

Article

# No Difference in Overall Survival and Non-Breast Cancer Deaths after Partial Breast Radiotherapy Compared to Whole Breast Radiotherapy—A Meta-Analysis of Randomized Trials

Jan Haussmann<sup>1</sup>, Wilfried Budach<sup>1</sup>, Stefanie Corradini<sup>2</sup> , David Krug<sup>3</sup>,  
Balint Tamaskovics<sup>1</sup> , Edwin Bölke<sup>1,\*</sup> , Freddy-Joel Djiepmo-Njanang<sup>1</sup>,  
Ioannis Simiantonakis<sup>1</sup>, Kai Kammers<sup>4</sup> and Christiane Matuschek<sup>1</sup>

<sup>1</sup> Department of Radiation Oncology, Heinrich Heine University, 40225 Duesseldorf, Germany; Jan.Haussmann@med.uni-duesseldorf.de (J.H.); Wilfried.Budach@med.uni-duesseldorf.de (W.B.); Balint.Tamaskovics@med.uni-duesseldorf.de (B.T.); FreddyJoel.DjiepmoNjanang@med.uni-duesseldorf.de (F.-J.D.-N.); Ioannis.Simiantonakis@med.uni-duesseldorf.de (I.S.); matuschek@med.uni-duesseldorf.de (C.M.)

<sup>2</sup> Department of Radiation Oncology, LMU University, 81377 Munich, Germany; Stefanie.corradini@med.uni-muenchen.de

<sup>3</sup> Department of Radiation Oncology, University Hospital Schleswig-Holstein, 24105 Kiel, Germany; David.Krug@uksh.de

<sup>4</sup> Division of Biostatistics and Bioinformatics, Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; kai.kammers@jhu.edu

\* Correspondence: boelke@med.uni-duesseldorf.de

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**Abstract:** Purpose/objective: Adjuvant radiotherapy after breast conserving surgery is the standard approach in early stage breast cancer. However, the extent of breast tissue that has to be targeted with radiation has not been determined yet. Traditionally, the whole breast was covered by two opposing tangential beams. Several randomized trials have tested partial breast irradiation (PBI) compared to whole breast irradiation (WBI) using different radiation techniques. There is evidence from randomized trials that PBI might result in lower mortality rates compared to WBI. We aimed to reassess this question using current data from randomized trials. Material/methods: We performed a systematic literature review searching for randomized trials comparing WBI and PBI in early stage breast cancer with publication dates after 2009. The meta-analysis was performed using the published event rates and the effect sizes for overall survival (OS), breast cancer-specific survival (BCSS), and non-breast cancer death (NBCD) as investigated endpoints. Analysis of subgroups using different radiation techniques was intended. We used hazard ratios (HR) and risk differences (RD) to estimate pooled effect sizes. Statistical analysis was performed using the inverse variance heterogeneity model. Results: We identified eleven studies randomizing between PBI and WBI. We did not find significant differences in OS ( $n = 14,070$ ; HR = 1.02; CI-95%: 0.89–1.16;  $p = 0.810$ , and  $n = 15,203$ ; RD =  $-0.001$ ; CI-95%:  $-0.008$ – $0.006$ ;  $p = 0.785$ ) and BCSS ( $n = 15,203$ ; RD = 0.001; CI-95%:  $-0.002$ – $0.005$ ;  $p = 0.463$ ). PBI also did not result in a significant decrease of NBCD ( $n = 15,203$ ; RD =  $-0.003$ ; CI-95%:  $-0.010$ – $0.003$ ;  $p = 0.349$ ). A subgroup analysis by radiation technique also did not point to any detectable differences. Conclusion: In contrast to a previous assessment of mortality, we could not find a detrimental effect of WBI on OS or NBCD. A longer follow-up might be necessary to fully assess the long-term mortality effects of PBI compared to WBI.

**Keywords:** cancer; investigation; study; radiation therapy; randomized

## 1. Introduction

The standard treatment of early stage breast cancer is breast conservation surgery followed by whole breast irradiation (WBI) and appropriate systemic therapy. This regime has been shown to be equivalent to mastectomy in terms of overall survival in numerous randomized trials [1–7]. The analysis of local recurrences in the treated breast suggested that the majority occur at the original tumor location [8–11]. This led to the hypothesis that adjuvant treatment of the tumor bed might be equally effective to whole breast radiotherapy and potentially associated with less side effects.

Multiple randomized trials addressing this question, using a multitude of techniques, have been conducted [12–17]. A pooled analysis of randomized trials reported a reduced non-breast cancer survival (NBCD) and overall survival (OS) rate in patients undergoing WBI as compared to patients treated with partial breast irradiation (PBI) [18]. This result was surprising, given the relatively short follow-up of the majority of the included trials. Over the last decade, it has been increasingly accepted that WBI contributes in a dose dependent way to major coronary events [19,20] and other secondary malignancies, including lung cancer [20]. It is hypothesized that PBI might lower the occurrence of these late adverse events by reducing the dose to the corresponding organs at risk.

