health. In all cases, SF-36 scales yield a score from 0 to 100, with a higher score indicating better quality of life. The HADS contains two subscales measuring anxiety and depression, with scores ranging from 0 to 21.49 Higher scores indicate greater levels of anxiety or depression. The HRQoL standardised scores assessed at baseline and during the subsequent seven follow-ups at 6, 12, 18, 24, 36, 48, and 60 months were summarised as means and change scores from baseline within each group. Recurrence, death.
Notes	Patients were excluded if they had persistent complications of primary treatment; were unable to comply with the study protocol including completing specialist follow-up; or were actively observed at a cancer centre for another primary cancer. KPS</=70 is one of the SCEs because patients usually have high functional status when recurrence is first diagnosed. Low functional status could suggest

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Grunfeld 2006 *(Continued)*

	the potential for poor management of recurrence-related symptoms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted using a computer-generated centre-specific schedule.
Allocation concealment (selection bias)	Low risk	By a telephone call to the trial co-ordinating centre of the Ontario Clinical Oncology Group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A committee that was blinded to treatment allocation adjudicated all events.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Study conducted before the registration of the protocol was mandatory.
Other bias	Low risk	The sponsors of the research had no role in any aspect of the development, conduct, analysis, or reporting of the study.

Gulliford 1997

Methods	Randomised controlled trial. 1 Breast clinic, England 211 eligible patients, 196 accepted randomisation. No information about randomisation method. Median follow-up: 16 months 13 excluded after randomisation
Participants	196 women with: -history of breast cancer proved by biopsy. -no recurrence of the disease. -no symptoms suggesting recurrence. -only tamoxifen like adjuvant treatment. -home telephone. -English speaker.
Interventions	Conventional group (N = 96): 1. Breast self examination monthly. 2. Immediate telephone access if symptoms or doubts were developed. 3. Mammography scheduled depending on primary surgery (every year for 5 years and every 2 years thereafter if lumpectomy, every 2 years since second year if mastectomy). 4. Clinical visits scheduled depending on time from diagnosis (every 3 months the first year, every 4 months the second year, every 6 months from years 3 to 5 and annually thereafter) Mammography only group (N = 97): 1, 2 and 3 are the same. 4. Clinical visits scheduled only with mammography.
Outcomes	Acceptability of randomised allocation. Use of telephone and GP.

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Gulliford 1997 *(Continued)*

	Satisfaction with allocation to follow-up.
Notes	Calculation of sample size not reported. Small sample size and short duration of follow-up -16 months-.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Study conducted before the registration of the protocol was mandatory.
Other bias	Low risk	No other bias.

Rosselli Del Turco 1994

Methods	Multicentre randomised controlled trial. 12 breast clinics in Italy (oncologic centres). Randomisation by telephone, stratified by institution. Inclusion within 6 months of surgery. Follow-up at 5 and10 years. Adjuvant therapy and treatment of recurrence according to national guidelines. Intention-to-treat analysis.
Participants	1243 women younger than 70. Histologically-confirmed, unilateral invasive carcinoma of the breast with no evidence of metastases.
Interventions	Intensive group (N = 622): -Physical exam every 3 months for 2 years and then every 6 months for 3 years. -Two-view chest roentgenography every 6 months. -Radionuclide bone scan every 6 months. -Annual mammography. Control group (N = 621): -Physical exam every 3 months for 2 years and then every 6 months for 3 years. -Annual mammography.
Outcomes	Overall survival. Disease-free survival.
Notes	Calculation of sample size not reported. 161 patients (12.9%) were lost to follow-up at some point during the study and were included in the analysis (similar distribution between experimental and control group).

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Rosselli Del Turco 1994 *(Continued)*

Vital status information available for all except 10 patients (.8%).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Low risk	Randomisation was centrally performed, individual case of allocation was communicated by telephone.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 161 (12.9%) patients were lost to clinical follow-up at some point. 86 patients intensive vs 75 patients non intensive follow-up
Selective reporting (reporting bias)	Unclear risk	Study conducted before the registration of the protocol was mandatory
Other bias	Low risk	No other bias

CC: usual practice
FP: family physician
HRQoL: health-related quality of life
SCE: serious clinical event
M: distant metastases
N: regional lymph nodes
T: primary tumour

DATA AND ANALYSES

Comparison 1. Non-intensive follow-up vs intensive follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	2563	Hazard Ratio (95% CI)	0.98 [0.84, 1.15]
2 Overall survival by age	2		Hazard Ratio (95% CI)	Subtotals only
2.1 <= 40	2	272	Hazard Ratio (95% CI)	1.08 [0.65, 1.80]
2.2 > 40	2	2291	Hazard Ratio (95% CI)	0.95 [0.78, 1.16]
3 Overall survival by tumour size	2		Hazard Ratio (95% CI)	Subtotals only
3.1 T1	2	1156	Hazard Ratio (95% CI)	0.80 [0.55, 1.17]
3.2 T2	2	1186	Hazard Ratio (95% CI)	0.92 [0.73, 1.17]

