The Role of Radiotherapy Fractionation And Volume In Patients With Early Breast Cancer After Conserving Surgery: A Systematic Review And Network Meta-Analysis

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Research

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Abstract

Background: Hypofractionated whole breast irradiation (HF-WBI) can achieve the same treatment effect as conventional fractionated whole breast irradiation (CF-WBI) within limits, without increasing adverse reactions. Because of its characteristics of reducing the number of radiation therapy (RT) during the COVID-19 Pandemic, it is recommended as the first choice of treatment for patients with early breast cancer after breast conserving surgery. However, the choice of RT is still under exploration. Here, we conducted a network meta-analysis to evaluate the problem comprehensively using data from new randomized trials.

Methods: We analyzed data from eligible studies for published events for ipsilateral breast tumor recurrence (IBTR), distant metastasis, total deaths, and non-breast cancer-related deaths. Statistical analysis was performed using a fixed-effects or random-effects model in cases of low and high heterogeneity, respectively. Network meta-analysis was conducted using a node-splitting model for two-category data among three RTs based on a Bayesian approach.

Results: 16 studies with 23,418 patients were included. For IBTR, pairwise comparison showed that CF-WBI was significantly better than PBI, and HF-WBI was similar to CF-WBI. HF-WBI was superior to PBI, but the difference was not significant. However, indirect comparison of three RTs by network meta-analysis showed that HF-WBI was significantly better than PBI (OR=0.67, CI95%: 0.46–0.95). Paired and network meta-analyses found no significant differences in other endpoints among three radiotherapies.

Conclusion: This meta-analysis demonstrated PBI was associated with increased IBTR compared with HF-WBI or CF-WBI in early-stage breast cancer patients.

1. Background

Changes in radiation therapy (RT) fractionation have long been studied in relation to various types of cancer, including breast cancer. The standard treatment for early breast cancer is breast-conserving surgery supplemented by whole-breast irradiation (WBI) and appropriate systemic therapy. However, a long course of conventional fractionated WBI (CF-WBI) for 5–6 weeks not only increases the economic burden on patients, but also affects the turnover of medical resources, thus limiting the popularity of breast-conserving surgery. Breast cancer tissue is as sensitive to fraction size as dose-limiting healthy tissues, so RT schedules can be greatly simplified by the delivery of fewer, larger fractions without compromising effectiveness or safety, and possibly improving both[1]. Moderate hypofractionated WBI (HF-WBI), defined as a daily dose of 265–330 cGy, is delivered in 13–16 fractions[2]. Four large randomized controlled trials demonstrated that HF-WBI provided equivalent local control and overall survival to CF-WBI[1-4]. The American Society for Radiation Oncology (ASTRO) guidelines in 2018 therefore broadened the HF-WBI adaptive population, with no restrictions on age, stage, or chemotherapy. A scheme of 40.0–42.5 Gy/15–16 fractions was suggested[5]. National Comprehensive Cancer Network guidelines currently recommend that WBI should be given priority to HF-WBI scheme. However, HF-WBI is only used in 34.5% of patients in the United States[6], and in as few as 12.1% of patients in China[7]. The slow adoption of HF-WBI in Asia and the United States may be related to physicians’ concerns about the cosmetic side effects, especially when used in conjunction with tumor-bed boost and chemotherapy, or its use in patients with different breast sizes, or the absence of validation outside Canada and the United Kingdom[6]. Several randomized controlled trials are currently comparing the effects of HF-WBI and CF-WBI in terms of local tumor control, breast appearance (cosmesis), late toxicity, overall survival, and patient satisfaction[8-13].

On the other hand, analysis of local recurrence in patients treated for early breast cancer indicates that most recurrence occurs at the initial tumor location[14-17]. This suggests that irradiation of the tumor bed alone may be equally effective to WBI, with fewer side effects. Multiple randomized trials using different techniques have provided conflicting results for tumor control, toxicity, and survival, mainly due to the heterogeneity of the trials and small sample sizes[18-26]. Based on these trials, ASTRO and the German Association of Radiology Oncology produced their accelerated PBI (APBI) criteria for patient selection and recommendations for irradiation methods[27,28]. Over recent decades, increasing attention has been paid to the dose-dependent effects of WBI on major coronary artery events[29,30] and secondary malignancies, including lung cancer[30]. PBI is presumed to reduce the occurrence of these late adverse events by reducing the radiation dose to the corresponding organs.