We aimed to reassess this question and include recently published trials and trials with longer follow-up.

## 2. Material and Methods

On 10 April 2020, we performed a literature review according to the published PRISMA guideline [21]. We searched the MEDLINE as well as the EMBASE and EBM review platforms. Further, we screened the major meetings for published abstracts. The chosen keywords were (“radiation therapy” or “radiotherapy” or “irradiation”) AND (“breast cancer” or “carcinoma of the breast”) AND (“partial” or “targeted”) AND (“randomized” OR “randomised” OR “randomly”).

We included randomized controlled trials that investigated patients suffering from invasive breast cancer or carcinoma in situ comparing PBI to WBI. Trials had to be published after 31 December 2009, in order to include comparable modern techniques. We excluded trials that solely included carcinoma in situ patients.

We extracted the provided hazard ratios and event numbers from the identified trials to estimate the effect sizes, comparing WBI to PBI in the endpoints of overall survival (OS) as well as breast cancer-specific survival (BCSS), non-breast cancer death (NBCD), and cardiac deaths (CD). The definition of the analyzed endpoints was adopted from the published trials. When no specific event numbers were given in the publications, we calculated the events with the assumption that total mortality events equal the sum of deaths from breast cancers plus the non-breast cancer deaths. When no hazard ratios were reported, we estimated the hazard ratio and their corresponding 95% confidence interval by reconstructing all events from the published survival curves or using the method published by Parmar and Tierney [22,23]. When hazard ratios were neither reported nor estimable, we used the absolute number of events and calculated the risk differences and the corresponding confidence interval.

We used the inverse variance of heterogeneity model (ivhet) to estimate the pooled effect sizes. This method favors larger trials, uses a more conservative estimation of the confidence limits, and produces lesser observed variances compared to the random effects model [24]. Zero event correction was applied, where appropriated [25]. *p*-values below the threshold of 0.05 were considered statistically significant.

The measurement of heterogeneity within the meta-analysis was obtained with Cochran’s Q-test with the corresponding *p*-values [26,27]. Further, we also described the  $I^2$  statistics where we defined values above 25% as considerable heterogeneity [28]. Funnel plots were created for a visual analysis of publication bias. Statistical analysis was performed using the Microsoft Excel add-in MetaXL 5.3 (EpiGear International, Sunrise Beach, Australia). Plots were created using Microsoft Excel for Microsoft Office 365 Pro Plus (Redmond, Washington, WA, USA).

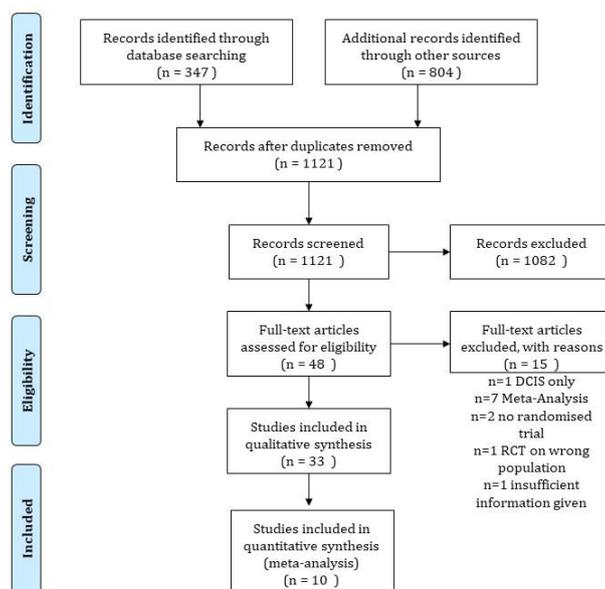
In order to compare different techniques, we pooled the results of each one of external beam radiation, intraoperative radiotherapy using electrons or photons as well any brachytherapy, including single- or multicatheter based approaches. We recognize that this approach ignores the detailed differences between the individual techniques, which each have their own advantages. However, creating a subgroup for any techniques makes a general comparison impossible and ignores the basic approaches to each treatment.

As the TARGIT-group has recently updated the long-term results of the postpathology or delayed treatment subgroup, we decided to split the trial into the original prepathology group with shorter follow-up and postpathology group with longer follow-up, as we felt that this approach allowed the most appropriate estimation of the desired comparison.

The assessments of other oncological endpoints as well as adverse events were not the aim of this investigation and will be reported separately.

### 3. Results

The literature search as shown in Figure 1 identified eleven studies randomizing an overall number of 15,438 patients. A total of ten trials reported event numbers for the endpoints of OS, BCSS, and NBCD. Eight trials allowed an estimation of the hazard ratios for OS.



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

An overview of the included studies is given in Table 1.