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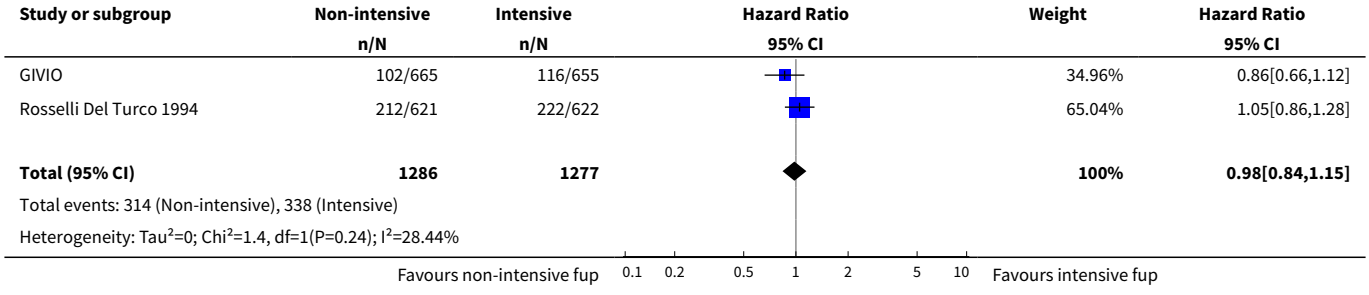
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 T3	2	167	Hazard Ratio (95% CI)	1.44 [0.91, 2.30]
4 Overall survival by lymphonodal status	2		Hazard Ratio (95% CI)	Subtotals only
4.1 N-	2	1379	Hazard Ratio (95% CI)	1.35 [0.94, 1.94]
4.2 N+	2	1184	Hazard Ratio (95% CI)	0.84 [0.68, 1.04]
5 Overall survival 5 years	2	2563	Hazard Ratio (95% CI)	0.96 [0.80, 1.15]
6 Disease-free survival	2	2563	Hazard Ratio (95% CI)	0.84 [0.71, 1.00]
7 Disease-free survival by age	2		Hazard Ratio (95% CI)	Subtotals only
7.1 <= 40	2	272	Hazard Ratio (95% CI)	0.94 [0.59, 1.47]
7.2 > 40	2	2290	Hazard Ratio (95% CI)	0.84 [0.70, 1.01]
8 Disease-free survival by tumour size	2		Hazard Ratio (95% CI)	Subtotals only
