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Partial Breast Irradiation or Whole Breast Radiotherapy for Early Breast Cancer: A Meta-Analysis of Randomized Controlled Trials

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■ **Abstract:** The purpose of the study was to compare treatment outcomes in patients with breast cancer treated with partial breast irradiation (PBI) and of those treated with whole breast-radiation therapy (WBRT). We conducted a systematic review and meta-analysis of published randomized clinical trials comparing PBI versus WBRT. Primary outcome was overall survival and secondary outcomes were locally, axillary, supraclavicular, and distant recurrences. A search of the literature identified three trials with pooled total of 1,140 patients. We found no statistically significant difference between partial and whole breast radiation arms associated with death (OR 0.912, 95% CI 0.674–1.234, p = 0.550), distant metastasis (OR 0.740, 95% CI, 0.506–1.082, p = 0.120), or supraclavicular recurrences (pooled OR 1.415, 95% CI 0.278–7.202, p = 0.560). However, PBI was statistically significantly associated with an increased risk of both local (pooled OR 2.150, 95% CI, 1.396–3.312; p = 0.001) and axillary recurrences (pooled OR 3.430, 95% CI, 2.058–5.715; p < 0.0001) compared with whole breast-radiation. Partial breast irradiation does not seem to jeopardize survival and may be used as an alternative to whole breast-radiation. Nevertheless the issue of loco-regional recurrence needs to be further addressed. ■

Key Words: breast cancer, partial breast irradiation, radiation therapy, whole breast radiotherapy

Several randomized trials supported the management of early stage operable breast cancer with breast-conserving surgery (BCS) and radiotherapy (RT) compared to modified radical or Halsted radical mastectomy (1–5). Solid data support that long-term survival rate among women who undergo BCS is the same as that among women who undergo radical mastectomy. However, while BCS eventually results in similar survival rates with radical mastectomy, it is accompanied by a higher rate of local recurrences (2) and 6 weeks postoperative whole breast radiotherapy (WBRT) is recommended to achieve local control of the disease (6,7).

The majority of breast tumor recurrences are in the immediate vicinity of the lumpectomy cavity (8–11). Breast cancer relapses outside of the original tumor bed appear to occur with the same frequency following lumpectomy regardless of whether or not adjuvant whole breast irradiation is delivered (8–11). Consequently, the main benefits of adjuvant RT are related only to the radiation delivered at the breast tissue immediately surrounding the tumor bed. Targeted RT approach may therefore be a more realistic choice compared to WBRT. Moreover, due to the limited access to radiation facilities and the time needed for WBRT (12–14), a considerable population of potentially eligible women for BCS either elects to have a mastectomy, or complete their local treatment with lumpectomy alone (15,16).

Several phase II trials which supported the efficacy of partial breast irradiation (PBI) demonstrate comparable long-term local and regional control rates and significantly better cosmetic results when compared to the corresponding results of conventional WBRT (17–19). However, a small number of phase III trials comparing standard WBRT versus

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limited field irradiation have been already published (20–22).

Due to the lack of sufficiently powered results from the existing phase III trials, we conducted a systematic review and meta-analysis to evaluate the current randomized evidence for the role of PBI in breast cancer treatment.

MATERIAL AND METHODS

Identification of Randomized Studies

We searched the Cochrane Central Trials Registry, PubMed and ISI Web of Science without year and language restriction. The last search was updated on June 2008. We used the searching algorithm: (partial OR accelerated partial OR APBI OR PBI OR multicatheter interstitial brachytherapy OR interstitial brachytherapy OR balloon catheter brachytherapy OR mammosite OR intracavitary brachytherapy OR intraoperative OR IORT OR conformal external beam OR 3D-CRT) AND (radiation therapy OR radiotherapy OR irradiation OR brachytherapy) AND (mammary OR breast) AND (cancer OR malign* OR neoplas* OR carcinom*). In addition, we tried to identify any previous systematic review of randomized trials in this field. We scrutinized the references of all eligible trials. Cross-searches were performed in MEDLINE using the names of investigators who were lead authors in at least one eligible trial.

Eligibility Criteria

We considered eligible all randomized controlled studies comparing WBRT versus limited field or partial radiation therapy after BCS in patients with breast cancer.