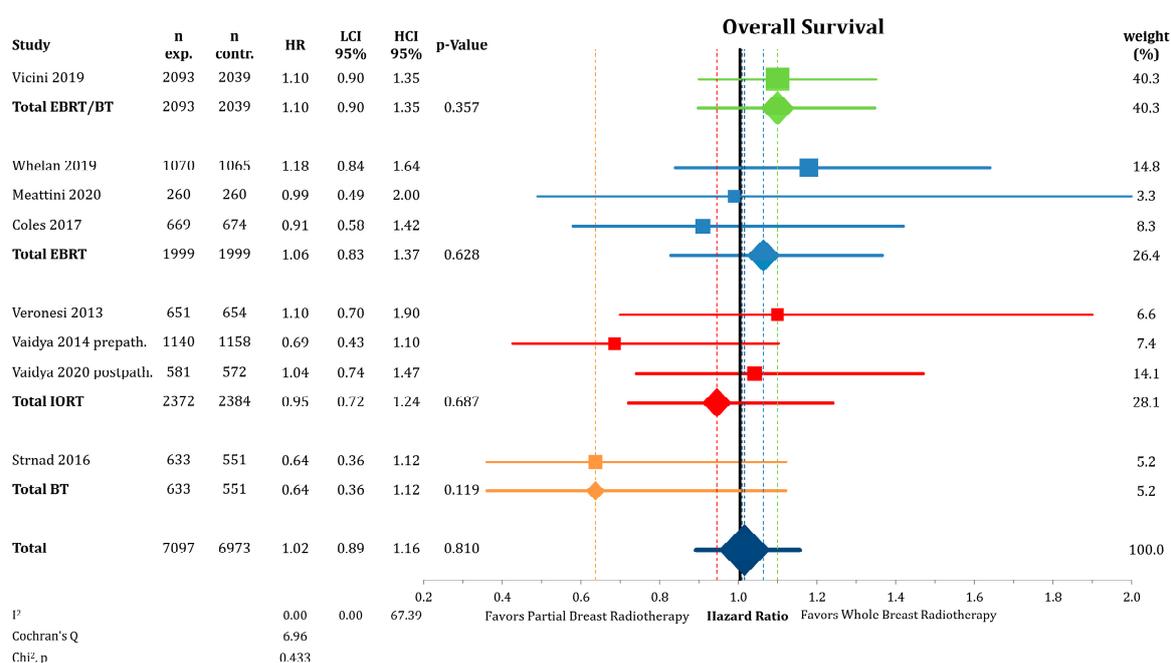
The included trial populations consisted mainly of node negative, hormone receptor positive, low-risk breast cancer patients. There were 1527 (10.0%; range: 0–24%; median: 0%) patients with ductal carcinoma in situ (DCIS) and 12640 participants with hormone receptor positive disease included (82.7%; range: 56–96%; median: 88.8%). Concerning high risk factors, undifferentiated grading (grade 3) was present in 2422 patients (15.8%; range: 0–27%; median: 11.3%) and positive lymph nodes in 1377 participants (9.0%; range: 0–26%; median: 3.0%). There were 2566 (16.8%) women below 50 years included (range: 0–38%; median: 12.0%). Between 3% and 29% received chemotherapy as part of their treatment (n = 2213; 15.4%; median: 10.7%) and 6941 took endocrine therapy (62.7%; range 49–90%; median: 67.3%).

Table 1. Overview of the included trials.