8.1 T1	2	1156	Hazard Ratio (95% CI)	0.72 [0.52, 1.00]
8.2 T2	2	1186	Hazard Ratio (95% CI)	0.83 [0.67, 1.04]
8.3 T3	2	166	Hazard Ratio (95% CI)	1.35 [0.82, 2.21]
9 Disease-free survival by lymphonodal status	2		Hazard Ratio (95% CI)	Subtotals only
9.1 N-	2	1379	Hazard Ratio (95% CI)	0.84 [0.62, 1.14]
9.2 N+	2	1183	Hazard Ratio (95% CI)	0.83 [0.68, 1.02]
10 number of metastasis detected in an asymptomatic way	1	249	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]

Analysis 1.1. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 1 Overall survival.



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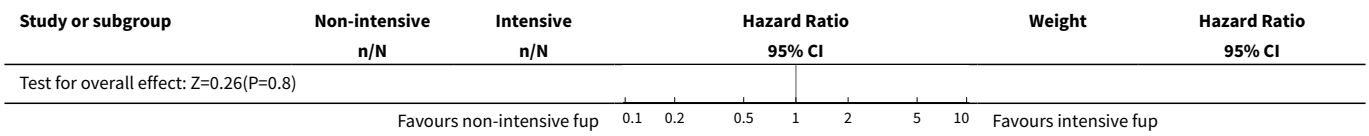
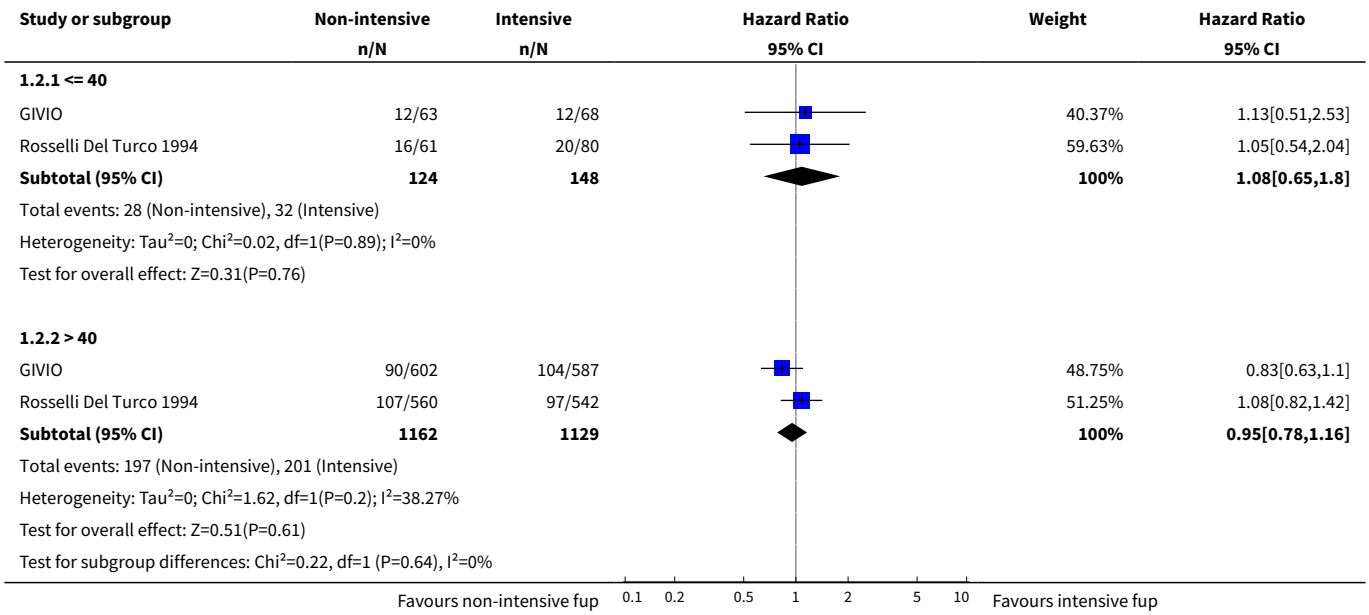
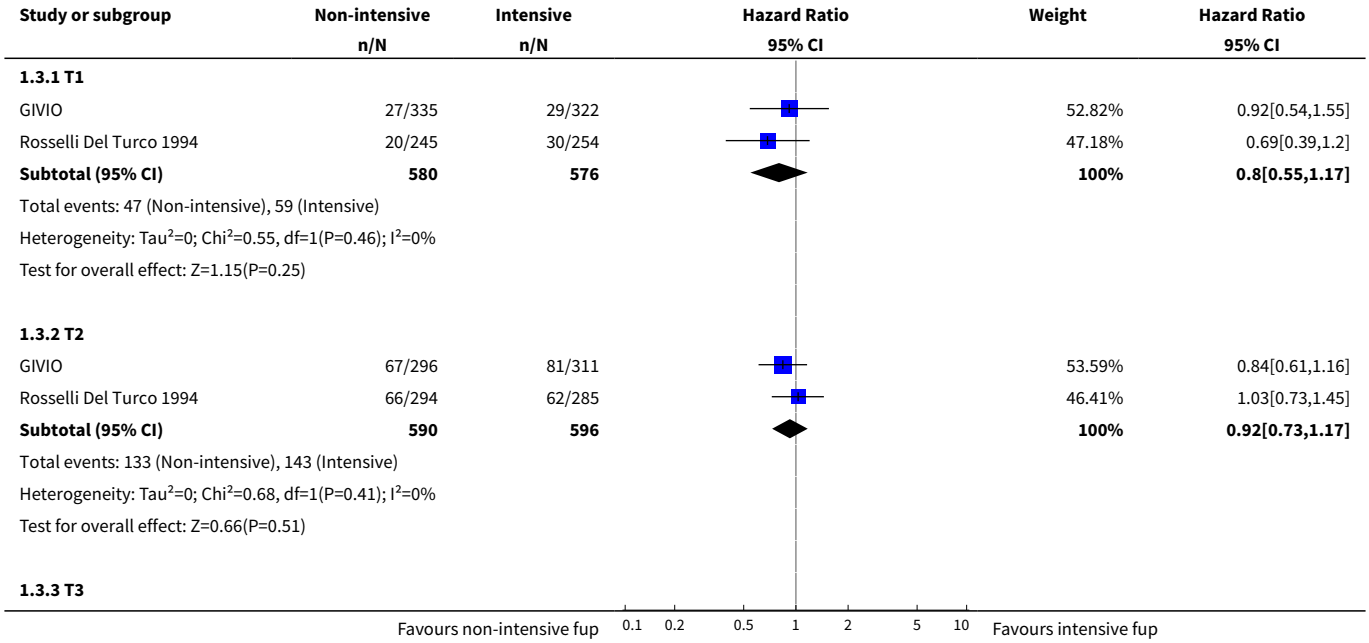