We excluded trials comparing two different partial irradiation techniques or two different schedules or doses of the same radiation technique. We also excluded meeting abstracts (because they have not undergone yet full peer review), single arm studies, non-randomized and pseudo-randomized trials (e.g. those with alternate allocation of subjects).

Data Extraction and Outcomes

From each eligible trial we recorded for both arms the following items: authors' names, journal and year of publication, country of origin, years of patient enrollment, and number of centers involved; number of patients randomized and analyzed per arm, age, tumor size, nodal status, histologic type, tumor grade, percentage of estrogen-receptor and progesteron-receptors positive tumors. We also recorded the irradiation technique used, study design, randomization mode, allocation concealment, withdrawals description, and blinding.

The main outcome was the overall survival rate, whereas secondary outcomes included the number of local recurrences, true and elsewhere breast recurrences (EBR), axillary recurrences, supraclavicular recurrences, and distant recurrences between compared arms.

Local recurrence was defined as any detection of cancer in the treated breast. We defined true recurrences (23) the ipsilateral local recurrences detected within 2 cm from the surgical clips. Recurrences detected at least 2 cm from the surgical clips were defined as elsewhere breast recurrences (EBR).

When data required for analyses were lacking in original reports, we contacted the original authors.

Statistical Analysis

For every primary study, two by two tables were constructed and odds ratios (OR) of PBI versus WBRT were calculated for each outcome. Heterogeneity of OR's between trials was analyzed using the chi-squared statistic (with a level of significance of 0.1). Pooled OR's and their 95% confidence intervals (CI) were calculated, in case of homogeneous studies, with a fixed effects model, according to the Mantel-Haenzel method (24). Statistical analyses were done using STATA statistical software (version 8.0; Stata Corp LP, TX, USA).

RESULTS

Eligible Trials Characteristics

The electronic searches yielded 3,093 hits; 1,776 from MEDLINE, 1,160 from ISI Thompson and 157 from Cochrane Central. Of those 29 trials were scrutinized in full text. Twenty five reports were considered ineligible (Fig. 1). Of the remaining four trials, three (22,25,26) presented updated results and cosmetic outcomes from the same Hungarian study. Two studies (20,27) which presented updated results from the Manchester study were retrieved from cross-checking of references. For the meta-analysis, we used the last peer-reviewed report for each study. Thus, three eligible trials were included in the meta-analysis with a total of 1,140 patients: 575 had been randomized to

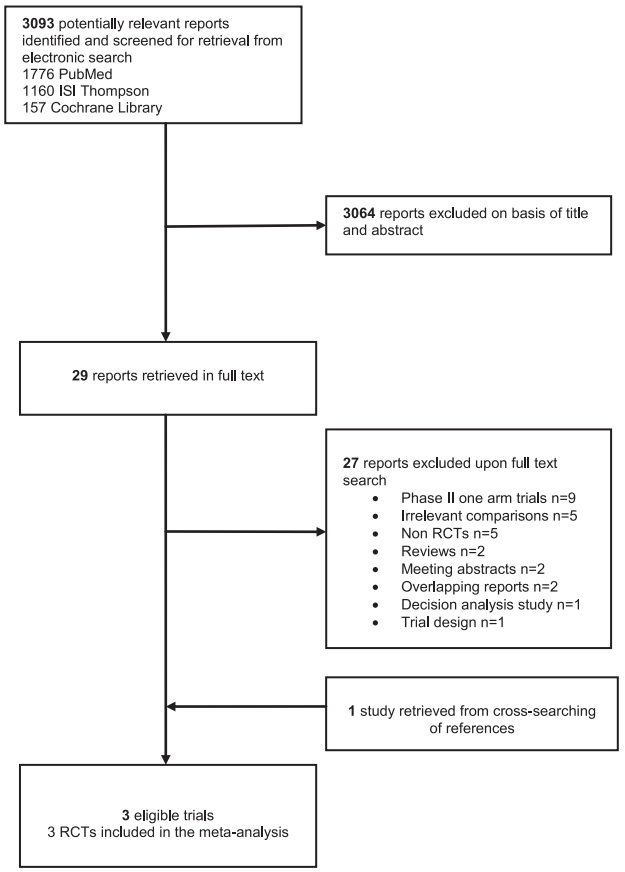


Figure 1. Flowchart diagram of studies selection.