| Study               | Synonym                | Additional Publications  | Y Trial         | FU   | N Total | Med. Age | Stat. Setting | Prim. EP             | Pop   | Strat.   | PBI Technique                    | PBI Dose                            | WBI Dose                              | G3    | DCIS | N+  | HR+  | Her2+ | CTx  | ET   | Boost |
|---------------------|------------------------|--|-----------------|------|---------|----------|---------------|----------------------|---|--|----------------------------------|-------------------------------------|---------------------------------------|-------|------|-----|------|-------|------|------|-------|
| Vicini 2019 [29]    | NSABP B-39             | Vicini et al. 2019 [30]<br>White et al. 2019 [31]  | 2005–2013       | 10.2 | 4216    | 54       | Equiv.        | IBTR                 | IBC or DCIS;<br>T < 3 cm,<br>≤N1; R0;<br>>18y           | Stage, Menopausal, ER, CTx                               | 3DCRT, single- and multicath. BT | 34/3.4;<br>38.5/3.85<br>10x in 5-8d | 50/2;<br>50.4/1.8;<br>opt.<br>Boost   | 26%   | 24%  | 10% | 81%  | n.r.  | 29%  | n.r. | 80%   |
| Whelan 2019 [32]    | RAPID                  | Olivotto et al. 2013 [33]<br>Peterson et al. 2015 [34]<br>Whelan et al. 2019 [35]  | 02/2006–07/2011 | 8.6  | 2135    | 61       | noninf        | IBTR                 | IBC or DCIS;<br>T < 3cm;R0;<br>N0; >40 y;<br>unifocal   | Age > < 50;<br>Histology,<br>T > < 1.5 cm;<br>ER, Center | 3DCRTIMRT                        | 38.5/3.85<br>BID in 5-8d            | 50/2;<br>42.5/2.66<br>+ opt.<br>Boost | 16%   | 18%  | 0%  | 84%  | 6%    | 13%  | 55%  | 21%   |
| Meattini 2020 [36]  | Florence               | Livi et al. 2010 [37]<br>Livi et al. 2015 [38]<br>Meattini et al. 2017 [39]  | 03/2005–06/2013 | 10   | 520     | n.r.     | noninf        | IBTR                 | IBC or DCIS;<br>T < 2.5 cm;<br>>40 y;<br>BCS +          | None   | IMRT                             | 30/6                                | 50/2 + opt.<br>10/2                   | 11.4% | 11%  | 10% | 96%  | 4%    | 4%   | 61%  | n.r.  |
| Veronesi 2013 [13]  | ELIOT                  |  | 11/2000–12/2007 | 5.8  | 1305    | nr       | noninf        | IBTR                 | IBC;<br>T < 2.5 cm;<br>R0;<br>48–75y;<br>unifocal       | T < 1–1.4 > cm   | IORT e-                          | 21/21                               | 50/2 + opt.<br>10/2                   | 20.9% | 0%   | 27% | 91%  | 3%    | 8%   | 88%  | n.r.  |
| Vaidya 2014 [12]    | TARGIT-A               | Vaidya et al. 2010 [40]<br>Andersen et al. 2012 [41]<br>Sperk et al. 2012 [42]<br>Weizel et al. 2013 [43]<br>Keshtgar et al. 2013 [44]<br>Corica et al. 2016 [45]<br>Corica et al. 2018 [46] | 03/2000–06/2012 | 2.4  | 3375    | Mean 63  | noninf        | IBTR                 | IDC;<br>T < 2.5 cm;<br>R0; >45 y;<br>unifocal           | Center, timing   | IORT x                           | 20/20                               | n.r.                                  | 14.2% | 0%   | 16% | 92%  | 12%   | 12%  | 66%  | 38%   |
| Vaidya 2020 [47]    | TARGIT-A postpathology |  | 03/2000–06/2012 | 9    | 1153    | Mean 63  | noninf        | IBTR                 | IDC;<br>T < 2.5 cm;<br>R0; >45y;<br>unifocal            | Center, timing   | IORT x                           | 20/20                               | n.r.                                  | 6%    | 3%   | 5%  | 98%  | 6%    | 4%   | 87%  | n.r.  |
| Strnad 2016 [15]    | GEC Estro              | Polgar et al. 2017 [48]<br>Schäfer et al. 2018 [49]  | 04/2004–07/2009 | 6.6  | 1328    | 62       | noninf        | IBTR                 | IBC or DCIS;<br>T < 3 cm;<br>R0; N0;<br>>40 y;<br>BCS + | Center, Menopausal, stage                                | Multicath. BT                    | 32/4;<br>30.3/4.3 or PDR            | 50/2;<br>50.4/1.8;<br>opt.<br>Boost   | 8.3%  | 5%   | 6%  | 95%  | n.r.  | 11%  | 90%  | 98%   |
| Coles 2017 [16]     | Import low             | Bhattacharya et al. 2019 [50]<br>Bhattacharya et al. 2019 [51]<br>Bhattacharya et al. 2019 [52]  | 05/2007–10/2010 | 6    | 1343    | 62       | noninf        | IBTR                 | IDC;<br>T < 3 cm;<br>>50 y;<br>pN0-1                    | Center   | 3DCRT                            | 40/2.67 QD                          | 40/2.67                               | 9.7%  | 0%   | 3%  | 95%  | 4%    | 5%   | 80%  | n.r.  |
| Polgar 2013 [14]    | Budapest               | Polgar et al. 2004 [53]<br>Polgar et al. 2007 [54]<br>Polgar et al. 2017 [48]  | 1998–2004       | 10.5 | 258     | Mean 59  | noninf        | LR                   | IBC;<br>T < 2 cm;<br>N0; R0;<br>G1-2;<br>unifocal       | None   | Multicath. BT<br>3DCRT           | BT:36.4/5.2<br>BID;<br>e-50/2 QD    | 50/2 + opt.<br>16/2                   | 0.0%  | 0%   | 5%  | 88%  | n.r.  | 3%   | 99%  | 0.8%  |
| Offeresen 2017 [55] | DBCG PBI               |  | 2009–2016       | 3    | 882     | 66       | noninf        | Breast Induration 3y | IBC, T1,<br>R0, >60 y,<br>G1-2,<br>HER2-<br>pN0         | Center, ET   | 3DCRT                            | 40/2.66 QD                          | 40/2.66                               | <1.0% | 0%   | 0%  | 100% | 0%    | n.r. | 80%  | n.r.  |

In terms of radiation technique, six studies used photon or electron based PBI, three studies utilized intraoperative radiotherapy (IORT), whereas three trials investigated interstitial brachytherapy using single- and multicatheter based methods. The PBI schedules consisted of conventionally fractionated RT, once daily hypofractionated RT (QD RT) as well as accelerated hypofractionated RT schedules (twice daily/BID RT). There was no evidence of publication bias according to the funnel plots (not shown). Median follow-up of the included trials ranged between 2.4 and 10.5 years.

