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

Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, Palli D, Roselli del Turco M, Liberati A

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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.

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 strategy
We searched, the Breast Cancer Group's specialized register (May 14, 2004), the Cochrane Controlled Trial Register (Cochrane Library Issue 1, 2004), Medline (January 1966 - May 2004) and EMBASE (1988 - May 2004). 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 reviewers independently assessed trial quality and eligibility for inclusion in the review. 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
Four RCTs involving 3055 women with breast cancer (clinical stage I, II or III) were included. Two of these 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 0.96, 95% confidence interval 0.80 to 1.15) or disease-free survival (hazard ratio 0.84, 95% confidence interval 0.71 to 1.00) emerged. No differences in overall survival and disease-free survival emerged in subgroup analyses according to patient age, tumour size and lymph node status before primary treatment. In 1999, 10-year follow-up data became available for Rosselli Del Turco and no significant differences in overall survival were found.

One RCT (296 women) compared follow-up performed by a hospital-based specialist to follow-up performed by general practitioners. No significant differences in time to detection of recurrence and quality of life emerged. Patient satisfaction was greater among patients treated by general practitioners.
One RCT (196 women) compared regularly scheduled follow-up visits to less frequent visits restricted to the time of mammography. No significant differences emerged in interim use of telephone and frequency of GP's consultations.

Authors' conclusions

This updated review of RCTs conducted almost 20 years ago suggest 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 one RCT, follow-up care performed by trained general practitioners working in an organized practice setting had comparable effectiveness to that delivered by hospital-based specialists in terms of quality of life and time to detection of distant metastases.

PLAIN LANGUAGE SUMMARY

The recent update confirms that a regular physical and yearly mammogram are as effective as more intense methods of examination in detecting recurrent breast cancer.

Follow-up examinations are common for women after primary treatment for breast cancer. This is done to detect recurrences at an early stage and begin treatment for any relapses quickly. These tests can include liver scans, tumour markers, chest x-rays and blood and liver function tests. The review of trials found that follow-up programs based on a regular physical exam and yearly mammogram appear to be as effective as the more intensive approaches. This was measured by detection of recurrences of cancers, overall survival and quality of life.

BACKGROUND

Follow-up (care after primary treatment) of women with breast cancer should have several aims. These include provision of; physical and psychosocial rehabilitation, monitoring of treatment effectiveness including short and long term toxicity, and detecting recurrence or new cancers. In actual practice, however, follow-up care is offered with the main objective of detecting distant recurrences at an early stage, so that treatment for any relapse can be started.

In this context, terms such as "routine testing", "follow-up" or "surveillance" indicate the regular use of laboratory or instrumental tests in otherwise asymptomatic patients to detect distant metastases earlier. The type of tests can vary by hospital and/or doctor but they typically include routine haematological and liver function tests, tumour markers, chest X ray, and bone and liver scans.

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 (Loprinzi 1994). 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). A randomised design is thus the only valid way to get an unconfounded estimate of the effectiveness of different follow-up strategies.

OBJECTIVES

The objective of this review is to assess the effectiveness of different policies of routine follow-up testing on morbidity, mortality and quality of life in breast cancer patients after primary treatment. Specifically the effectiveness of the following types of routine follow-up policies will be 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.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials comparing different approaches to follow-up after completion of primary treatment. Additional information was extracted and reviewed from prospective non-randomised studies but was 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 intervention

- 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

- 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.
- Overall survival
- Occurrence of metastases detected in a asymptomatic state
- Health related quality of life

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Breast Cancer Group methods used in reviews.

The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group was searched on the 14th of May 2004. Details of the search strategy applied by the Group to create the register, and the procedure used to code references, are described in the Group's module on the Cochrane Library.

Using the Breast Cancer Groups search strategy and the addition of the concept of follow-up we searched the Cochrane Controlled Trial Register (Cochrane Library Issue 1, 2004), MEDLINE (January 1966 - May 2004) and EMBASE (1988 - May 2004). We also ran our own search strategy (see below) in MEDLINE and EMBASE (OVID) on April 30, 2004 to maximize the possibility of finding relevant studies. We then compared the results of both searches. References from retrieved articles were also checked and the Breast Cancer Group confirmed that meeting abstracts were searched and any relevant RCT was included in their register.