Several new trials have published results, while several large trials have updated longer follow-up results. The interventions to be compared are more than 2 (in this case, 3) and not all articles report all three single comparisons (PBI vs. CF-WBI, PBI vs. HF-WBI, and CF-WBI vs. HF-WBI), so network meta-analysis is done. We conducted a comprehensive assessment of three RT modalities (PBI, HF-WBI, and CF-WBI) based on the results of recently published trials and update long-term follow-up trials data to evaluate and compare the effectiveness of PBI, HF-WBI, and HF-WBI.

2. Methods

This meta-analysis was carried out in accordance with the Cochrane Collaboration Handbook of Interventions Systematic Reviews[31]. The study followed the PRISMA reporting guidelines[32]. This review was prospectively registered in the PROSPERO database (Registration Number CRD42020219183).

Search strategy

We searched the following databases on 10 October 2020: Cochrane Central Register of Controlled Trials (2019, via the Cochrane Library), Central Register of Controlled Trials (CENTRAL, 2017 issue 7, via Wiley), MEDLINE 1966 to 25 July 2019, via Pubmed), and Embase (1988 to July 2019, via Elsevier). The electronic search was conducted with no language, publication year, or publication status restrictions. The selected search terms included (((early breast neoplasm) OR (early breast tumor) OR (early human mammary carcinoma) OR (early human mammary neoplasm) OR (early breast cancer)) AND ((whole-breast irradiation) OR (WBI) OR (APBI) OR (accelerated partial breast irradiation) OR (accelerated partial irradiation) OR (PBI) OR (partial breast irradiation) OR (interstitial brachytherapy) OR (multicatheter interstitial brachytherapy) OR (MIB) OR (balloon catheter brachytherapy) OR (intracavitary brachytherapy) OR (intraoperative radiotherapy) OR (IORT) OR (conformal external beam) OR (three-dimensional conformal radiotherapy) OR (3D-CRT) OR (intensity-modulated radiation therapy) OR (IMRT)) OR (intraoperative radiotherapy) OR (SIBT) OR (stereotactic body radiotherapy) OR (SBRT) OR (interstitial radiation) OR (radiotherapy) OR (RT)) AND (breast cancer) AND (randomized controlled trial) OR (clinical trial) OR (clinical study) OR (clinical trials) OR (clinical) OR (trials) OR (randomized) OR (controlled) OR (clinical trials) OR (randomized controlled trials) OR (RCT)).
Study inclusion/exclusion criteria

After the literature search, we included CF-WBI, HF-WBI, and PBI as the interventional postoperative RT arms in patients with early breast cancer. We pooled the results of different PBI techniques, such as external-beam radiation, intraoperative RT using electrons or photons, as well brachytherapy, including single- or multi-catheter-based approaches. The patients had to have undergone breast-conserving surgery and to have histologically confirmed primary breast cancer, either invasive or in situ breast cancer. The boost was assessed by the physicians in each study according to the risk of recurrence. Adjuvant systemic treatments were allowed. The included trials were published after 1 January 2000, to include comparable modern technologies. We excluded trials that compared different HF-WBI radiotherapy. The FAST[8] and FAST FORWARD[33] studies shortened 3–5 weeks of treatment to just 1 week, to explore the efficacy and safety of single-week ultra-hypofractionation. We included the FAST study but excluded the FAST FORWARD study in our analysis, because of the lack of a control arm. The TARGIT group recently updated the long-term results for the post-pathology or delayed-treatment subgroup, and we therefore split the trial into an original pre-pathology group and a delayed group, to allow the most appropriate estimation of the desired comparison. The START study included two studies, Start A and Start B. Data for the longest follow-up period were published jointly in 2013. According to the authors’ intention, we obtained data for the two studies from the joint paper.

Data extraction

The data were extracted by two independent reviewers (Chen and Yang). A third reviewer resolved any disagreements (Chang). 16 studies with 23,418 patients were included. The outcome indicators in this study were the number of ipsilateral breast tumor recurrences (IBTR), distant metastases, total deaths, and non-breast cancer-related deaths recorded at the endpoints in each included study. IBTR included tumor-bed relapse and new tumors in the ipsilateral breast. Distant metastasis of breast cancer was defined as metastases at all sites outside the quadrant where the tumor was located. Studies evaluating acute and late side effects and cosmetic effects used different evaluation criteria. It was therefore not possible to classify these indicators, which will be examined in another systematic review.