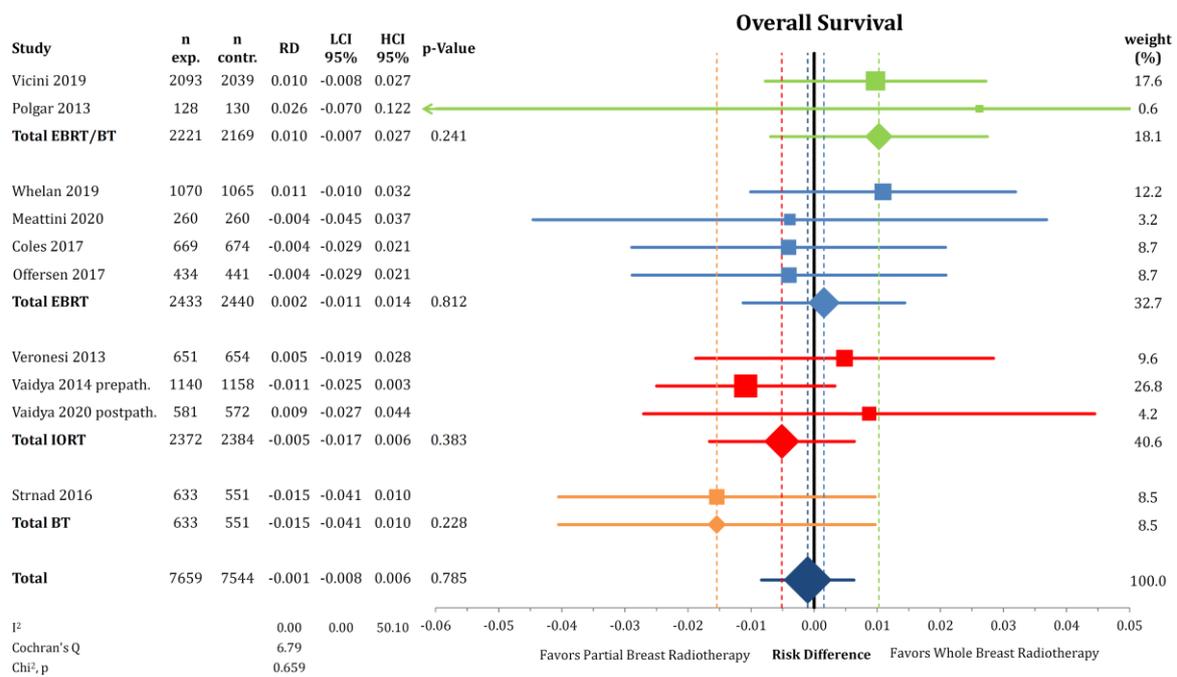
Figure 2 shows the analysis of OS between PBI and WBI, which was not statistically different between the groups ( $n = 14,070$ ; HR = 1.02; CI-95%: 0.89–1.16;  $p = 0.810$ ). There was no detectable heterogeneity ( $I^2 = 0.00$ ). We found no significant differences in the subgroup analysis by radiation technique.



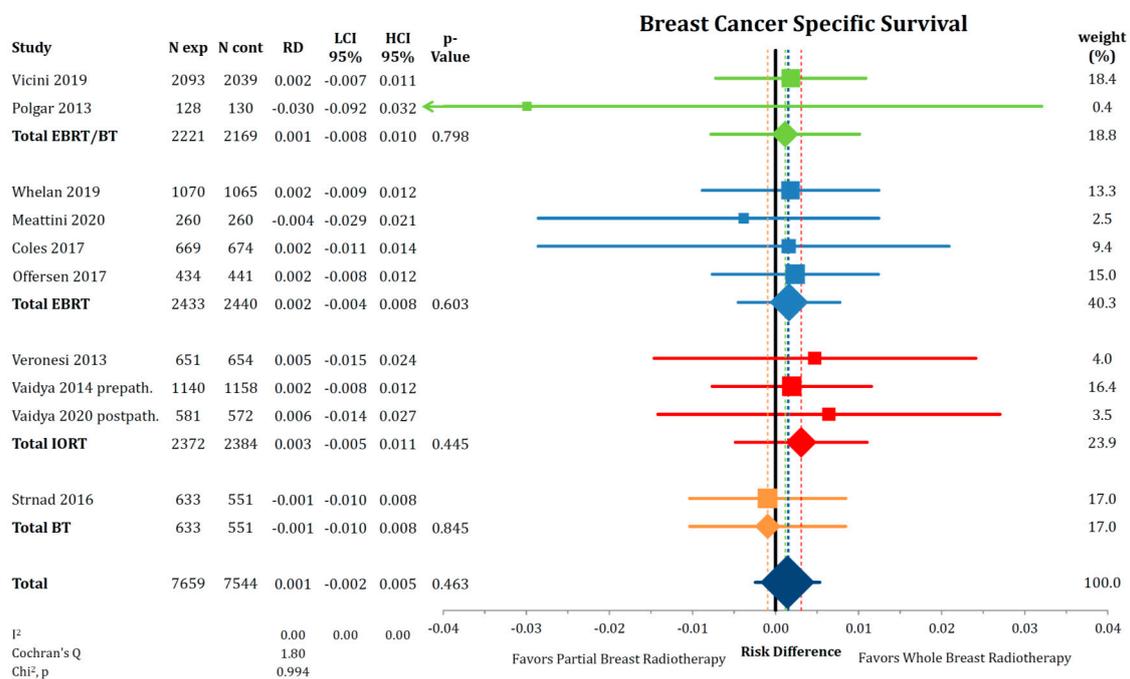
**Figure 2.** Comparison of overall survival by hazard ratios between partial- and whole breast radiation using a forest plot and the inverse variance heterogeneity model. Trials are grouped by radiation technique. Quadrats and diamonds represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

