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Clinical Investigation

Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials

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Summary

Our meta-analysis of 5-year data from published randomized trials of partial-breast irradiation (alone or within a risk-adapted approach) versus whole-breast irradiation for invasive breast cancer treated with lumpectomy found no difference in breast cancer mortality (n = 4489; difference, 0.000% [95% confidence interval (CI), −0.7 to +0.7]; $P = .999$). Partial-breast irradiation was better than whole-breast irradiation for non−breast -cancer mortality (n = 4231; difference, 1.1% [95% CI, −2.1% to −0.2%]; $P = .023$) and total mortality (difference, 1.3% [95% CI, −2.5% to 0.0%]; $P = .05$), leading to a 25% relative risk reduction.

Purpose: With earlier detection and more effective treatment, mortality from breast cancer continues to fall and it has become increasingly important to reduce the toxicity of treatments. Partial-breast radiation therapy, which focuses radiation to the tumor bed, may achieve this aim. We analyzed mortality differences in randomized trials of partial-breast irradiation (PBI).

Methods and Materials: We included data from published randomized trials of PBI (alone or as part of a risk-adapted approach) versus whole-breast irradiation (WBI) for invasive breast cancer suitable for breast-conserving therapy. We identified trials using PubMed and Google searches with the terms "partial breast irradiation" OR "intraoperative radiotherapy" OR "IMRT" OR ("accelerated" AND "radiation") AND "randomised/randomized," as well as through discussion with colleagues in the field. We calculated the proportion of patients who had events in each randomized arm at 5 years' follow-up and created a forest plot using Stata, version 14.1.

Results: We identified 9 randomized trials of PBI versus WBI in invasive breast cancer; 5-year outcomes were available for non−breast cancer mortality in 5 trials (n = 4489) and for breast cancer mortality in 4 trials (n = 4231). The overall mortality was 4.9%. There was no detectable heterogeneity between the trials for any of the outcomes. There was no difference in the proportion of patients dying of breast cancer (difference, 0.000% [95% confidence interval (CI), −0.7 to +0.7]; $P = .999$). Non−breast cancer mortality with PBI was lower than with WBI (difference, 1.1% [95% CI, −2.1% to −0.2%]; $P = .023$). Total mortality with PBI was also lower than with WBI (difference, 1.3% [95% CI, −2.5% to 0.0%]; $P = .05$).

Conclusions: Use of PBI instead of WBI in selected patients results in a lower 5-year non−breast cancer and overall mortality, amounting to a 25% reduction in relative terms. This information should be included when breast-conserving therapy is proposed to a patient. © 2016 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Concern over toxicity of radiation therapy after breast-conserving surgery is particularly relevant today as earlier diagnosis and more effective treatments have vastly improved the prognosis for women with early breast cancer. Many such women now die as the result of a cause other than the breast cancer. Furthermore, up to 50% of screen-detected cancers are overdiagnosed and would have not posed any threat to the women in the first place (1). It is therefore important to ensure that our treatments do not increase the risk of non−breast cancer deaths.

Several of the randomized clinical trials of partial-breast irradiation (PBI) appear to have found small differences in non−breast cancer mortality favoring PBI (2-8). Even though these trials used diverse methods to irradiate the breast (interstitial wires, intraoperative radiation therapy, external beam radiation therapy), they all aimed to only irradiate the immediate vicinity of the tumor bed to achieve good breast cancer control while sparing other organs.

We performed a meta-analysis of PBI versus wholebreast irradiation (WBI) in women undergoing breast-conserving therapy for the outcomes of breast cancer mortality, non−breast cancer mortality, and total mortality.

Methods and Materials

For this meta-analysis, we considered all published randomized controlled trials comparing PBI versus WBI for breast cancer treated with breastconserving therapy. We identified trials using PubMed and Google searches with the terms "partial breast irradiation" OR "intraoperative radiotherapy" OR "IMRT" OR ("accelerated" AND "radiation") AND "randomised/randomized," as well as through discussion with colleagues in the field. Searches were carried out during November 2015.

It remains unclear what length of follow-up is required to obtain robust data on non−breast cancer mortality. Historical studies have suggested that one needs to wait 10 or 15 years for such differences to arise; however, in more recent trials differences seem to appear much earlier. We planned to include all randomized trials that reported the number of breast cancer and non−breast cancer deaths at 5 years. For the TARGIT-A trial (risk adapted targeted intraoperative radiation therapy [TARGIT IORT] vs whole-breast external beam radiation therapy [EBRT]), we used

the data from the initial 1222 patients who had a median follow-up of 5 years.