Risk of bias assessment

Two review authors (Chen and Yang) independently evaluated all relevant clinical studies for methodological quality. Each review author performed this assessment using the Cochrane Collaboration’s Risk of Bias tool, which included quality of random allocation concealment, description of dropout and withdrawal, intention-to-treat analysis, and blinding procedures for treatment and outcome assessments[34]. A third reviewer resolved any disagreements by discussion (Chang).

Statistical analysis

Statistical analysis was performed using the GeMTC package in R (version 4.0.2). A node-splitting model[35] for two-category data among all three intervention arms based on a Bayesian approach was established. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to determine the favored arm. Network consistency was analyzed by calculating the ratio of direct and indirect treatment effects within each comparison, with 95% CIs. If the 95% CI was >1.00 or < 1.00, the difference was considered significant (p<0.05). I² was used to assess the risk of bias in each model. I² < 50% means that there is a low risk of bias in the model.

3. Results

Study characteristics

The flowchart with the process of the studies selection is detailed as shown in Figure 1. 16 studies retrieved fulfilled the inclusion criteria for this review (Table 1). A total of 23,418 patients were included, most of them with node negative, hormone receptor positive, tumor stage T1-T2 and N0 low-risk breast cancer patients. The intention-to-treat principle was respected for all analyses. Hypofractionated doses ranged from 2.7 to 6.0 Gy and total doses from 28.5 to 43.5 Gy. Tumor bed boosting and regional lymph node irradiation were not permitted in some trials, and mandated in others. Except for the natural defect blinding, all studies were considered as high quality and low risk of bias. Although there were some differences in patient selection criteria, adjuvant therapy regimens and the RT technique included in the trial, local control rates were similar in the CF-WBI group, suggesting that it may be a way to control differences in selection[1,8-13,18-21,36].

Breast Cancer Ipsilateral Breast tumor recurrence

Sixteen studies reported IBTR, including seven studies for HF-WBI vs CF-WBI, seven studies for PBI vs CF-WBI, and two studies for PBI vs HF-WBI. The network meta-analysis (Figure 2) showed that CF-WBI was significantly better than PBI (OR=1.5; CI95%: 1.2–2.0; p<0.05) and HF-WBI was also significantly better than PBI (OR=1.5; CI95%: 1.1–2.1; p<0.05). There was no significant difference (OR=0.97; CI95%: 0.72–1.3; p>0.05) between the HF-WBI and CF-WBI groups. Among them, only two RCTs compared IBTR between the HF-WBI and PBI groups. There was no significant difference according to pairwise meta-analysis (OR=1.1;
CI95%: 0.58–2.0; \( p>0.05 \), but network meta-analysis using indirect comparison of the three intervention arms showed that HF-WBI was significantly better than PBI (Figure 2). There were no detectable heterogeneity between all trials in the network meta-analysis (\( I^2 <50 \)).

**Distant metastasis**

Thirteen studies reported distant metastasis, including five studies for HF-WBI vs CF-WBI, six studies for PBI vs CF-WBI, and two studies for HF-WBI vs PBI. The network meta-analysis (Figure 3) showed that there was no significant difference in the HF-WBI vs CF-WBI comparison (OR=1.1; CI95%: 0.81–1.4; \( p>0.05 \)), the PBI vs CF-WBI comparison (OR=1.0; CI95%: 0.76–1.4; \( p>0.05 \)), and the PBI vs HF-WBI comparison (OR=0.98; CI95%: 0.66–1.4; \( p>0.05 \)). There was detectable heterogeneity between HF-WBI and CF-WBI groups (\( I^2 = 66.7 \% \)). But, even with moderate heterogeneity, this part of comparison yielded interpretable results, with no significant difference between CF-WBI and HF-WBI in distant metastasis.

**Total deaths**

Thirteen studies reported total deaths, including five studies for HF-WBI vs CF-WBI, six studies for PBI vs CF-WBI, and two studies for HF-WBI vs PBI. Figure 4 shows the network meta-analysis of total deaths among three RTs, which was not statistically different between each other. There were no detectable heterogeneity between the trials (\( I^2 = 0 \)).

**Non-breast cancer deaths**

Eleven studies reported non-breast cancer-related deaths, including four studies for HF-WBI vs CF-WBI, six studies for PBI vs CF-WBI, and one study for HF-WBI vs PBI. Figure 5 shows the network meta-analysis of non-breast cancer deaths among three RTs, which was not statistically different between each other. There were no detectable heterogeneity between the trials (\( I^2 < 50 \% \)).