Analysis 1.2. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 2 Overall survival by age.



Analysis 1.3. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 3 Overall survival by tumour size.



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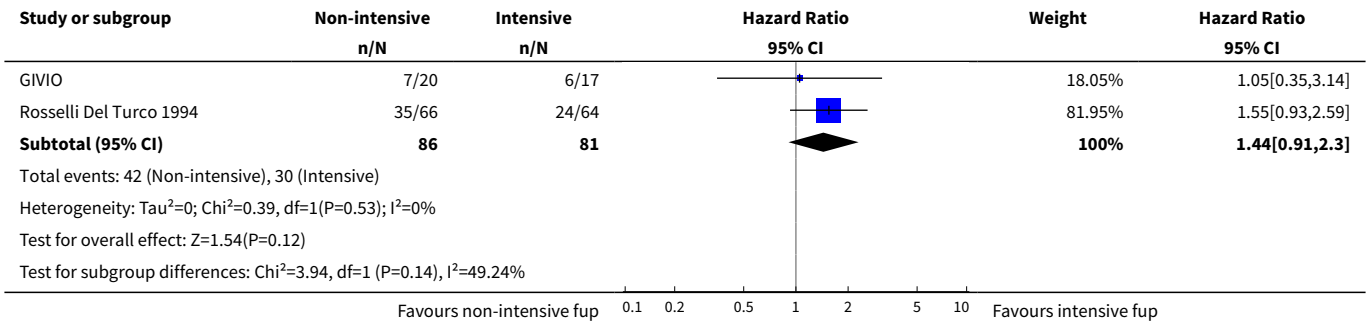
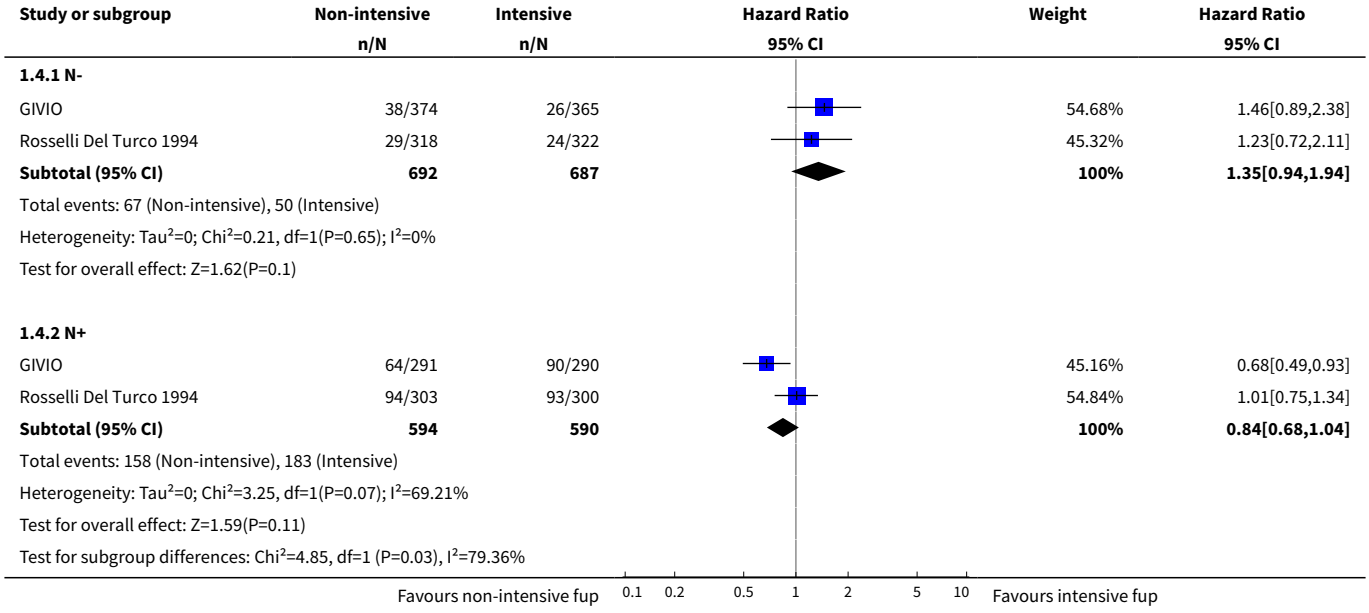
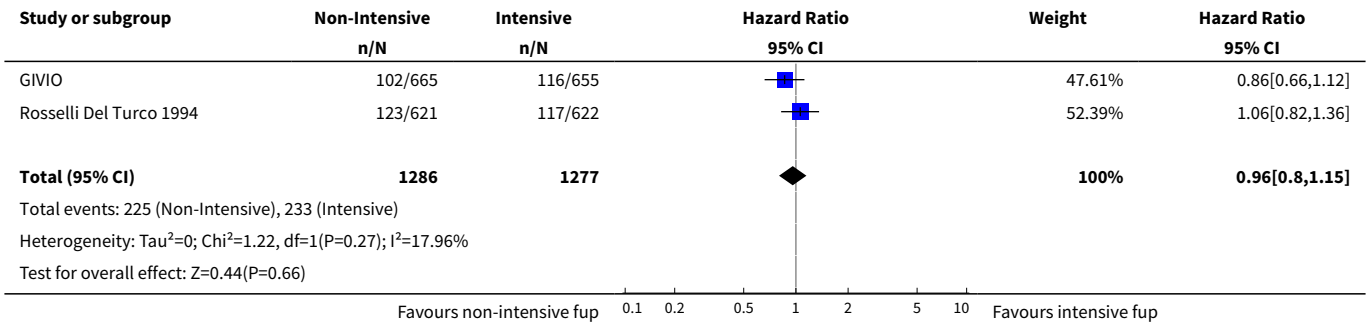


Analysis 1.4. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 4 Overall survival by lymphonodal status.



Analysis 1.5. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 5 Overall survival 5 years.