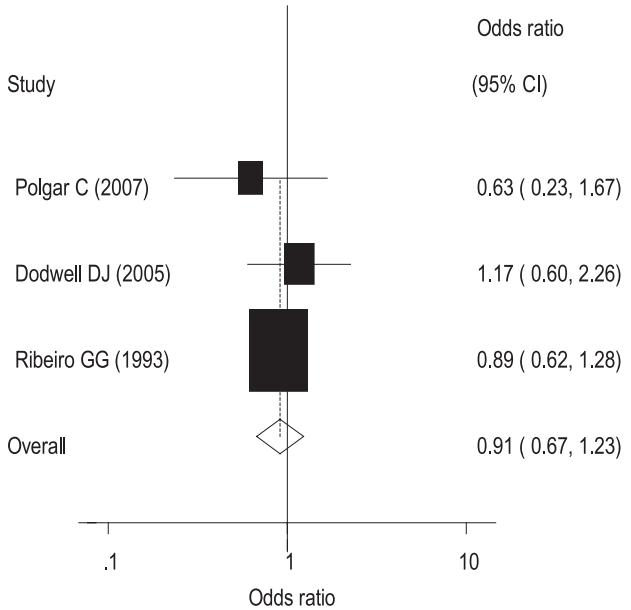


Figure 2. Meta-analysis of survival for the comparison between partial breast irradiation or whole breast radiation therapy. Legend: Each study [Polgar et al. (22), Dodwell et al. (21), Ribeiro et al. (20)] is shown by the point estimate of the odds ratio (square proportional to the weight of each study) and 95% confidence interval (CI) for the odds ratio (extending lines); the summary odds ratio (Overall) and 95% confidence intervals are shown by diamonds. Values >1 indicate that partial breast irradiation worsens survival relative to whole breast radiation.

whole breast irradiation and 565 to limited field or PBI (Fig. 1).

Table 1 shows the key characteristics of the included trials. Two out of three trials were conducted according to ''intention-to-treat'' analysis and described reasons for withdrawal from the study. In one trial, five patients were excluded for the analysis with description of the withdrawal reasons. Two trials (20,22) described model of randomization and (20,22) the model of allocation concealment.

Meta-analysis

Survival data were available for all the eligible studies. Overall 214 deaths were included in the meta-analysis. No significant differences for the risk of death were observed between compared arms [OR 0.912, 95% CI, 0.674–1.234, p = 0.550] (Fig. 2). Odds Ratios [OR] were homogeneous between studies (heterogeneity χ^2 = 1.11, p = 0.575).

Forest plots for secondary outcomes are presented in Fig. 3. Partial breast radiation therapy resulted in a

Table 1. Baseline Characteristics of Eligible Studies

Study [ref]	Year	Enrollment interval (year)	Arms	No. patients analyzed	Median age (mean), year	Median follow-up, months	Quality of studies
Ribeiro et al. (20)	1993	1982–1987	Wide-field radiation	355	52	96	Randomization: balanced block design
			Limited-field radiation	353	53	96	Allocation concealment: central randomization by telephone call
Dodwell et al. (21)	2005	1986–1990	Whole-breast radiation	90	51.5	65	Randomization: no declare
			Tumor-bed radiation	84	52	65	Allocation concealment: none
Polgar et al. (22)	2007	1998–2004	Whole-breast radiation	130	(58)	66	Randomization: sealed envelopes in block of 10
			Partial breast irradiation	128	(59)	66	Allocation concealment: sealed-envelope