**5. Conclusions**

In summary, this meta-analysis demonstrated PBI was associated with increased IBTR compared with HF-WBI or CF-WBI in early-stage breast cancer patients, and further research is still needed to compare the adverse effects and cosmesis of three distinct RT approach. There were no statistically difference among the RTs in terms of distant metastases, total deaths, and non-breast cancer mortality.

**Abbreviations**

CF-WBI: Conventional Fractionated Whole Breast Irradiation  
HF-WBI: Hypofractionated Whole Breast Irradiation  
PBI: Partial Breast Irradiation  
IBTR: Ipsilateral Breast Tumor Recurrence  
LR: Local relapse  
LRR: Local-regional relapse  
RT: Radiation therapy  
APBI: Accelerated partial breast irradiation

**Declarations**

**Author Contributions:**

Wen-Hui Li: Conceptualization. Xian Chen: Methodology, Software. Tong-xin Yang: Data curation, Writing, Original draft preparation. Yao-Xiong Xia: Visualization, Investigation. Qi Shen: Supervision. Yu Hou, Li Wang, Lan Li: Software, Validation. Li Chang: Writing, Reviewing and Editing. All authors have read and agreed to the published version of the manuscript.

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**Ethics approval and consent to participate** — Not applicable

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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| Study | Synonym | Study Period | Maximum Follow-up, year | No. | Median Age | Primary Endpoints | population | PBI Technique | PBI Dose | CF-WBI Dose |
|-------|---------|--------------|-------------------------|-----|------------|-------------------|------------|---------------|----------|-------------|
| Vaidya 2020 | TARGIT-A | 03/2000–06/2012 | 8.6 | 2298 | Mean 63 | IBTR | IDC; T < 2.5cm; R0; >45 y; unifocal | IORT x | 20/20 | 30/2 - 50/2 |
| Vaidya 2020 | delayed TARGIT-A | 03/2000–06/2012 | 9 | 1153 | Mean 63 | IBTR | IDC; T < 2.5cm; R0; >45 y; unifocal | IORT x | 20/20 | 30/2 - 50/2 |
| Meattini 2020 | Florence | 03/2005–06/2013 | 10 | 520 | 62.8 | IBTR | IBC or DCIS; T < 2.5cm; R0; >45 y; unifocal | IMRT | 30/6 | 50/2 + 10/2 TBB |
| Whelan 2019 | RAPID | 02/2006–07/2011 | 8.6 | 2135 | 61 | IBTR | IBC or DCIS; T < 2.5cm; R0; N0; >40 y; unifocal | 3DCRT, IMRT | 38.5/3.85 in 5-8d | (192) 50/2; (873) 42.5/2.66; † |
| Vicini 2019 | NSABP B-39 | 2005–2013 | 10.2 | 4216 | 54 | IBTR | IBC or DCIS; T < 3 cm; R0; N0; >40 y; unifocal | 3DCRT, single- and multi-cath. BT | 34/3.4; 38.5/3.85 in 5-8d | 50/2; 50.4/1.8; opt.Boost |
| Stmad 2016 | GEC Estro | 04/2004–07/2009 | 6.6 | 1328 | 62 | IBTR | IBC or DCIS; T < 3 cm; R0; N0; >40 y | Multicath. BT | 32/4; 30.3/4.3 or PDR | 50/2; 50.4/1.8; opt.Boost |
| Veronesi 2013 | ELIOT | 11/2000-12/2007 | 5.8 | 1305 | nr | IBTR | IBC; T < 2.5 cm; R0; 48-75y; unifocal | IORT electron | 21/21 | 50/2 + opt.10/2 |
| Polgar 2013 | Budapest | 1998-2004 | 10.5 | 258 | Mean 59 | local recurrence | IBC; T < 2 cm; R0; N0; Gl-2; unifocal | Multicath. BT 3DCRT | BT: 36.4/5.2 BID; e: 50/2 QD | 50/2 + opt.16/2 |
| Coles 2017 | Import low | 05/2007-10/2010 | 6 | 1343 | 62 | IBTR | IDC; T < 3 cm; R0; N0; >50 y; pN0-I | 3DCRT | 40/2.67 QD | |
| Owen 2006 | RMH/GOC | 01/1986–03/1998 | 9.7 | 1410 | 54.5 | IBTR | IBC; T1-3, N0-1, M0 | IORT | 50/2 | |
| Whelan 2010 | Canadian | 04/1993-09/1996 | 12 | 1234 | n.r | IBTR | IBC; T1-3, N0-1, M0 | IORT | 50/2 | |
| Spooner 2012 | | 08/1985-12/1992 | 16.9 | 358 | 59 | time to first locoregional relapse | clinical stage I and II | IORT | 50/2 | |
| Haviland 2013 | START A | 01/1991–12/2002 | 12.4 | 2236 | 57 | LRR, normal tissue effects and quality of life | IBC; T1-3, N0-1, M0 | IORT | 50/2 | |
| Haviland 2013 | START B | 01/1991–12/2002 | 12.4 | 2215 | 57.4 | LRR, normal tissue effects and quality of life | IBC; T1-3, N0-1, M0 | IORT | 50/2 | |
| Wang 2020 | | 08/2010-11/2015 | 5 | 729 | 46 | LR | 18-70 y; T1/2; R0; N0 | IORT | 50/2 + opt. 10/2 | |
| Brunt 2020 | FAST | 10/2004-3/2007 | 10 | 915 | mean 62.9 | photographic change in beast appearance | ≥ 50y; IBC; T<3cm; R0; N0 | IORT | 50/2 | |