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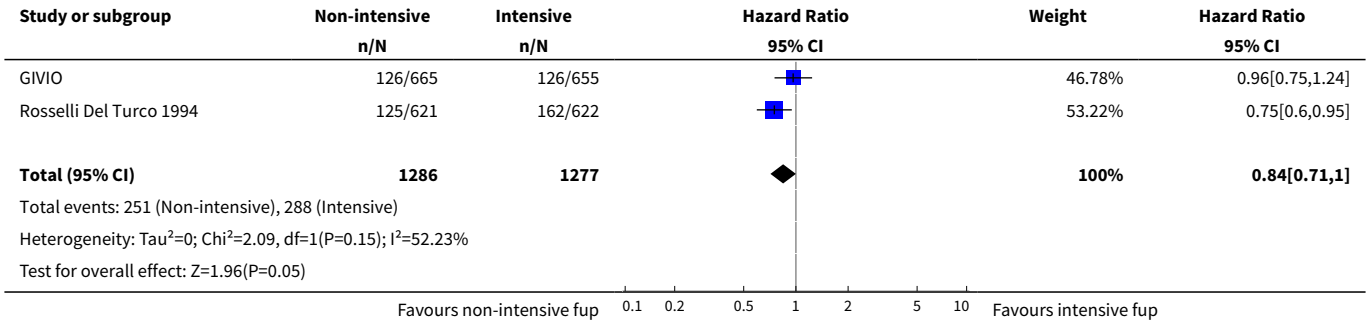
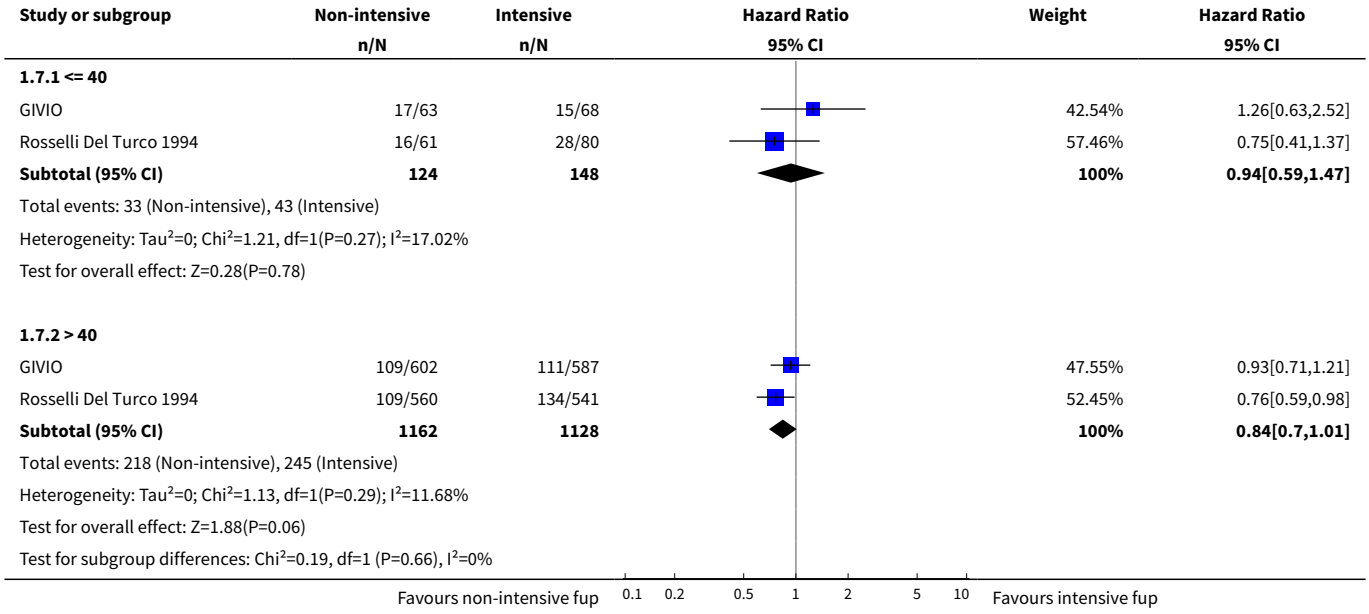
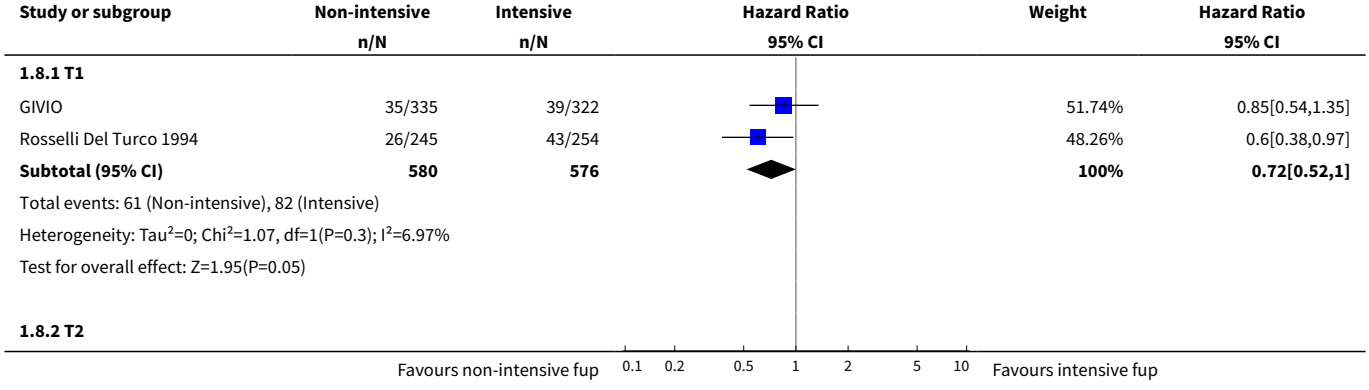
Analysis 1.6. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 6 Disease-free survival.



Analysis 1.7. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 7 Disease-free survival by age.



Analysis 1.8. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 8 Disease-free survival by tumour size.