MEDLINE (OVID):
1.Search mammograph* or breast screen* Field: Title/Abstract
2.Search Breast self examination* Field: Title/Abstract
3.Search CA-15-3 or CA 27 or MUC 1 or MCA or CA 549 or CEA or Cathepsin-D or routine bone scan* or chest radiography or chest radiogram or liver ultrasonogr* or computed tomography scan or Radionuclide Imaging or scintigraphy or blood cell count or haematologic test or hematologic test or liver function test Field: Title/Abstract
4.Search Follow-up or postoperative surveillance or surveillance or routine test Field: Title/Abstract
5.Search "Diagnosis"[MeSH]
6.Search "Mammography"[MeSH]
7.Search "Liver/ultrasonography"[MeSH]
8.Search "Liver Diseases/ultrasonography"[MeSH]
9.Search "Follow-Up Studies"[MeSH]
10.#1-9/or
11.Search milk or tender* or lactat* or feeding or fed Field: Title/Abstract
12.Search "Milk, Human"[MeSH:NoExp]
13.Search "Breast Feeding"[MeSH:NoExp]
14.Search "Lactation"[MeSH]
15.#11-14/or
16.#10 not #15
17.Search mammar* and (neoplasm* or cancer* or tumour* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraduct* or lobular or medullary) Field: Title/Abstract
18.Search fibrocystic or lymphedema or mastectom* Field: Title/Abstract
19.Search breast and (neoplasm* or cancer* or tumour* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraduct* or lobular* or medullary*) Field: Title/Abstract
20.Search "Breast Neoplasms"[MeSH]
21.Search "Neoplasms, Glandular and Epithelial"[MeSH]
22.Search "Lymphedema"[MeSH:NoExp]
23.Search "Mastectomy"[MeSH]
24.Search "Fibrocystic Disease of Breast"[MeSH:NoExp]
25.#17-24/or
26.#25 and #16
27.Search RANDOMIZED CONTROLLED TRIAL Field: Publication Type
28.Search CONTROLLED CLINICAL TRIAL Field: Publication Type
29.Search RANDOMIZED CONTROLLED TRIALS
30.Search RANDOM ALLOCATION
31.Search DOUBLE BLIND METHOD
32.Search SINGLE BLIND METHOD
33.#27-32/or
34.Search CLINICAL TRIAL Field: Publication Type
35.Search "Clinical Trials"[MeSH] Field: Publication Type
36.Search clin* near trial* Field: Title
37.Search clin* near trial* Field: Title/Abstract
38.Search (singl* or doubl* or trebl* or tripl*) near (blind* or mask*) Field: Title/Abstract
39.Search placebos
40.Search placebo* Field: Title
41.Search placebo* Field: Title/Abstract
42.Search random* Field: Title
43.Search random* Field: Title/Abstract
44.Search research design

45.Search volunteer*
46.Search crossover
47.Search versus
48.Search latin square
49.Search "Cross-Over Studies"[MeSH]
50.#34 -49/or
51.#50 or #33
52.#26 and 51
53.Search #52 Field: All Fields, Limits: Human

EMBASE (OVID)
1.(mammograph$ or breast screen$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
2.Breast self examination$.mp.
3.exp breast examination/
4.(CA-15-3 or CA 27 or MUC 1 or MCA or CA 549 or CEA or Cathepsin-D or routine bone scan$ or chest radiography or chest radiogram or liver ultrasonogr$ or computed tomography scan or Radionuclide Imaging or scintigraphy or blood cell count or haematologic test or hematologic test or liver function test).mp.
5.exp diagnosis/
6.mammography/
7.exp Liver/ and exp echography/
8.follow-up/
9.(follow-up or postoperative surveillance or surveillance or routine test).mp.
10.1-9/or
11.(milk or tender$ or lactat$ or feeding or fed).mp.
12.Breast Milk/
13.Breast Feeding/
14.Lactation/
15.11-14/or
16.10 not 15
17.(mammar$ and (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraduct$ or lobular or medullary)).mp
18.(fibrocystic or lymphedema or mastectom$).mp.
19.(breast and (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraduct$ or lobular$ or medullary$)).mp.
20.(neoplasms, glandular and epithelial).mp.
21.Breast Tumor/
22.Breast Carcinoma/
23.Lymphedema/
24.exp Mastectomy/
25.exp Breast Disease/
26.17-25/or
27.26 and 16
28.random$.ti,ab.
29.factorial$.ti,ab.
30.(crossover$ or cross over$ or cross-over$).ti,ab.
31.placebo$.ti,ab.
32.(doubl$ adj blind$).ti,ab.
33.(singl$ adj blind$).ti,ab.
34.assign$.ti,ab.
35.allocat$.ti,ab.
36.volunteer$.ti,ab.
37.CROSSOVER PROCEDURE.sh.
38.DOUBLE-BLIND PROCEDURE.sh.
39.RANDOMIZED CONTROLLED TRIAL.sh.
40.SINGLE-BLIND PROCEDURE.sh.
41.28-40/or
42.exp ANIMAL/ or NONHUMAN/ or exp ANIMAL EXPERIMENT/
43.exp HUMAN/
44.43 and 42
45.42 not 44
46.41 not 45
47.46 and 27

METHODS OF THE REVIEW

Each potentially eligible study was independently assessed by two reviewers for inclusion in the review and for quality. No disagreements regarding eligibility occurred.
Methodological quality of the studies was assessed by evaluating the method of randomisation, whether a calculation of sample size had been performed beforehand, how patients lost to follow-up after randomisation had been handled in the analysis, and whether analysis was on an "intention to treat" basis. Finally the clinical relevance of outcomes and the appropriateness of the timing of their assessment were considered (i.e. length of follow-up). Given the nature of the interventions under investigation, the use of blinding techniques was not considered necessary.