1. According to The Cochrane Collaboration's Risk of Bias Tool, a total of six bias items were judged by review authors, which are random sequence generation (selection bias), allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome
assessment (detection bias), Incomplete outcome data (attrition bias) and Selective reporting (reporting bias). The risk of bias summary for each included study is listed in this column, where ◁ represents low risk of bias, ◀ represents high risk of bias, and ○ represents unclear risk of bias.

2. Abbreviations: No: number; n.r.: not reported; PBI: partial breast irradiation; CF-WBI: conventional fractionated whole breast irradiation; HF-WBI: Hypofractionated whole breast irradiation; G3: pathology grade 3; x photons; y years; IDC: Invasive ductal carcinoma; LR: Local recurrence; LRR, local-regional relapse; DCIS: Ductal carcinoma in situ; N+: lymph nodule positive; Multicath.BT: multicatheter brachytherapy; HER-2+: HER-2 positive; HT: Adjuvant therapy with hormone; IBC: Invasive ductal carcinoma; IMRT: Intensity-modulated radiotherapy; CTx: chemotherapy; ET: endocrine therapy; IBTR: ipsilateral breast tumor recurrence; IORT: intraoperative radiotherapy; HR+: hormone receptor positive; R0: R0 excision, the surgical margin was negative; N0: No lymph node metastasis; T: T stage of tumor; M0: No distant metastasis.

Figures

Figure 1
Consort diagram showing the results of the literature review according to the PRISMA guidelines.
**Figure 2**

Comparison of IBTR by forest plots with odds ratios using conventional pair-wise meta-analysis and network meta-analysis, and network meta-ranking. Circle and quadrats represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

| Study            | Events | Total | Events | Total | Events | Total | Weight | Odds Ratio (95% CI) | I² |
|------------------|--------|-------|--------|-------|--------|-------|--------|---------------------|----|
| **PBI vs CF-WBI**|        |       |        |       |        |       |        |                     |    |
| Meantini 2020    | 6      | 260   | 9      | 260   | 4.8%   |       | 1.6 (0.53, 4.6)    |      |
| Polgar 2013      | 4      | 130   | 3      | 128   | 2.4%   |       | 0.73 (0.14, 3.7)   |      |
| Strnad 2016      | 5      | 651   | 9      | 633   | 10.9%  |       | 1.6 (0.52, 5.1)    |      |
| Vaidya 2020 Delayed TARGIT-A | 79 | 572 | n.r. | 106 | 581 | 10.6% | 1.4 (1.0, 1.9) |      |
| Vaidya 2020 TARGIT-A | 13 | 1158 | n.r. | 36 | 1140 | 21.2% | 2.9 (1.5, 5.6) |      |
| Veronesi 2013    | 4      | 654   | 21     | 651   | 12.0%  |       | 6.0 (1.8, 18.3)   |      |
| Vicioli 2019     | 71     | 2036  | 90     | 2069  | 36.0%  |       | 1.2 (0.91, 1.7)   |      |
| Pooled (pair-wise) | 182 | 5361 | 274 | 5462 | 100.0% |       | 1.6 (1.2, 2.4) | 53.5% |
| Indirect (back-calculated) | 1.9 | 0.78, 2.1 |       |        |        |        |                     |    |
| Pooled (network) | 1.5 | 1.2, 2.0 |       |        |        |        |                     | 44.6% |
| **PBI vs HF-WBI**|        |       |        |       |        |       |        |                     |    |
| Coles 2017       | 9      | 674   | 6      | 669   | 38.6%  |       | 0.65 (0.22, 1.9)   |      |
| Whelan 2019      | n.r.   | 28    | 1065   | 37    | 1070   | 61.4% | 1.3 (0.81, 2.2)    |      |
| Pooled (pair-wise) | 37 | 1739 | 43 | 1739 | 100.0% |       | 1.1 (0.58, 2.0) | 30.1% |
| Indirect (back-calculated) | 1.7 | 1.1, 2.5 |       |        |        |        |                     |    |
| Pooled (network) | 1.5 | 1.1, 2.1 |       |        |        |        |                     | 26.3% |