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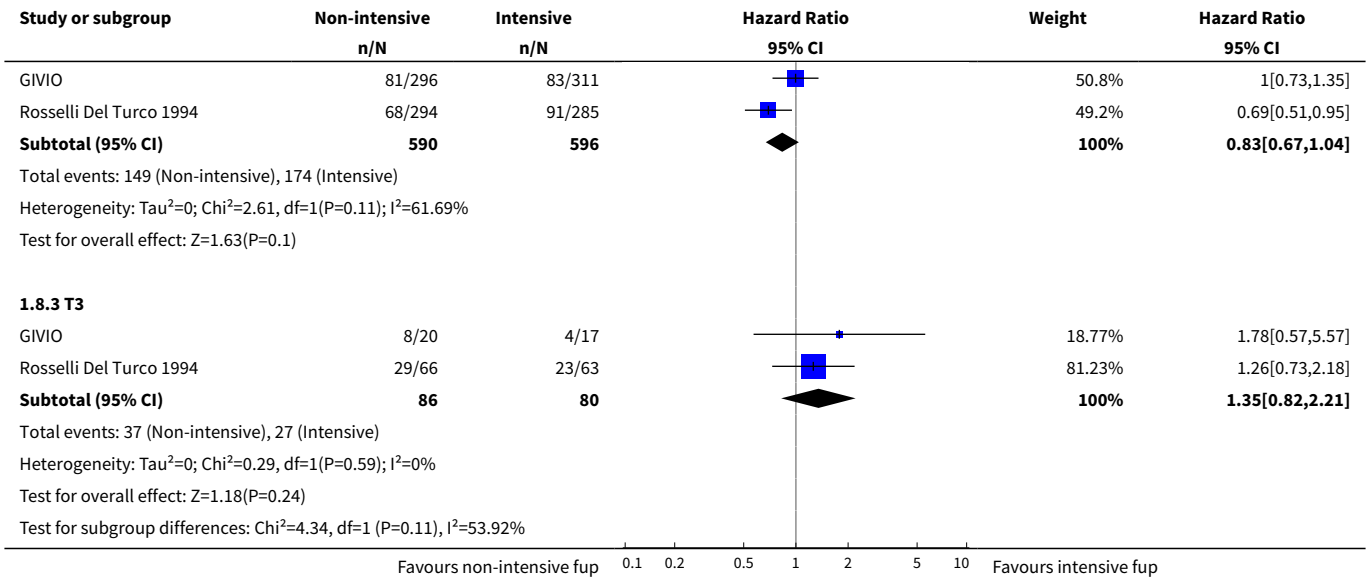
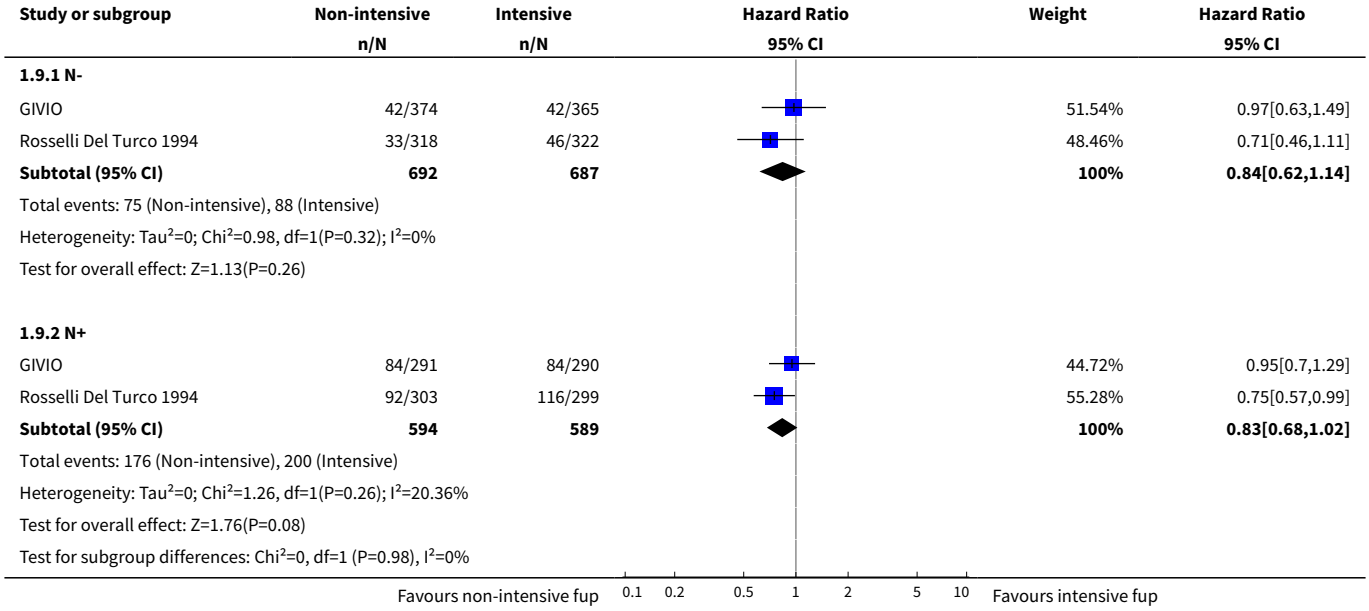
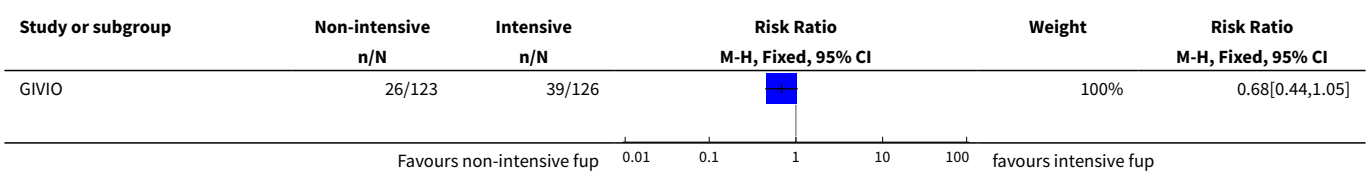


Analysis 1.9. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 9 Disease-free survival by lymphonodal status.



Analysis 1.10. Comparison 1 Non-intensive follow-up vs intensive follow-up, Outcome 10 number of metastasis detected in an asymptomatic way.