Relevant information to analyse the above mentioned indicators was collected using the scheme reported in the table "Characteristics of included studies". When a meta-analysis was performed (i.e. for the GIVIO and Rosselli Del Turco trials) individual patient data were used. Mortality and disease free survival were calculated using the log rank "O-E" and its variance (V) for each study. Subgroup analyses by age, tumour size and lymph node status before primary treatment were carried out 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. (Greco 1998, De Lena 1995).

As this is an update of an earlier review, the new analysis includes 10-year follow-up data from Rosselli Del Turco and was performed using summary data from the most recent publication supplemented with information provided by the authors (Rosselli Del Turco see secondary reference). The "O-E" and V were indirectly calculated by using the Mantel-Haenszel estimate of the HR and its confidence intervals reported in the paper.

DESCRIPTION OF STUDIES

This update includes information from 2 new reports. The first provides 10-year follow-up summary data on the Roselli Del Turco trial (Rosselli Del Turco see secondary reference), the second explores a new outcome, patient satisfaction with care, in the Grunfeld study (Grunfeld see secondary reference).

Four studies met the inclusion criteria. All of them are multicentre randomised controlled trials comparing different types of follow-up in breast cancer patients. Overall, these studies included 3055 women (the number of patients ranged from 196-1320) with breast cancer (clinical stages I, II or III) with no evidence of recurrence after their primary surgical treatment.
Outcomes are overall survival and disease-free survival from two trials. Information on health related quality of life was extracted from two trials. The median follow-up time available in the 4 trials varies from 16 to 120 months.

The trials included in this review explore three different follow-up strategies:

- Two trials (GIVIO and Rosselli Del Turco) 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 are overall survival, disease free survival and, in one trial (GIVIO), health related quality of life.

- One trial (Grunfeld) compared follow-up offered by a specialist at the hospital with follow-up offered by a general practitioner. It included 296 women. Its outcomes are time to detection of recurrence and health related quality of life.

- One trial (Gulliford) 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.

METHODOLOGICAL QUALITY

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 was 0.8%. In both trials (Rosselli Del Turco and GIVIO) approximately 10% of the patients discontinued follow-up care, with a similar distribution between intensive and clinical groups. Survival data was available for those lost to follow up and was included in the analyses (intention to treat analysis).

The Grunfeld and Gulliford trials were not designed to assess mortality. 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.

RESULTS

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

The updated metanalysis for overall survival of the GIVIO and Rosselli Del Turco trials found no significant survival advantage in the intensive surveillance group; Hazard ratio 0.98 (95% Confidence Interval 0.84 to 1.15).
The Hazard ratio was 0.84 (95% Confidence Interval 0.71 to 1.00) for disease free survival after 5 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 trial.
No significant differences in mortality between the strategies in respect to the subgroup analyses by age, tumour size and nodal status were found at 5 years. See summary of analyses for details.
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 a asymptomatic phase. 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, Logarer 1990, Rutgers 1989, Vestergaard 1989, Mahoney 1986, Hietanen 1986, Wickerhan 1986, Pandya 1983).
Data regarding quality of life were available just for the GIVIO trial. Questionnaires were administered 4 times between 6 and 60 months with an average response rate of 73.5%; overall no significant difference was found between the two follow-up strategies.

- 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)

The Grunfeld trial, comparing follow-up offered by a hospital based specialist with follow-up offered by a general practitioner, shows no differences in time to detection of recurrence between the groups. In the hospital group, the median time from first symptoms suggesting recurrence to confirmation by a hospital specialist was 21 days, in the general practice group it was 22 days. The median difference was 1.5 days.
The number of recurrences was different in the two groups (10/148 general practice group, 16/148 hospital group, not statistically significant) probably because of the short time of follow-up for the trial.
Quality of life shows an expected small deterioration for both groups during the trial. The hospital group has a statistically sig-

nificant increase in symptom scores for fatigue, dyspnoea and appetite loss. There is 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 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 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 secondary reference). 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.

- Regular follow-up versus surveillance on demand.

The Gulliford trial comparing conventionally scheduled follow-up and less frequent follow-up (restricted to the time of mammography) shows 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 assessment is available of these patients in relation to their quality of life.
No significant differences have been found between the groups in regard to the use of telephone and visits to general practitioners during the trial. Aproximately 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.