We obtained similar results regarding OS when analyzing risk differences, as depicted in Figure 3. The absolute difference in the proportion of patients dying between the groups was 0.1% ( $n = 15,203$ ; RD = -0.001; CI-95%: -0.008–0.006;  $p = 0.785$ ) without any noticeable heterogeneity ( $I^2 = 0.00$ ). In absolute terms, the percentages of patients alive in the trials were 93.17% with PBI and 93.40% with WBI in cumulative numbers at the last reported follow-up point using the raw data.

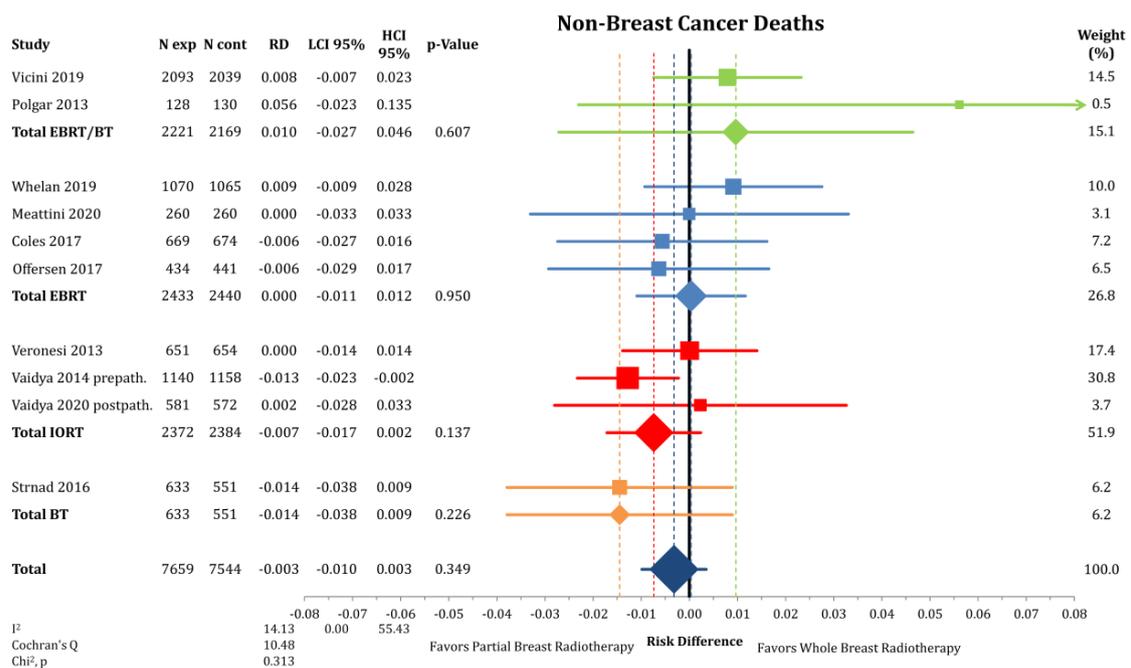
Breast cancer-specific survival was also not different between PBI and WBI with a risk difference of 0.1% ( $n = 15,203$ ; RD = 0.001; CI-95%: -0.002–0.005;  $p = 0.463$ ) without any detectable heterogeneity ( $I^2 = 0.00$ ) (Figure 4). The cumulative incidence of death from breast cancer was 2.0% after PBI and 1.9% after WBI. Additionally, mortality due to other causes than breast cancer (NBCD) was not different in the PBI group compared to WBI with a risk difference of 0.3% ( $n = 15,203$ ; RD = -0.003; CI-95%: -0.010–0.003;  $p = 0.349$ ) (Figure 5). The analysis revealed no heterogeneity between the trials ( $I^2 = 14.13$ ). Cumulatively, 4.8% in the PBI and 4.7% in the WBI arms of the included patients died from other causes than breast cancer.