**Figure 3**

Comparison of IBTR by forest plots with odds ratios using conventional pair-wise meta-analysis and network meta-analysis, and network meta-ranking. Circle and quadrats represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

| Study            | Events | Total | Events | Total | Events | Total | Weight | Odds Ratio (95% CI) | I² |
|------------------|--------|-------|--------|-------|--------|-------|--------|---------------------|----|
| **PBI vs CF-WBI**|        |       |        |       |        |       |        |                     |    |
| Meantini 2020    | 8      | 260   | 7      | 260   | 6.1%   |       | 0.86 (0.30, 2.5)   |      |
| Polgar 2013      | 11     | 130   | 7      | 158   | 3.0%   |       | 0.61 (0.22, 1.7)   |      |
| Strnad 2016      | 5      | 551   | 5      | 633   | 13.9%  |       | 0.86 (0.24, 3.2)   |      |
| Vaidya 2020 Delayed TARGIT-A | 67 | 572 | n.r. | 71 | 581 | 13.5% | 1.0 (0.73, 1.5) |      |
| Veronesi 2013    | 35     | 654   | 33     | 651   | 15.3%  |       | 0.94 (0.58, 1.5)   |      |
| Vicioli 2019     | 49     | 2036  | 65     | 2069  | 48.3%  |       | 1.3 (0.80, 1.9)    |      |
| Pooled (pair-wise) | 175 | 4203 | 189 | 4342 | 100.0% |       | 1.0 (1.0, 1.4) | 0.0% |
| Indirect (back-calculated) | 1.1 | 0.60, 2.0 |       |        |        |        |                     |    |
| Pooled (network) | 1.0 | 0.76, 1.4 |       |        |        |        |                     | 0.0% |
| **PBI vs HF-WBI**|        |       |        |       |        |       |        |                     |    |
| Coles 2017       | 13     | 674   | 12     | 669   | 38.6%  |       | 0.93 (0.41, 2.1)   |      |
| Whelan 2019      | n.r.   | 18    | 1065   | 20    | 1070   | 61.4% | 1.1 (0.58, 2.1)    |      |
| Pooled (pair-wise) | 31 | 1739 | 32 | 1739 | 100.0% |       | 1.0 (1.0, 1.4) | 0.0% |
| Indirect (back-calculated) | 0.98 | 0.81, 1.5 |       |        |        |        |                     |    |
| Pooled (network) | 0.98 | 0.88, 1.4 |       |        |        |        |                     | 0.0% |
Comparison of distant metastasis by forest plots with odds ratios using conventional pair-wise meta-analysis, network meta-analysis, and network meta-ranking. Circles and quadrats represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

![Forest plots for distant metastasis](image)

**Figure 4**

Comparison of total death by forest plots with odds ratios using conventional pair-wise meta-analysis, network meta-analysis, and network meta-ranking. Circles and quadrats represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

![Forest plots for total death](image)