Data extraction

Data were independently extracted by 2 authors (J.S.V. and M. Bulsara).

Statistical analysis

We used the absolute number of events and calculated the proportion of patients who had events in each randomized arm. We calculated the difference in this proportion and its confidence interval (CI). A forest plot was created by standard meta-analysis methods using weighted values. Statistical analysis was performed with Stata, version 14.1 (command *metan*; StataCorp, College Station, TX). For completion, we used both the random-effects model and the fixed-effects model to analyze the data.

Publication bias

We have considered all trials comparing PBI with WBI that have been performed to date. We considered only the published results. Publication bias is unlikely because the main outcome in this article is mortality, which is a secondary outcome in all these trials. The decision to publish or to withhold publication would not have been influenced by this outcome.

Assessment of study quality

As there are only a handful of studies, we included all studies in which data were available. Only the TARGIT-A trial report (3) has mentioned that the cause of death was ascertained by a senior clinician who was blinded to the randomization allocation. However, all other studies have reported the cause of death, and we have trusted the published report and used the raw numbers that were reported.

A patient was involved in the discussions leading to the development of the research question and outcome measures, and her priorities, experience, and preferences influenced it. The patient was not involved in the actual conduct of this meta-analysis but has seen and commented on the early drafts and final version.

Results

We identified 9 published randomized trials (3, 5-12), of which 8 had reported outcome data. The Canadian RAPID trial (Randomized Trial of Accelerated Partial Breast Irradiation) (12) outcomes have not been reported yet. Three trials [Christie Hospital (n=708) (9), Leeds (n=174) (10), and Barcelona (n=102) (11)] have not reported numbers of breast cancer and non−breast cancer deaths and could not be included. The National Surgical Adjuvant Breast and Bowel Project-B 39 (NSABP-B-39) trial is still recruiting, and the Intensity Modulated Partial Organ RadioTherapy-Low (IMPORT-LOW) trial results are yet to be published.

The Budapest trial authors report only the first event (5) and have not reported apportioning of their 9 breast cancer deaths between the two randomized arms. Because the 5-year estimate of breast cancer survival favored PBI (98.3% [95% CI, 96.0%-100%] for PBI vs 96.0% [95% CI, 92.4%-99.6%] for WBI), this trial's exclusion would work against favoring PBI for breast cancer mortality. We only included the non−breast cancer deaths from the aforementioned trial in the meta-analysis. Thus 5 trials (n=4489) were included for the analysis of non−breast cancer mortality (3, 5-8) and 4 trials for the analysis of breast cancer and overall mortality (n=4231) (3, 6-8). In addition, in this trial, overall survival with PBI (94.6%) was better than with WBI (91.8%). Again, we could not include these data because the exact numbers of events for overall survival and breast cancer survival were not available. If we could have included these values, it would have strengthened the results rather than diluting them.

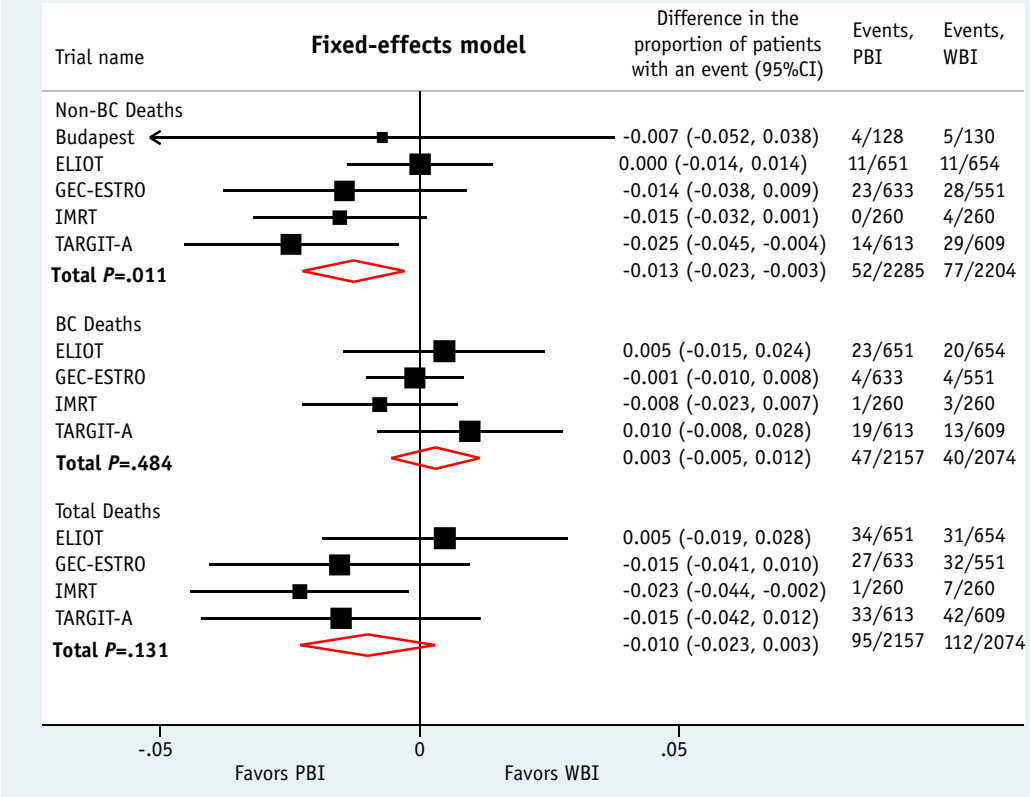
The forest plot is shown in Figure 1. There was no detectable heterogeneity between the trials for breast cancer mortality ($P=.360$), non−breast cancer mortality ($P=.318$), or total mortality ($P=.346$).