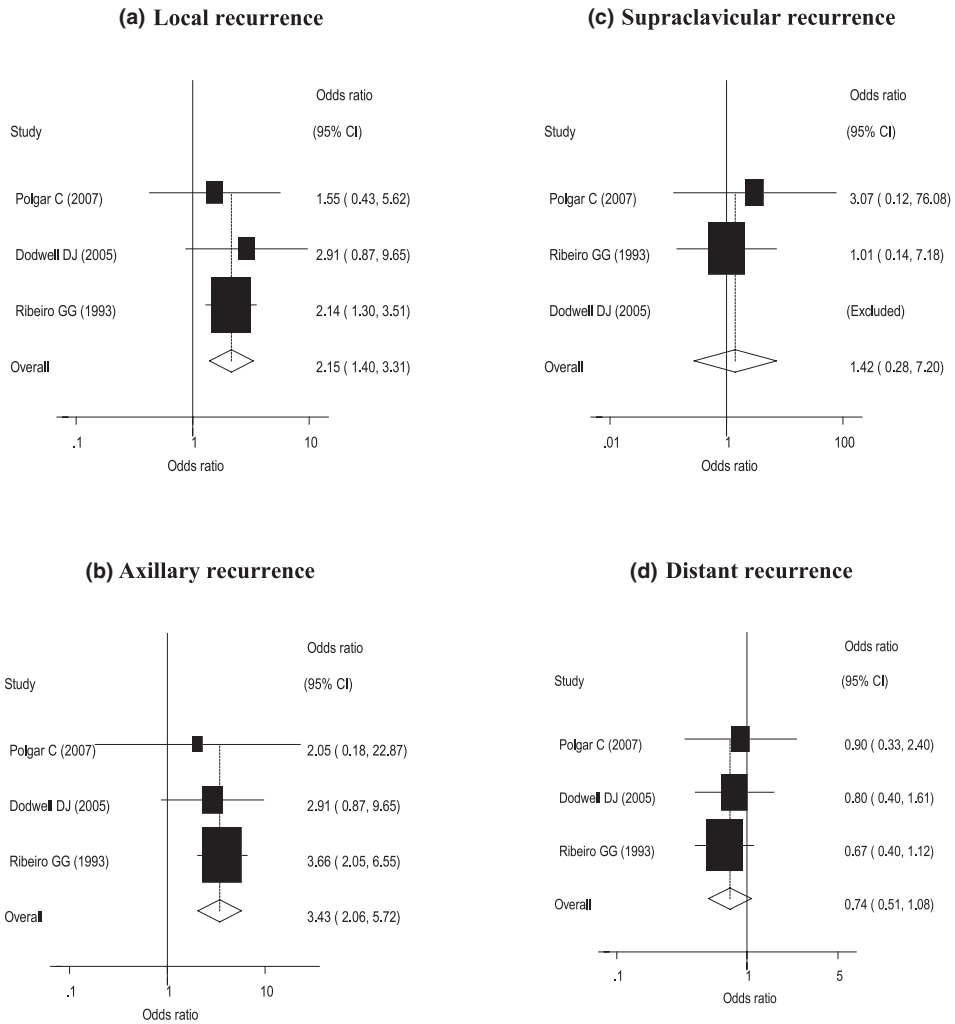


Figure 3. Meta-analysis for secondary outcomes with partial breast irradiation compared with whole breast radiation. Legend: In each panel, each study [Polgar et al. (22), Dodwell et al. (21), Ribeiro et al. (20)] is shown by the point estimate of the odds ratio (square proportional to the weight of each study) and 95% confidence interval (CI) for odds ratio (extending lines); the summary odds ratio and 95% confidence intervals are also shown by diamonds. For all panels, values >1 indicate that partial breast irradiation has a worse outcome compared with whole breast radiation. (a) Local recurrence, (b) Axillary recurrence, (c) Distant recurrence, (d) Supraclavicular recurrence.

statistically significant higher risk for developing local recurrences [pooled OR 2.150, 95% CI, 1.396–3.312; p = 0.001] and axillary recurrences [pooled OR 3.430, 95% CI, 2.058–5.715; p < 0.0001].

No difference was observed for supraclavicular recurrences [pooled OR 1.415, 95% CI 0.278–7.202, p = 0.560] and distant recurrences [pooled OR 0.740, 95% CI, 0.506–1.082, p = 0.120] among investigational arms.

No statistically significant between-study heterogeneity was observed for any of the four secondary outcomes.

Since only one study (22) clearly set the true recurrence and EBR rates, these issues were not included in final analyses.

DISCUSSION

Our meta-analysis supports that PBI is a safe treatment modality since it does not seem to jeopardize survival when compared to standard WBRT. Indeed risk for death is comparable among both treatment modalities. Anyhow, considering the relative short follow-up of the studies included in meta-analysis, studies with longer follow-up might be of value in confirming our result at long term. Supraclavicular and distant recurrences did not differ among PBI arms and WBRT arms. However, PBI was associated with statistically significant increased risk for local and axillary recurrences.