**Figure 3.** Comparison of overall survival by risk difference between partial- and whole breast radiation using a forest plot and the inverse variance heterogeneity model. Trials are grouped by radiation technique. Quadrats and diamonds represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

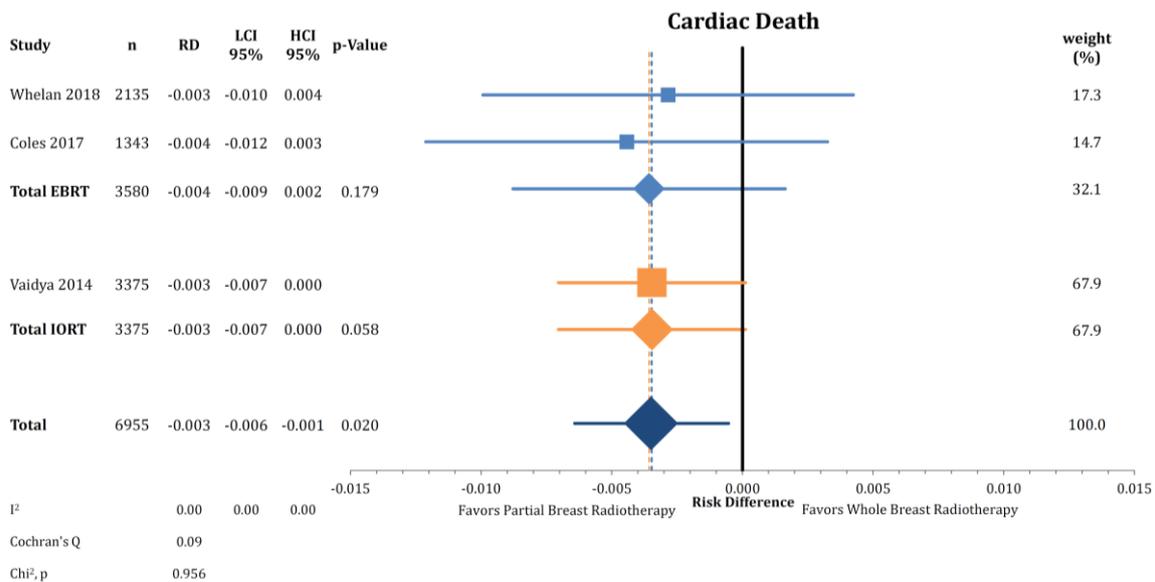


**Figure 4.** Comparison of breast cancer-specific survival by risk difference between partial- and whole breast radiation using a forest plot and the inverse variance heterogeneity model. Trials are grouped by radiation technique. Quadrats and diamonds represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.



**Figure 5.** Comparison of non-breast cancer death by risk difference between partial- and whole breast radiation by a forest plot. Trials are grouped by radiation technique. Quadrats and diamonds represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

Three trials further reported on cardiac death as part of NBCD (Figure 6). Pooling the risk differences, we obtained a significant reduction in cardiac deaths of 0.3% in patients treated with PBI ( $n = 6955$ ;  $RD = -0.003$ ;  $CI-95\%: -0.006-0.001$ ;  $p = 0.020$ ). The test for heterogeneity showed no significant effect ( $I^2 = 0.00$ ).



**Figure 6.** Comparison of cardiac death by risk difference between partial- and whole breast radiation using a forest plot. Trials are grouped by radiation technique. Quadrats and diamonds represent individual trials and pooled effect sizes with corresponding 95% confidence intervals.

#### 4. Discussion

In women with low-risk breast cancer, partial breast irradiation, in comparison to whole breast irradiation, does not result in a reduction in overall or non-breast cancer mortality. This result stands in contrast to the previously published analysis by Vaidya and colleagues, which reported a “small yet statistically and clinically significant difference between PBI and WBI favoring PBI” in OS and NBCD [18]. Is this paper to be regarded as an updated version of the previous meta-analysis or are there substantial differences explaining the different conclusions? The most notable difference between the meta-analyses is the enlarged patient numbers included as well as the lengthened follow-up time in our investigation. The previous analysis described the outcome data of 4231 to 4489 patients in the investigated endpoints in four to five trials, with only one trial following their patients longer than a median of more than 5–6 years. In contrast, this analysis included 8 to 10 trials with more than three times the size, with up to 15,212 patients treated within the studies reporting on a median follow-up longer than eight years in five trials.

Both analyses are very similar regarding the statistical outcome measure (risk differences) and the trial inclusion criteria. However, the model used to pool and compare the effect sizes was different, as we utilized the inverse variance heterogeneity model instead of the random and fixed effect models. The reasons for this are described above. Nonetheless, replacing the *ivhet* with the random effects model in our analysis did not change the forthcoming effect sizes (results not shown) and thus maintained the interpretation of the results.

The analysis by Vaidya et al. included more patients treated with brachytherapy or intraoperative radiotherapy (~87%) [18]. Does this varying distribution of PBI techniques explain the different outcome? Our results do not support this interpretation, as the estimation of heterogeneity did not suggest an effect by different trials. Three of the included trials (about 24% of trial population) predominantly applied WBI in a hypofractionated, accelerated schedule [16,32,55]. This treatment schedule has been shown to cause lower rates of acute as well as late adverse events, which could have introduced some heterogeneity in the control arms. The pooled analysis of the START trials described numerically lower event numbers in the trials after 10 years of follow-up [56]. If the estimated alpha/beta ratios for late cardiac events are estimated correctly, one could expect lower long-term cardiac morbidity after shorter course radiation treatment.