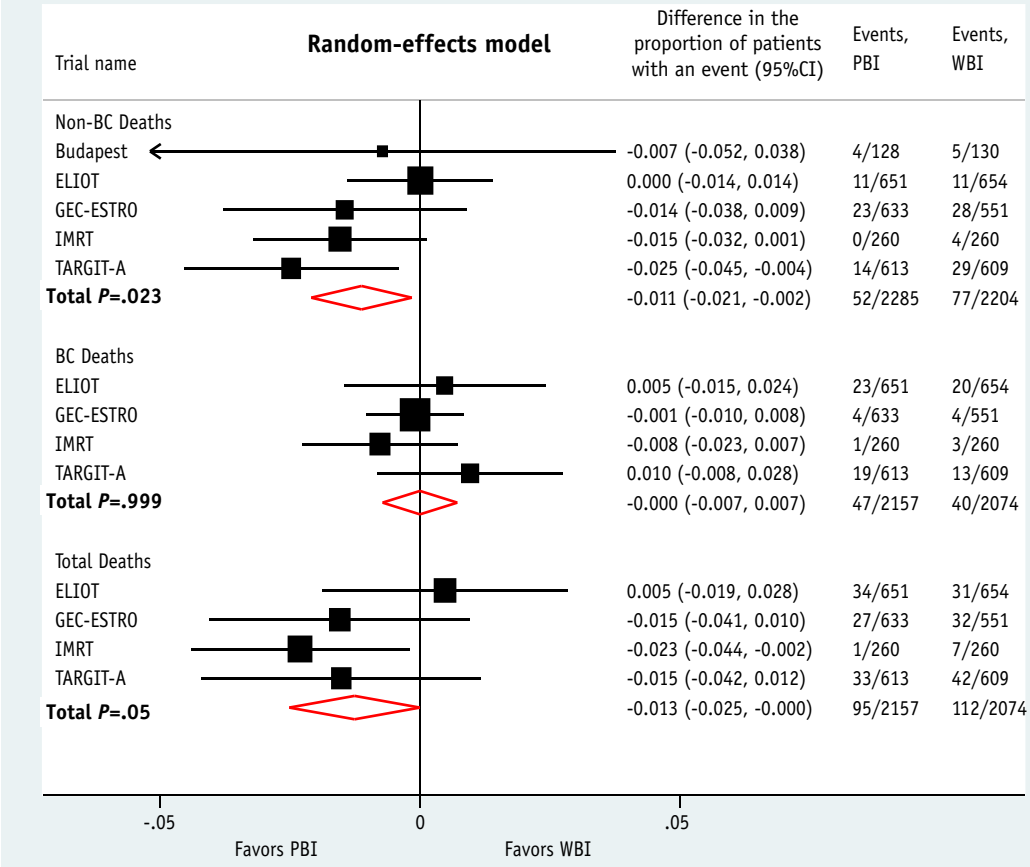
In both the fixed-effects and random-effects models, there was no difference in breast cancer mortality with PBI and WBI: the difference in the proportion of patients dying of breast cancer was 0.000% (95% CI, −0.7% to +0.7%; $P=.999$) for the random-effects model and 0.3% (95% CI, −0.5% to +1.2%; $P=.484$) for the fixed-effects model.