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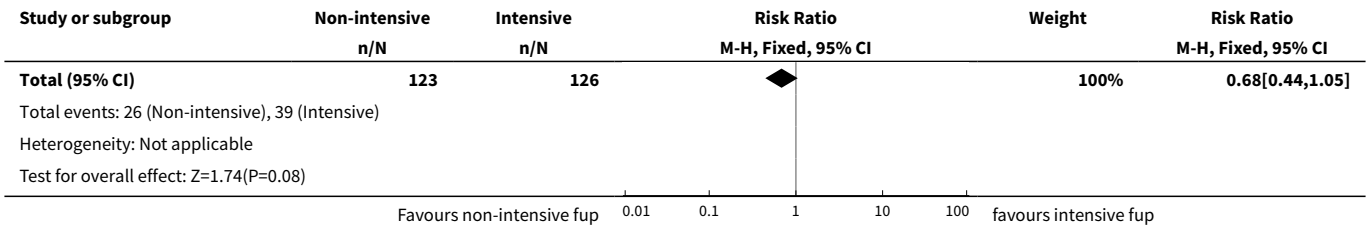
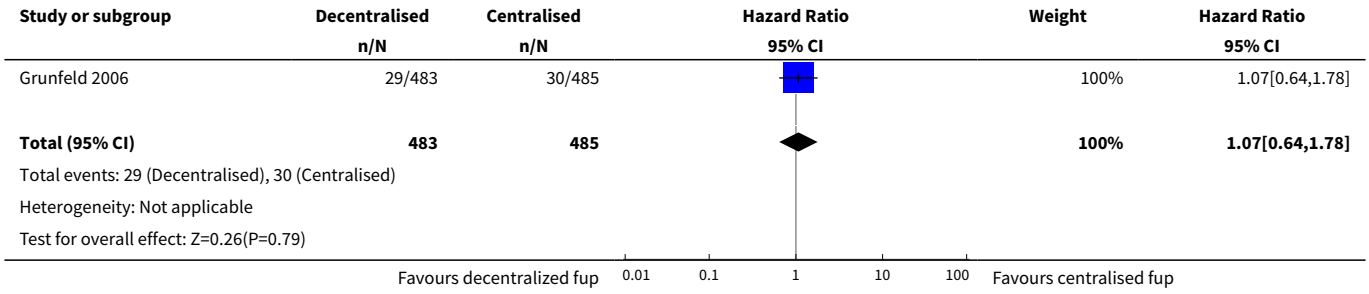


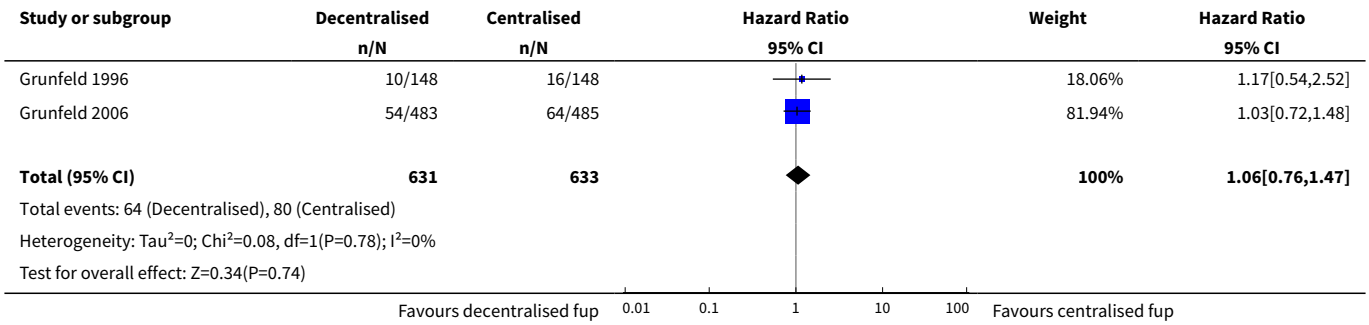
Comparison 2. Centralised vs decentralised follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1	968	Hazard Ratio (95% CI)	1.07 [0.64, 1.78]
2 Disease-free survival	2	1264	Hazard Ratio (95% CI)	1.06 [0.76, 1.47]

Analysis 2.1. Comparison 2 Centralised vs decentralised follow-up, Outcome 1 Overall survival.



Analysis 2.2. Comparison 2 Centralised vs decentralised follow-up, Outcome 2 Disease-free survival.



ADDITIONAL TABLES

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Table 1. Comparison Guidelines on Selected Breast Cancer Follow-up Components

Guidelines	Mammography	Clinical visit (history and physical exam)	Self-breast examination	Intensive follow-up	Others
(ASCO 2013)	Yearly. For women who have undergone breast-conserving surgery, a post-treatment mammogram should be obtained 1 year after the initial mammogram and at least 6 months after completion of radiation therapy.	Every 3 to 6 months for the first 3 years, every 6 to 12 months for years 4 and 5, and annually thereafter.	Monthly	Not recommended	Gynecologic follow-up for all women.
(ESMO 2013)	Every 1 to 2 years.	Every 3 to 4 months in the first 2 years, every 6 months from years 3 to 5, and annually thereafter.	Not specified	Not recommended	Annual gynaecological examination for women on tamoxifen; regular bone mineral density evaluation and lipid profile for women on aromatase inhibitors.
(NCCN 2014) version 2.2014	Yearly.	Every 4 to 6 months for 5 years, and annually thereafter.	Not specified	Not recommended	Annual gynaecological examination for women on tamoxifen; regular bone mineral density evaluation for women on aromatase inhibitors or who experienced premature ovarian failure.

APPENDICES

Appendix 1. 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.

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(Continued)

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	exp Breast Neoplasms/
12	(milk or tender* or lactat* or feeding or fed).ti,ab.
13	exp Milk, Human/
14	exp Breast Feeding/
15	exp Lactation/
16	12 or 13 or 14 or 15
17	11 not 16
18	exp Follow-Up Studies/
19	(follow-up or follow-up care or follow-up stud* or centralised follow-up or decentralised follow-up or postoperative surveillance or routine).ti,ab.
20	18 and 19
21	10 and 17 and 20
22	limit 21 to humans

Appendix 2. Embase

#38

#37 AND [humans]/lim AND [embase]/lim

#37

#9 AND **#33** AND **#36**

#36

#34 AND **#35**

#35

'follow up'/exp OR **'follow up'**

#34

'follow up':ab,ti OR **'follow-up care'**:ab,ti OR **'follow-up study'**:ab,ti OR **'centralised follow-up'**:ab,ti OR **'decentralised follow-up'**:ab,ti OR **'postoperative surveillance'**:ab,ti OR **routine**:ab,ti