DISCUSSION

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 first became available in 1994, when the results of the two RCTs were published in the same issue of the Journal of the American Medical Association. They have been endorsed by an international Consensus Conference held at the end of 1994 (De Lena 1995). Subsequently several international practice guidelines (ANAES 2000, ASCO 1999, Australasian 1997, BCCA 2001, Canadian Med As 1998, ESMO 2001, ICSI 2003, Malaysian MOH 2002, Mauriac 2003, NCCN 2004, NHMRC 2001, NHMRC 2003, NICE 2002, SIGN 1998, Temple 1999), though with some variation in terms of frequency of visits and mammography, all endorse a less intensive clinical follow-up (see Table 01).

However, despite the evidence and consensus that intensive follow-up schemes provided no benefit on survival, surveys throughout the late 90s 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 behavior 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.

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, 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.

Patient satisfaction with care was assessed in the same RCT (Grunfeld secondary reference) and found women favored general practitioners' over specialists' care in a hospital setting. Although, 1/3 of the eligible patients chose not to participate in the study.

Compared to other areas in medicine it is worth noting that two of the four 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

generalisibility 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.

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

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 as long as the care is organized in such a way that access to hospital care is easy when required.

Implications for research

Over the last decade many studies have been conducted on estrogen receptors and other tumour markers to determine their usefulness in diagnosis, prognosis, treatment monitoring and prediction of recurrence. In post-treatment follow-up these tests are commonly used once metastatic disease is confirmed to inform treatment choices (ASCO 2000, Basuyau 2003, ASCO 1999, Nicolini 2003). The current controversy stems from different views about the applicability of the results of these "old" trials to the current clinical practice. This would call for new RCTs testing different follow-up strategies using current treatments as baseline but it is unclear whether anyone wants to embark on this endeavour. The evidence from RCTs summarized here must, however, be interpreted with caution bearing in mind that studies were conducted almost two decades ago when some interventions currently used in the advanced setting, were not available. Whether these new treatment options have had a clinically relevant impact on survival remains controversial (Fossati 2001).

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 mortality 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 behavior compared to guideline recommendations to determine to what extent the evidence has been transferred into practice.

POTENTIAL CONFLICT 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

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	GIVIO
Methods	Multicentre randomised controlled trial. 26 general hospitals, Italy. Randomization 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, noninflammator, 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 lymphonodes), 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, gammaglutamyltrans-peptidasa) -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. Diseases free survival. Health related quality of life (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.
Allocation concealment	A – Adequate

Study	Grunfeld
Methods	Randomised controlled trial. 2 district general hospitals, England. Eligible patients were invited to participate by letter.

Characteristics of included studies (*Continued*)

	296/445 agreed to participate Randomization by telephone in blocks of eight. Calculation of sample size reported. Follow-up 18. months Time to diagnosis assessed blinded by masking allocation information on clinical records.
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. Health related quality of life 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 .7%.
Allocation concealment	A – Adequate

Study	**Gulliford**
Methods	Randomised controlled trial. 1 Breast clinic, England 211 eligible patients, 196 accepted randomization. No information about randomization method. Median follow-up: 16 months 13 excluded after randomization
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 randomized allocation. Use of telephone and GP. Satisfaction with allocation to follow-up.
Notes	Calculation of sample size not reported. Small sample size and short duration of follow-up.
Allocation concealment	B – Unclear

Study	**Rosselli Del Turco**
Methods	Multicentre randomized controlled trial. 12 breast clinics in Italy (oncologic centres). Randomization 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). Vital status information available for all except 10 patients (.8%).
Allocation concealment	A – Adequate

