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Systematic review

Accelerated partial irradiation for breast cancer: Systematic review and meta-analysis of 8653 women in eight randomized trials

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ABSTRACT

Background and purpose: Accelerated partial breast irradiation (APBI) is the strategy that allows adjuvant treatment delivery in a shorter period of time in smaller volumes. This study was undertaken to assess the effectiveness and outcomes of APBI in breast cancer compared with whole-breast irradiation (WBI). *Material and methods:* Systematic review and meta-analysis of randomized controlled trials of WBI versus APBI. Two authors independently selected and assessed the studies regarding eligibility criteria. *Results:* Eight studies were selected. A total of 8653 patients were randomly assigned for WBI versus APBI. Six studies reported local recurrence outcomes. Two studies were matched in 5 years and only one study for different time of follow-up. Meta-analysis of two trials assessing 1407 participants showed significant difference in the WBI versus APBI group regarding the 5-year local recurrence rate (HR = 4.54, 95% CI: 1.78–11.61, $p = 0.002$). Significant difference in favor of WBI for different follow-up times was also found. No differences in nodal recurrence, systemic recurrence, overall survival and mortality rates were observed. *Conclusions:* APBI is associated with higher local recurrence compared to WBI without compromising other clinical outcomes.

Since the early 90s breast-conserving therapy (BCT) has been established as a safe and standard-of-care procedure for patients with early stage breast cancer. Breast-conserving surgery followed by whole breast irradiation (WBI) with or without the inclusion of lymph node chains yields equivalent results regarding local control and overall survival when compared to radical mastectomy alone in several phase III randomized trials [1–6]. Even for patients considered to be at low risk of ipsilateral tumor recurrence, radiation therapy (RT) has been associated with a significant reduction in disease relapse [7]. Moreover, WBI is related to very low toxicity rates with a minor impact on the long-term quality of life, and good outcomes [8].

Nevertheless, WBI usually involves 25–30 daily fractions comprising 5–6 weeks of treatment in conventional schedule, and about 3 weeks in hypofractionated fashion [9]. In the United States of America, data regarding treatment delivery have demonstrated that 10–40% of patients submitted to breast-conserving surgery do not perform adjuvant WBI [10–12]. Some features that frequently prevent patients from receiving their prescribed radiation course are age (older patients are less likely to receive radiotherapy), the socioeconomic status, the travel distance to a radiotherapy facility that may involve higher costs with transport and temporary lodging, the possibility of not having the appropriate family support during the period of radiotherapy, absence from work during such treatment, among others [13]. Therefore, due to the restricted access to RT centers and the time period required for WBI, a significant number of women theoretically eligible for BCT are treated with mastectomy or quadrantectomy alone [12,14,15].

For early stage breast cancer, the most common sites of disease relapse are around the tumor bed. Cancer recurrences outside the initial site seem to happen with equal incidence following BCT whether or not adjuvant WBI is used. Hence, the highest benefits of irradiation are associated to the dose delivered at the tissue neighboring the tumor bed [16,17]. In this scenario, accelerated partial breast irradiation (APBI), that delivers treatment to a

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limited volume of tissue around the tumor cavity only (partial breast irradiation), and delivering a larger than standard dose per fraction within each treatment (accelerated irradiation) has emerged as an alternative approach to WBI. When compared to WBI, APBI allows adjuvant treatment to be delivered after BCT over a shorter period of time (1 week or less). Several methods are available to perform APBI such as intraoperative radiotherapy (IORT) with electrons or gamma rays, external-beam radiotherapy and brachytherapy [18]. APBI may optimize the radiation treatment and improve outcomes of patients that otherwise would decline WBI. Moreover, APBI is normally associated with less cost than WBRT [19].

Several trials have already demonstrated the efficacy of APBI regarding local control rates and cosmetic outcomes [20–22]. In addition, some other randomized trials were undertaken comparing WBI with APBI strategies. Therefore, this systematic review and meta-analysis was performed to assess the effectiveness and outcomes of APBI compared with WBI in the adjuvant treatment of patients with breast cancer.

Methods and methods

Study design

This was a systematic review carried out in accordance with The Cochrane Collaboration Handbook of Interventions Systematic Reviews [23]. The manuscript was arranged using the PRISMA Statement as reporting guidance [24].