### Table 1: Comparison of distant metastasis by forest plots with odds ratios

| Study                  | CF-WBI Events | Total Events | CF-WBI Total | Events | Total | PBI Events | Total | PBI Total | Weight | Odds Ratio (95% CI) | I²  |
|------------------------|---------------|--------------|--------------|--------|-------|------------|--------|-----------|--------|---------------------|-----|
| Brunt 2020             | 23            | 302          | 66           | 613    | 13.9% |            |        |           |        | 1.0 (0.9, 1.2)      |     |
| Haviland 2013 START A  | 38            | 749          | 81           | 1487   | 33.9% |            |        |           |        | 1.0 (0.73, 1.0)     | 1.0 |
| Haviland 2013 START B  | 62            | 1105         | 53           | 1110   | 33.6% |            |        |           |        | 0.84 (0.50, 1.0)    |     |
| Whetlen 2010           | 44            | 612          | 40           | 622    | 18.7% |            |        |           |        | 0.98 (0.67, 1.0)    |     |
| Pooled (pair-wise)     | 167           | 2768         | 222          | 3832   | 100.0%|            |        |           |        | 0.95 (0.71, 1.0)    |     |
| Indirect (back-calculated) | 1.0 (0.56, 2.0) |            |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    |     |
| Pooled (network)       |               |              |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    | 0.0 |
| PBI vs CF-WBI          |               |              |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    | 0.0 |

### Table 2: Comparison of total death by forest plots with odds ratios

| Study                  | CF-WBI Events | Total Events | CF-WBI Total | Events | Total | PBI Events | Total | PBI Total | Weight | Odds Ratio (95% CI) | I²  |
|------------------------|---------------|--------------|--------------|--------|-------|------------|--------|-----------|--------|---------------------|-----|
| Brunt 2020             | 12            | 260          | 13           | 260    | 5.4%  |            |        |           |        | 1.1 (0.56, 2.5)     |     |
| Polgár 2013            | 10            | 130          | 10           | 126    | 2.7%  |            |        |           |        | 1.0 (0.40, 2.6)      | 1.0 |
| Vaidya 2020 TARGIT-A   | 42            | 572          | 44           | 581    | 11.9% |            |        |           |        | 1.0 (0.66, 1.6)      |     |
| Vaidya 2020 TARGIT-A   | 74            | 1158         | n.r.         | 45     | 1440  | 23.8%      |        |           |        | 0.69 (0.41, 0.88)    | 0.0 |
| Venesini 2013          | 11            | 654          | 11           | 651    | 13.5% |            |        |           |        | 1.0 (0.42, 2.4)      |     |
| Pooled (pair-wise)     | 130           | 2036         | 150          | 2069   | 42.7% |            |        |           |        | 0.95 (0.72, 1.2)     |     |
| Indirect (back-calculated) | 0.87 (0.50, 1.5) |            |              |        |       |            |        |           |        | 0.93 (0.73, 1.2)     | 26.1%
| Pooled (network)       |               |              |              |        |       |            |        |           |        | 0.95 (0.72, 1.2)     |     |

Non-breast Cancer Death

| Study                  | CF-WBI Events | Total Events | CF-WBI Total | Events | Total | PBI Events | Total | PBI Total | Weight | Odds Ratio (95% CI) | I²  |
|------------------------|---------------|--------------|--------------|--------|-------|------------|--------|-----------|--------|---------------------|-----|
| Brunt 2020             | 23            | 302          | 66           | 613    | 13.9% |            |        |           |        | 1.0 (0.9, 1.2)      |     |
| Haviland 2013 START A  | 38            | 749          | 81           | 1487   | 33.9% |            |        |           |        | 1.0 (0.73, 1.0)     | 1.0 |
| Haviland 2013 START B  | 62            | 1105         | 53           | 1110   | 33.6% |            |        |           |        | 0.84 (0.50, 1.0)    |     |
| Whetlen 2010           | 44            | 612          | 40           | 622    | 18.7% |            |        |           |        | 0.98 (0.67, 1.0)    |     |
| Pooled (pair-wise)     | 167           | 2768         | 222          | 3832   | 100.0%|            |        |           |        | 0.95 (0.71, 1.0)    |     |
| Indirect (back-calculated) | 1.0 (0.56, 2.0) |            |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    | 0.0 |
| Pooled (network)       |               |              |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    | 0.0 |
| PBI vs CF-WBI          |               |              |              |        |       |            |        |           |        | 0.97 (0.74, 1.3)    | 0.0 |

![Forest plots for non-breast cancer death](image)
Figure 5

Comparison of non-breast cancer deaths by forest plots with odds ratios using conventional pair-wise meta-analysis, network meta-analysis, and network meta-ranking. Circles and quadrats represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.