A given explanation for a hypothesized reduced mortality is that with PBI, especially with focal therapy (BT, IORT), lower doses are applied to the heart. This might translate to fewer late cardiac adverse events like ischemic heart disease, chronic heart failure, or cardiac arrhythmia. This is supported by the hypothesis-generating analysis of cardiac death, which demonstrated that PBI resulted in fewer cardiac deaths. However, we detected no variation between EBRT and IORT with numerically similar risk differences (Figure 6), which leads to the conclusion that the effect may be independent of the applied technique. Given the extensive efforts in modern radiation oncology of keeping the heart doses as low as possible using different techniques, like cardiac shielding and deep-inspiration breath hold (DIBH), we anticipate the difference to be lower than estimated here [57]. Unfortunately, an analysis of NBCD or cardiac death divided by laterality of breast cancer was not possible. Early results of a randomized trial of radiotherapy, including the internal mammary nodes, using DIBH compared to free-breathing in patients with left-sided breast cancer found reduced cardiac doses and improved left ventricular ejection fraction in the DIBH group [58,59]. Classically, it has always been assumed that the cardiovascular harm from tangential radiation therapy manifests at 10+ years of follow-up [60]. We would, however, caution the interpretation that PBI reduces the cardiac death rate compared to WBI. Firstly, the trials that actually reported on cardiac deaths are very limited ( $n = 3$ ). Secondly, the attribution of a cause of death is often difficult and subject to possible inconsistency. Lastly, cardiac deaths are a substantial component of the non-breast cancer mortality events, which demonstrated no difference between PBI and WBI.

Possible shortcomings of this analysis include the still relatively limited median follow-up between 5 and 10 years. The included data are publication-based data, rather than individual patient-based

data (IPD), which would be generally desirable. Further, a comprehensive assessment of the different PBI techniques was not possible, as the NSABP B-39 and Budapest trials did not report separately on the effects of EBRT and BT in the investigated endpoints.

How does this analysis compare to other publications? The meta-analysis by Hickey et al. also reports no effect of PBI on OS and BCSS, similar to our analysis [61]. In contrast, in the paper published by Korzets and colleagues in 2019, PBI led to reduced non-breast cancer death (OR = 0.55; CI-95%: 0.41–0.73) with a trend for improved overall survival (OR = 0.84; CI-95%: 0.71–1.01) [23]. However, the investigation is limited by the lack of the inclusion of the RAPID and NSABP B-39 trials in the evaluation of NBCD as well as missing current data from RAPID, NSABP B-39, and Florence trials in the OS assessment. It is very possible that the long-term outcome data comparing PBI and WBI will show a clearer picture of what might be starting to transpire in the presented data and also makes common sense: PBI might be superior in terms of toxic effects of radiation, but might be slightly inferior in cancer control compared to WBI.

The included trials differ substantially in terms of included subgroups, as the inclusion criteria range from DCIS up to patients with multiple positive lymph nodes and triple negative disease. Current guidelines encourage the usage of different RT techniques and advise the selection of low-risk patients when using partial breast treatments [62–66]. In this analysis, we detected no difference of the PBI techniques, leading to the conclusion that all used treatment strategies appear to provide similar survival results.

## 5. Conclusions

In summary, our meta-analysis demonstrated that patients treated in randomized trials comparing partial to whole breast irradiation did not show any differences in mortality.

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## Abbreviations

|        |                                       |
|--------|---------------------------------------|
| 3DCRT  | 3D conventional radiation therapy     |
| BCS    | breast conserving surgery             |
| BID    | twice daily                           |
| BT     | brachytherapy                         |
| CTx    | chemotherapy                          |
| DCIS   | ductal carcinoma in situ              |
| e-     | electrons                             |
| EBRT   | external beam radiotherapy            |
| EP     | endpoint                              |
| ER     | estrogen receptor                     |
| ET     | endocrine therapy                     |
| FU     | follow-up                             |
| IBC    | invasive breast cancer                |
| IDC    | invasive ductal cancer                |
| IBTR   | in breast tumor recurrence            |
| IMRT   | intensity modulated radiation therapy |
| IORT   | intraoperative radiotherapy           |
| HR+    | hormone receptor positive             |
| LR     | local recurrence                      |
| Med.   | median                                |
| n      | number                                |
| N+     | nodal positive                        |
| Noninf | non-inferiority                       |
| n.r.   | not reported                          |
| PBI    | partial breast irradiation            |
| Pop    | Population                            |
| QD     | once daily                            |
| RT     | radiotherapy                          |
| q.o.d. | every other day                       |
| Stat.  | statistical                           |
| Strat. | stratification                        |
| WBI    | whole breast irradiation              |
| x      | photons                               |
| y      | years                                 |

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