ADDITIONAL TABLES

Table 01. Comparison Guidelines on Selected Breast Cancer Follow-up Components

Guidelines	Mammography (general)	Mammography (post conserving therapy)	Clinical Visit (History and physical exam)	Self-Breast Exam	Intensive Follow-up
1. ICSI , 2003	Yearly, indefinitely	Not addressed	Every 3-4 months for 2 years then every 6 months for 3 years	Not addressed	Not recommended
2. NCCN , 2004	Yearly	approximately 6-months after completion of radiotherapy	Every 4-6 months for 5 years, then every 12 months	Not addressed	Not recommended
3. FNCLCC (Mauriac), 2001	Yearly	approximately 6-months after completion of radiotherapy	Every 6 months for 5 years, then annually for 10 years	Not addressed	Not recommended
4. ESMO , 2001	Every 1-2 years	Not addressed	Every 3-6 months for 3 years then every 6-12 months for 2 years, then annually indefinitely	Not addressed	Not recommended
5. NHMCR , 2003	Yearly (at least), indefinitely	At 6-12 months after radiotherapy for conserved breast	Every 3 months in first 2 years, 6 months in next 3 years, then annually	Not addressed	Not recommended
6. NHMCR , 2001	Yearly (at least), indefinitely	At 6-12 months after radiotherapy for conserved breast	Every 3 months in first 2 years, 6 months in next 3 years, then annually	Not addressed	Not recommended
7. SIGN , 1998	Every 1-2 years	One year after treatment then every 1-2 years	Every 6 months for first 2 years, then annually	Not addressed	Not recommended
8. Canadian Task Force on Preventive Health Care (Temple) , 1999	No direct evidence to support practice	No direct evidence to support practice	No direct evidence to support practice	Not addressed	Not recommended
9. Canadian Medical Association , 1998	Yearly, indefinitely	Not addressed	Twice in the first 6 months, then annually	Taught to all women who want it	Not recommended
10. Malaysian	Yearly	approximately	Every 3-4 months	Monthly by	Not recommended

Table 01. Comparison Guidelines on Selected Breast Cancer Follow-up Components (*Continued*)

Guidelines					
Ministry of Health , 2002		6-months after completion of radiotherapy	for 2 years then every 6 months for 3 years	patient	
11. Royal Australasian College of Surgeons (Collins) , 1997	Yearly	Not addressed	Every 3-4 months for 2 years then every 6 months for 3 years	Not addressed	Not recommended
12. ANAES , 2000	At 6 and 12 months in the first year, then annually, indefinitely	At 6 and 12 months in the first year, then annually, indefinitely	At 6 and 12 months in the first year, then every 6 months for the first 5 years, then annually	Recommended on case by case basis	Not recommended
13. British Colombia Cancer Agency , 2001	Yearly	approximately 6-months after completion of radiotherapy, then annually	Every 4-6 months for 5 years, then annuallyPost conserving therapy5-6 weeks post radiation, every 6 months for 5 years, then annually	Taught to all women	Not recommended
14. ASCO , 1999	Yearly	approximately 6-months after completion of radiotherapy, then annually	Every 3-6 months for 3 years, then every 6-12 months for the next 2 years, then annually	Monthly by patient	Not recommended
15. NICE , 2002	Not addressed	Not addressed	Not addressed	Not addressed	Not recommended

* The guideline refereneces are included in Additional References.

ANALYSES

Comparison 01. Clinical follow-up vs intensive follow-up

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Overall Mortality	2	2553	Peto Odds Ratio 95% CI	0.98 [0.84, 1.15]
02 Overall Mortality 5 years	2	2563	Peto Odds Ratio 95% CI	0.96 [0.80, 1.15]
03 Mortality by age			Peto Odds Ratio 95% CI	Subtotals only
04 Mortality by tumor size			Peto Odds Ratio 95% CI	Subtotals only
05 Mortality by lymphonodal status			Peto Odds Ratio 95% CI	Subtotals only

06 Disease free survival	2	2562	Peto Odds Ratio 95% CI	0.84 [0.71, 1.00]
07 Disease free survival by age			Peto Odds Ratio 95% CI	Subtotals only
08 Disease free survival by tumor size			Peto Odds Ratio 95% CI	Subtotals only
09 Disease free survival by lymphonodal status			Peto Odds Ratio 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

Breast Neoplasms [pathology; *therapy]; Follow-Up Studies; Mammography; Neoplasm Staging; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

COVER SHEET

Title	Follow-up strategies for women treated for early breast cancer
Authors	Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, Palli D, Roselli del Turco M, Liberati A
Contribution of author(s)	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 analyzed the search results for inclusion of new studies, updated analyses and text according to new findings.
Issue protocol first published	1998/1
Review first published	2000/4
Date of most recent amendment	14 February 2006
Date of most recent SUBSTANTIVE amendment	08 August 2000
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	14 May 2004
Date authors' conclusions section amended	Information not supplied by author

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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 01 Overall Mortality

Review: Follow-up strategies for women treated for early breast cancer
Comparison: 01 Clinical follow-up vs intensive follow-up
Outcome: 01 Overall Mortality

Study	Non-Intensive (T) n/N	Intensive (C) n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
GIVIO	102/665	116/655		35.0	0.86 [0.66, 1.12]
Rosselli Del Turco	212/616	222/617		65.0	1.05 [0.86, 1.28]
Total (95% CI)				**100.0**	**0.98 [0.84, 1.15]**

Test for heterogeneity chi-square=1.40 df=1 p=0.24 I^2 =28.4%
Test for overall effect z=0.26 p=0.8

Analysis 01.02. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 02 Overall Mortality 5 years

Review: Follow-up strategies for women treated for early breast cancer

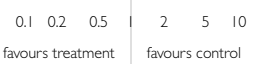
Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 02 Overall Mortality 5 years