Non−breast cancer mortality with PBI was significantly lower than with WBI (difference of 1.1% [95% CI, −2.1% to −0.2%], $P=.023$, by random-effects model and 1.3% [95% CI, −2.3% to −0.3%], $P=.011$, by fixed-effects model). Finally, total mortality was also lower with PBI compared with WBI (difference of 1.3% [95% CI, −2.5% to 0.0%], $P=.05$, by random-effects model and 1.0% [95% CI, −2.3% to 0.3%], $P=.13$, by fixed-effects model).

Discussion

In this meta-analysis we found that in women with breast cancer, there is a small but definite reduction in mortality when PBI is given instead of WBI. On the basis of the 2 statistical models, the absolute difference in non−breast cancer mortality is 1.1% to 1.3% and is statistically significant ($P=.023$ or $P=.011$). Because there was no difference in breast cancer mortality, the reduction in non−breast cancer mortality appears to translate into a reduction in overall mortality. The absolute difference in overall mortality is likely to be between 1.0% and 1.3%. The low P values of $P=.15$ or $P=.05$ indicate the improbability of observing this difference if there was no real difference between PBI and WBI. Given that the total mortality was


Trial name
Fixed-effects model
Difference in the proportion of patients with an event (95%CI)
Events, PBI
Events, WBI
Non-BC Deaths
Budapest -0.007 (-0.052, 0.038) 4/128 5/130
ELIOT 0.000 (-0.014, 0.014) 11/651 11/654
GEC-ESTRO -0.014 (-0.038, 0.009) 23/633 28/551
IMRT -0.015 (-0.032, 0.001) 0/260 4/260
TARGIT-A -0.025 (-0.045, -0.004) 14/613 29/609
Total P=.011 -0.013 (-0.023, -0.003) 52/2285 77/2204
BC Deaths
ELIOT 0.005 (-0.015, 0.024) 23/651 20/654
GEC-ESTRO -0.001 (-0.010, 0.008) 4/633 4/551
IMRT -0.008 (-0.023, 0.007) 1/260 3/260
TARGIT-A 0.010 (-0.008, 0.028) 19/613 13/609
Total P=.484 0.003 (-0.005, 0.012) 47/2157 40/2074
Total Deaths
ELIOT 0.005 (-0.019, 0.028) 34/651 31/654
GEC-ESTRO -0.015 (-0.041, 0.010) 27/633 32/551
IMRT -0.023 (-0.044, -0.002) 1/260 7/260
TARGIT-A -0.015 (-0.042, 0.012) 33/613 42/609
Total P=.131 -0.010 (-0.023, 0.003) 95/2157 112/2074
-.05
0
.05
Favors PBI
Favors WBI


Trial name
Random-effects model
Difference in the proportion of patients with an event (95%CI)
Events, PBI
Events, WBI
Non-BC Deaths
Budapest -0.007 (-0.052, 0.038) 4/128 5/130
ELIOT 0.000 (-0.014, 0.014) 11/651 11/654
GEC-ESTRO -0.014 (-0.038, 0.009) 23/633 28/551
IMRT -0.015 (-0.032, 0.001) 0/260 4/260
TARGIT-A -0.025 (-0.045, -0.004) 14/613 29/609
Total P=.023 -0.011 (-0.021, -0.002) 52/2285 77/2204
BC Deaths
ELIOT 0.005 (-0.015, 0.024) 23/651 20/654
GEC-ESTRO -0.001 (-0.010, 0.008) 4/633 4/551
IMRT -0.008 (-0.023, 0.007) 1/260 3/260
TARGIT-A 0.010 (-0.008, 0.028) 19/613 13/609
Total P=.999 -0.000 (-0.007, 0.007) 47/2157 40/2074
Total Deaths
ELIOT 0.005 (-0.019, 0.028) 34/651 31/654
GEC-ESTRO -0.015 (-0.041, 0.010) 27/633 32/551
IMRT -0.023 (-0.044, -0.002) 1/260 7/260
TARGIT-A -0.015 (-0.042, 0.012) 33/613 42/609
Total P=.05 -0.013 (-0.025, -0.000) 95/2157 112/2074
-.05
0
.05
Favors PBI
Favors WBI

only 4.9% (207 of 4231), in relative terms, this is a 25% reduced mortality with PBI; thus it would also be clinically significant. Given the high incidence of breast cancer, it could also translate into large numbers at a population scale. For example, if 25% of patients who receive the diagnosis in the United Kingdom every year are eligible for PBI (10,000 of 40,000), it would result in 130 fewer deaths.