Partial breast irradiation is a new radiation technique which offers some advantages compared with

WBRT. First, it offers increased convenience, due to shorter duration of radiation therapy (5–7 days versus 6 weeks). Considering that limited access to radiation facilities is a major barrier for women to be treated with RT, the reduction of the period needed for radiation delivering is extremely important. One study in the United States found that when the travel distance was less than 10 miles, 82% of patients received RT after BCS; when it was 50 to 75 miles, 69% received it; and when it was more than 100 miles, only 42% received it (14). By using accelerated PBI, more breast cancer patients will have the opportunity to undergo RT and conserve their breast (28). Furthermore, in countries with limited RT centers, patients treated with BCS may wait a prolonged time before beginning RT. As a consequence, there is a delay in the initiation of systemic treatment when indicated. A study of 7,800 patients suggests that delaying the initiation of conventional RT for 20 to 26 weeks after surgery was associated with decreased survival (29). Moreover, in PBI less radiation is delivered throughout normal breast tissue and other organs since treatment targets are more narrowly focused, and this could result in less adverse events and better cosmetic outcomes.

Although PBI seems to offers several advantages over WBRT, the key research question is whether this benefit is significant enough to outweigh a potential risk of recurrence within the untreated tissue in the breast receiving PBI, which could affect survival in breast cancer patients.

In our study, we found that a statistically significantly higher risk of both local and axillary recurrences were associated with partial than with whole breast radiation. The recurrence risk needs to be considered with caution in terms of biases of the eligible studies. In two studies (20,21) there were difficulties with target-volume definition. Furthermore, the study of Ribeiro et al. (20) has been heavily criticized for its older radiation technique and poor quality control, inadequate axillary and systemic management, and incomplete pathologic examination (30). In the same study, a single field-size was used for all patients in limited-field arm, irrespective of the tumor dimensions or other characteristics, which could have resulted in several instances of ''geographical miss''. When the results were analyzed according to the type of the primary tumor, it was found that limited-field RT was inadequate only for patients with infiltrating lobular cancers or cancers with an extensive intra-ductal component. Polgar et al.'s (22) trial, which is the only study with sufficient target-volume definition, showed no statistical significant differences in either local or axillary breast recurrences between the two arms.

The key question that needs to be clarified is whether PBI negatively affects survival of breast cancer patients. Our results indicate that PBI is a safe radiation delivering technique since the overall death rate compared with WBRT is comparable. It seems that the higher rate of loco-regional recurrences in PBI arms could not affect overall survival. This may be partially explained by the relatively short time of follow up. Regarding supraclavicular and distant recurrences, there were no differences between the two radiation techniques.

Some limitations do exist in our meta-analysis. First, the available randomized data for PBI is still limited, since only three randomized trials are available. Second, in the eligible studies a variety of PBI techniques were used and there may be differences in dosimetry, delivery, adverse effects, and outcomes among different modalities. Furthermore, despite the fact that the median follow-up time in eligible studies were 5 years in two studies (21,22) and 8 years in one (20), median time needed to compare ipsilateral breast true recurrence frequencies after BCS plus PBI with those after BCS plus WBRT is thought to be at least 7 to 8 years and even longer in order to demonstrate the impact on mortality (31). Our meta-analysis is based on data from trials whose results have been published, and we note that publication bias is a potential threat to the validity of the results. Moreover, we did not obtain up-dated individual patient data, the use of such data might have further enhanced the accuracy and reduced the uncertainty of the estimates (32,33). However, we found no evidence of between-study heterogeneity. Finally, considerable shortcomings emerge regarding the methodological quality of the trials included in our systematic review. Several quality parameters of the studies were not sufficiently reported. Allocation concealment and randomization model were adequate in two trials (20,22). Additionally while two of the trials described scientific hypothesis and statistical power calculations (21,22), none of the trials was powered enough due to low accrual rates.

Allowing for these caveats and considering the demonstrated comparable survival rates of PBI compared to whole breast radiation, our meta-analysis suggests that partial breast RT may be used as an alternative to WBRT. Nevertheless, the issue of loco-regional recurrence needs to be further addressed.

Ongoing phase III randomized trials (34–38) will further clarify whether PBI offers high efficacy with better cosmetic outcomes, and may finally define the role of different PBI techniques in the treatment of early operable breast cancer.

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