Study	Non-Intensive (T) n/N	Intensive (C) n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
GIVIO	102/665	116/655		47.6	0.86 [0.66, 1.12]
Rosselli Del Turco	123/621	117/622		52.4	1.06 [0.82, 1.36]
Total (95% CI)				**100.0**	**0.96 [0.80, 1.15]**

Test for heterogeneity chi-square=1.22 df=1 p=0.27 I^2 =18.0%

Test for overall effect z=0.44 p=0.7



Analysis 01.03. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 03 Mortality by age

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 03 Mortality by age

Study	Non-intensive (T) n/N	Intensive (C) n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 <=40					
GIVIO	12/63	12/68		40.4	1.13 [0.51, 2.53]
Rosselli Del Turco	16/61	20/80		59.6	1.05 [0.54, 2.04]
Subtotal (95% CI)				**100.0**	**1.08 [0.65, 1.80]**

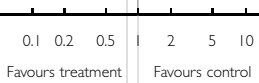
Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%

Test for overall effect z=0.31 p=0.8

02 >40					
GIVIO	90/602	104/587		48.7	0.83 [0.63, 1.10]
Rosselli Del Turco	107/560	97/542		51.3	1.08 [0.82, 1.42]
Subtotal (95% CI)				**100.0**	**0.95 [0.78, 1.16]**

Test for heterogeneity chi-square=1.62 df=1 p=0.20 I^2 =38.3%

Test for overall effect z=0.51 p=0.6



Analysis 01.04. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 04 Mortality by tumor size

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 04 Mortality by tumor size

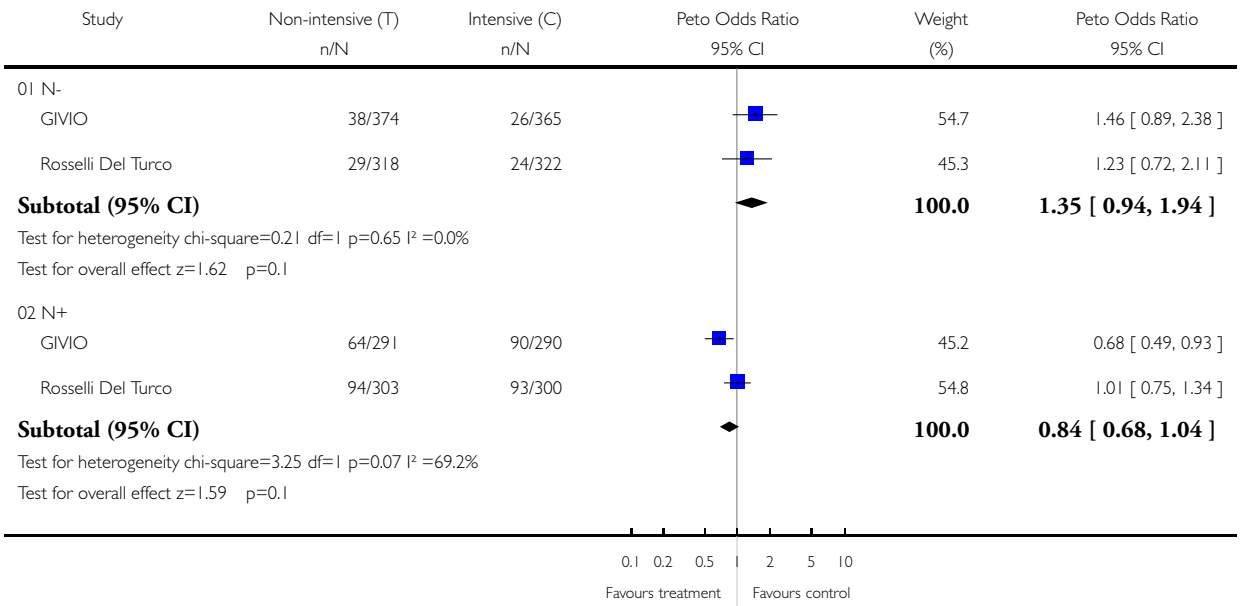
Study	Non-intensive (T) n/N	Intensive (C) n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 T1					
GIVIO	27/335	29/322		52.8	0.92 [0.54, 1.55]
Rosselli Del Turco	20/245	30/254		47.2	0.69 [0.39, 1.20]
Subtotal (95% CI)				**100.0**	**0.80 [0.55, 1.17]**
Test for heterogeneity chi-square=0.55 df=1 p=0.46 I^2 =0.0%					
Test for overall effect z=1.15 p=0.2					
02 T2					
GIVIO	67/296	81/311		53.6	0.84 [0.61, 1.16]
Rosselli Del Turco	66/294	62/285		46.4	1.03 [0.73, 1.45]
Subtotal (95% CI)				**100.0**	**0.92 [0.73, 1.17]**
Test for heterogeneity chi-square=0.68 df=1 p=0.41 I^2 =0.0%					
Test for overall effect z=0.66 p=0.5					
03 T3					
GIVIO	7/20	6/17		18.0	1.05 [0.35, 3.14]
Rosselli Del Turco	35/66	24/64		82.0	1.55 [0.93, 2.59]
Subtotal (95% CI)				**100.0**	**1.44 [0.91, 2.30]**
Test for heterogeneity chi-square=0.39 df=1 p=0.53 I^2 =0.0%					
Test for overall effect z=1.54 p=0.1					