Criteria for considering studies for this review

Studies assessing any modality of APBI compared with WBI were selected. Only randomized controlled trials including previously untreated breast cancer patients (those who had not received prior radiotherapy or prior chemotherapy) were eligible. Quasi-randomized and non-randomized studies were excluded. Adjuvant systemic treatments were allowed.

The main outcome measures were local recurrence, nodal recurrence, systemic recurrence, overall survival and mortality. Secondary outcome measures included toxicity (acute and late effects of radiation therapy-related toxicity) and cosmesis.

Search methods for identifying studies

The electronic search was conducted with no language, publication year or publication status restrictions. We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2014, Issue 2), MEDLINE (1966 to February 2014), EMBASE (1980 to July 2013) and LILACS (1982 to February 2014) (Supplementary Appendix 1). We also screened the reference lists of articles. For Medline search, research methodology filters previously published were used [25,26].

Selection of studies and assessment of the risk of bias

Relevant articles were selected and assessed by two reviewers, and their reference lists were searched for additional trials. Randomized trials identified by the search were assessed to determine whether they met the inclusion criteria. They were assessed by two independent reviewers (GNM and SAH). Disagreements were resolved by a third reviewer (RR).

The risk of bias of the included studies was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [23] and was carried out by two reviewers (GNM and RR) independently. When necessary, a third reviewer (HAC) solved disagreements. The studies were considered to have high, unclear or low risk of bias according to an assessment of the following items: generation of allocation sequences, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete data addressed, presence of biases in reports and other sources of bias that might influence the study's validity.

Statistical analysis

The size effect of the treatment for the time-to-event outcomes was calculated by the pooled hazard ratio (HR), followed by the confidence interval (CI) of 95%, from the Peto's method of fixed effect. The HR calculation was performed after imputation of the derivative of expected events (O-E) and log-rank variance (V) for each included study. For determining O-E, the Z-Score for two-tailed *p*-value was calculated based on relative risk of each study. The methods used for imputation were previously stated.

Risk ratio and 95% confidence intervals were calculated for dichotomous variables using the fixed-effect method. Sensitivity analyses were carried out excluding studies with high and unclear risk of bias. Heterogeneity was assessed using Chi-square test and I^2 test. When heterogeneity existed, the related reasons (methodological or clinical) were investigated.

Publication bias was checked through a funnel plot graphic. Review Manager [RevMan 2012] Version 5.2 software was used for statistical analyses [27].

Results

Study selection and characteristics of the included studies

The search strategy retrieved 1215 references. After screening of the titles and abstracts of these references, 1180 studies were excluded and 35 full-text articles were selected. Of these, ten papers, corresponding to eight studies fulfilled the eligibility criteria [Dodwell, 2005 [28]; Livi, 2010 [29]; Olivotto, 2013 [30]; Polgar, 2013 [31]; Polgar, 2007 [32]; Ribeiro, 1993 [33]; Ribeiro, 1990 [34]; Rodríguez, 2013 [35]; Vaidya, 2010 [36]; Vaidya, 2014 [37]; Veronesi, 2013 [38]] and were the subject of this analysis. The flowchart of the retrieved studies and the characteristics of the included studies are presented in Table 1 and Supplementary Material 1, respectively. A total of 8653 patients were randomly assigned for WBI versus APBI. Most included patients presented with tumor stage T1 or T2, and nodal stage N0.

Methodological quality of studies

The methodological quality of the included studies, assessed independently by two observers, is presented in Supplementary Materials 2 and 3. Overall, and in accordance with the Cochrane risk of bias table [23], all the eight studies were classified as high risk of bias taking into account the lack of blinding of patients and/or outcome assessors. However, except for this item (blinding), five studies were considered as high quality and low risk of bias [29,30,33,34,36–38] and the other three had unclear risk of bias [28,31,32,35].

Local recurrence

Analysis was performed according to follow-up outcomes. We used the intention-to-treat principle in analyzing data from the trials. We assessed heterogeneity both visually and statistically using the I^2 test of heterogeneity [24].

Six studies reported local recurrence outcome [28,31–38], but one study [29] did not report sufficient data to be included in the analysis (Fig. 1). Two studies [35,38] were matched in 5 years