#33

#27 NOT **#32**

#32

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

#31

'lactation'/exp OR **'lactation'**

#30

'breast feeding'/exp OR **'breast feeding'**

#29

'breast milk'/exp OR **'breast milk'**

#28

milk:ab,ti OR **tender***:ab,ti OR **lactat***:ab,ti OR **feeding**:ab,ti OR **fed**:ab,ti

#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 neoplasm'

#16

'early breast cancer'

#15

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

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'breast tumour'

#13

'breast carcinoma'/exp

#12

'breast neoplasm'

#11

'breast cancer'/exp

#10

'breast tumor'/exp

#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 3. 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*:ti,ab,kw (Word variations have been searched)

#3 locally advanced breast cancer* or locally advanced breast neoplas* or locally advanced breast tumour* or locally advanced breast tumor*:ti,ab,kw (Word variations have been searched)

#4 #2 or #3

#5 #1 and #4

#6 MeSH descriptor: [Follow-Up Studies] explode all trees

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#7 follow-up or follow-up care or follow-up stud* or centralised follow-up or decentralised follow-up or postoperative surveillance or routine:ti,ab,kw (Word variations have been searched)

#8 #6 and #7

#9 #5 and #8

Appendix 4. WHO ICTRP

Basic Searches:

1. Follow-up strategies for women treated for early breast cancer

2. Breast cancer AND follow-up

3. Breast cancer AND centralised follow-up

4. Breast cancer AND decentralised follow-up

5. Breast cancer AND postoperative surveillance

6. Breast cancer AND routine

Advanced Searches:

1. Title: Follow-up strategies for women treated for early breast cancer

Recruitment: All

2. Condition: breast cancer

Intervention: follow-up OR follow-up care OR follow-up studies

Recruitment: All

3. Condition: breast cancer

Intervention: centralised follow-up OR decentralised follow-up OR postoperative surveillance OR routine

Recruitment: All

Appendix 5. ClinicalTrials.gov

cancer

Basic Searches:

1. Follow-up strategies for women treated for early breast cancer

2. Breast cancer AND follow-up

3. Breast cancer AND centralised follow-up

4. Breast cancer AND decentralised follow-up

5. Breast cancer AND postoperative surveillance

6. Breast cancer AND routine

Advanced Searches:

1. Title: Follow-up strategies for women treated for early breast cancer

Recruitment: All studies

Study Results: All studies

Study Type: All studies

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Gender: All studies

2. Condition: breast cancer

Intervention: follow-up OR follow-up care OR follow-up studies

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

3. Condition: breast cancer

Intervention: centralised follow-up OR decentralised follow-up OR postoperative surveillance OR routine

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

WHAT'S NEW

Date	Event	Description
29 May 2016	Review declared as stable	In the last decade, only one new study has been published and the review findings remain consistent. Therefore, the results of this review confined to trials of specialist- and physician-led follow-up programmes are unlikely to change and future updates of this review are not planned

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 4, 2000

Date	Event	Description
4 July 2014	New citation required but conclusions have not changed	One new study was included, involving 968 patients (Grunfeld 2006). Full 'Risk of bias' tables were added. Conclusions remain unchanged
4 July 2014	New search has been performed	Performed search for new studies on 4 July 2014
8 March 2012	Amended	Additional table linked to text
26 August 2008	Amended	Converted to new review format.
8 August 2000	New citation required and conclusions have changed	Substantive amendment

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CONTRIBUTIONS OF AUTHORS

For the 2014 review update:
Ivan Moschetti and Michela Cinquini identified, selected and critically appraised the studies and completed the 'Risk of bias' table of all included studies. Both authors wrote the previous and current version of this review including updated analyses and text according to the new findings.
Alessia Levaggi and Matteo Lambertini reviewed the manuscript from a clinical point of view updating the introduction and the discussion, writing the implications for research section and updating the guidelines table.

For the previous versions of the review:
Paulina Rojas and Elena Telaro identified, selected and critically appraised the studies to be included in the review, and wrote the first draft.
Roldano Fossati designed the review, supervised the analysis of the data and reviewed the earlier drafts of the manuscript.
Antonio Russo analysed the data and reviewed the earlier drafts of the manuscript.
Domenico Palli and Marco Rosselli del Turco contributed to the development of the protocol and reviewed the manuscript of the final review.
Alessandro Liberati designed the review, supervised the assessment of the studies and reviewed the manuscript.
Ivan Moschetti and Laura Coe analysed the search results for inclusion of new studies, updated analyses and text according to new findings for the first update of this review.

DECLARATIONS OF INTEREST

Roldano Fossati (RF) and Alessandro Liberati (AL) were members of the Steering Group of the GIVIO study included in this review and wrote several review articles of the effect of follow-up care. The GIVIO trial (of which RF and AL were authors) was originally partially supported by a educational grant from Astra Zeneca Italia. No specific funding was available for the original conduct and update of this review. Ivan Moschetti, Michela Cinquini, Alessia Levaggi and Laura Coe do not have any conflict of interests.

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Internal sources

- No specific funding was available for the original conduct and update, Other.
- Ivan Moschetti and Michela Cinquini: Mario Negri Institute for Pharmacological Research IRCCS, Italy.

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External sources

- No resources of external support were provided, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2014 review update:

- outcomes have now been differentiated into primary and secondary, and
- additional text has been added to the background section of the review for completeness.

INDEX TERMS

Medical Subject Headings (MeSH)

Breast Neoplasms [*diagnosis] [mortality] [pathology] [*therapy]; Follow-Up Studies; General Practice; Mammography; Medical Oncology; Neoplasm Recurrence, Local [*diagnosis] [mortality]; Neoplasm Staging; Physical Examination; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

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