Analysis 01.05. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 05 Mortality by lymphonodal status

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 05 Mortality by lymphonodal status

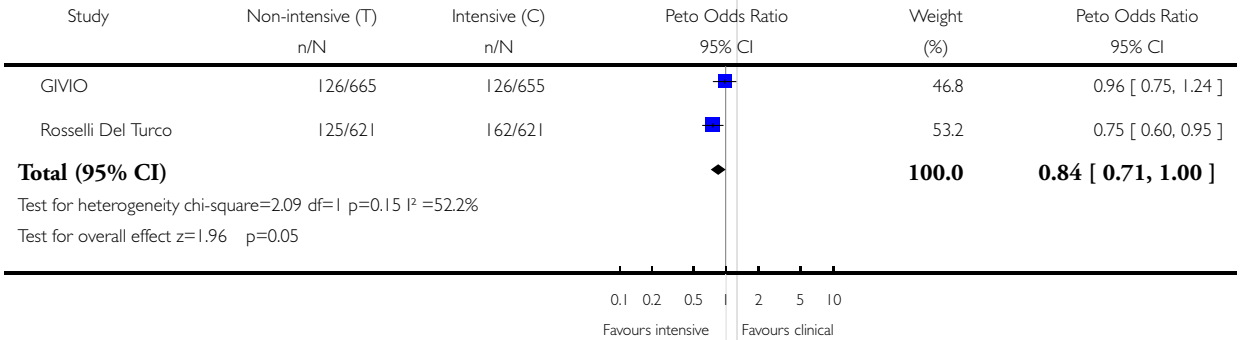


Analysis 01.06. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 06 Disease free survival

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 06 Disease free survival

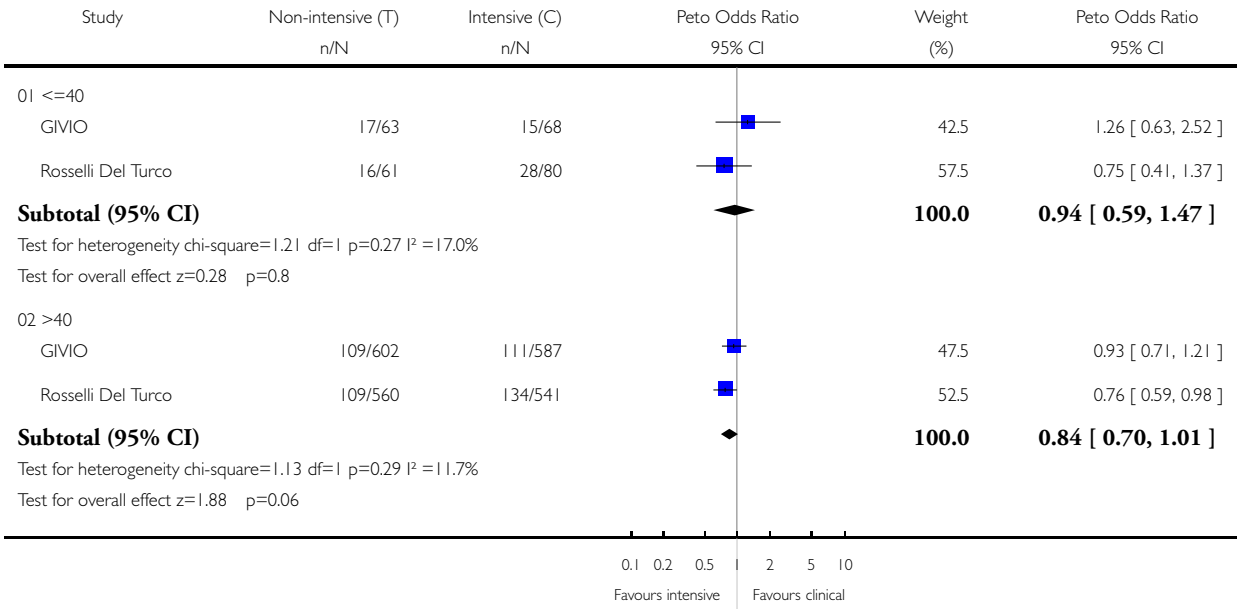


Analysis 01.07. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 07 Disease free survival by age

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 07 Disease free survival by age

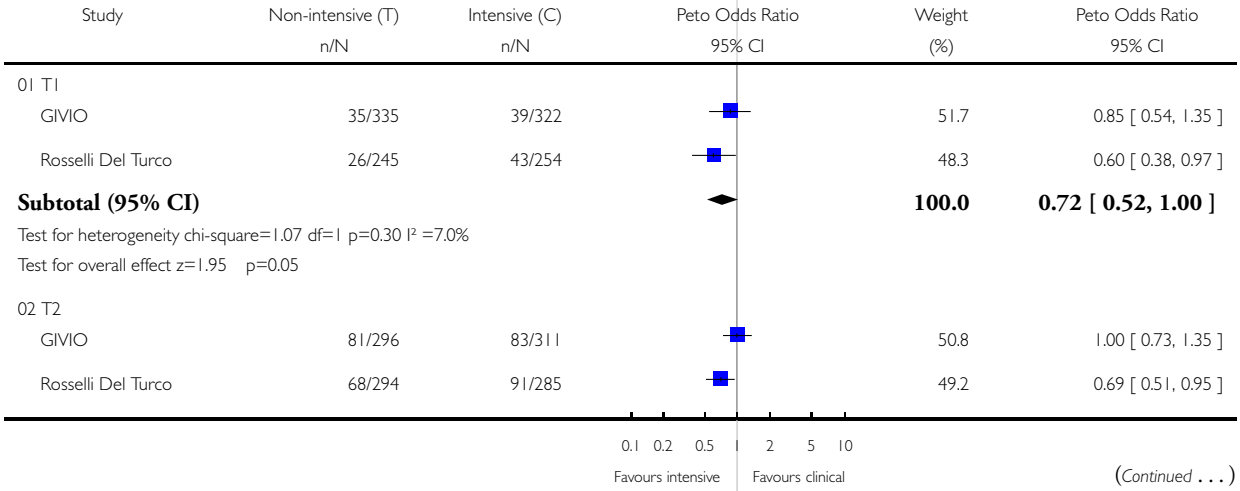


Analysis 01.08. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 08 Disease free survival by tumor size

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 08 Disease free survival by tumor size



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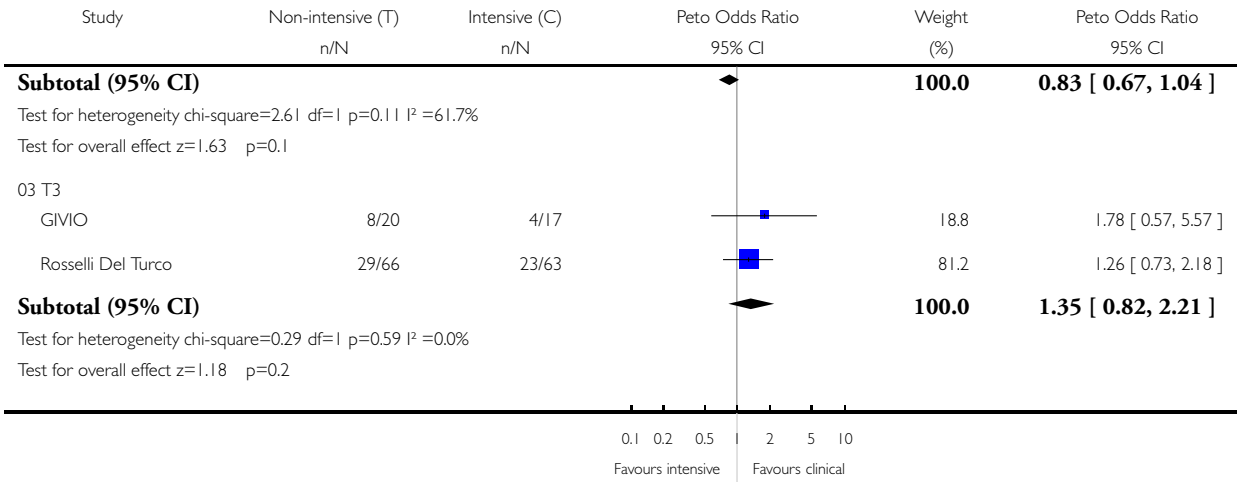

Analysis 01.09. Comparison 01 Clinical follow-up vs intensive follow-up, Outcome 09 Disease free survival by lymphonodal status

Review: Follow-up strategies for women treated for early breast cancer

Comparison: 01 Clinical follow-up vs intensive follow-up

Outcome: 09 Disease free survival by lymphonodal status