There are 2 popular statistical models for meta-analysis, the fixed-effects model and the random-effects model, and it is important to recognize the differences between them for careful interpretation of the results (13). Under the fixed-effects model, it is assumed that the true effect size for all studies is identical and the only reason that the effect size varies between studies is the within-study estimation error, and weights are assigned accordingly (based solely on the within-study variances); therefore, the smaller studies are largely ignored. By contrast, under the random-effects model, the goal is not to estimate one true effect but to estimate the mean of a distribution of effects. Because each study provides information about a different effect size, one needs to be sure that all these effect sizes are represented in the summary estimate. This means that one cannot discount a small study by giving it a very small weight (the way we would in a fixed-effects analysis). The estimate provided by that study may be imprecise, but it is information about an effect that no other study has estimated. By the same logic, we cannot give too much weight to a very large study (the way we might in a fixed-effects analysis). Our goal is to estimate the mean effect in a range of studies, and we do not want that overall estimate to be overly influenced by any one of them (13).

Therefore, the results from the random-effects model are more likely to be an accurate reflection of reality for the following reasons. First, the data come from a series of studies performed in different countries, and it would be unlikely that all the studies were functionally equivalent. The subjects and particularly the interventions varied, with radically different methods of delivering PBI, with differing dose rates beam energy, duration of treatment, and area covered (single-dose photons at 50 kV for 20-30 minutes for TARGIT IORT, single-dose electrons at 6 MeV for 4-6 minutes for electron intraoperative radiation therapy [ELIOT], multiple fractions using high energy for intensity modulated radiation therapy (IMRT), and radioactive wires for GEC-ESTRO [Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology]). Thus these studies differed in ways that would have affected the results, and therefore, we should not assume a common effect size.

As such, in these cases the random-effects model is more easily justified than the fixed-effects model. In addition, the goal of this analysis is usually to generalize to a range of populations. Therefore, if one did make the argument that all the studies used an identical, narrowly defined population, then it would not be possible to extrapolate from this population to others, and the utility of the analysis (based on a fixed-effects model) would be limited (13). In any case, in this particular meta-analysis, the specific results from the 2 models are not materially different.

About 15% of patients in the TARGIT arm of the TARGIT-A trial received EBRT as part of the risk-adapted approach. If receiving PBI instead of WBI indeed leads to reducing mortality, then including these patients should bias toward the null hypothesis and excluding them should strengthen the association between treatment with PBI or TARGIT IORT and improved overall survival. When we performed such a "sanity check" analysis, we found that, indeed, the risk difference in overall mortality increased from 1.5% to 1.75%. This result, albeit from a non-randomized comparison, could be considered akin to a dose-response relationship and reassured us that our findings were internally consistent.

The results of these meta-analyses demonstrate the hitherto underrecognized risks of whole-breast external beam radiation therapy. One might argue that radiation therapy techniques have improved in recent years, although these modern trials were conducted largely when cardiac sparing was being actively considered (14). However, we cannot be certain if cardiac sparing was actively used in these trials. We await randomized evidence for the effectiveness of cardiac-sparing techniques such as voluntary breath holding to assess whether it reduces cardiac damage.

There have been 2 published meta-analyses of trials of PBI (15, 16). However, we have addressed an important outcome that was not addressed in these publications. Lehman et al (15) used only the 3 older studies to evaluate overall and cause-specific survival and did not evaluate non−breast cancer deaths. Marta et al (16) included only 2 of the older trials in their analysis of overall survival and 4 trials in their analysis of breast cancer survival and did not evaluate non−breast cancer mortality. The results of both trials about breast cancer mortality are similar to our results. However, our study carefully evaluated non−breast cancer mortality and included all trials for which the data were available, and it found a small yet statistically and clinically significant difference between PBI and WBI favoring PBI.

Fig. 1. Forest plots representing meta-analysis of difference in mortality between partial-breast irradiation (PBI) and whole-breast irradiation (WBI) with fixed-effects model and random-effects model. The trials included for non−breast cancer (Non-BC) mortality were the Budapest trial (5), TARGIT-A (3), ELIOT (6), IMRT (7), and GEC-ESTRO (8). The median follow-up of all these trials was 5 to 6 years. Data from only the initial 1222 patients in the TARGIT-A trial, whose median follow-up was 5 years, were included. The Budapest trial was not included in the analysis of breast cancer (BC) deaths or total deaths because these figures were not available. As discussed, the random-effects model is more likely to reflect reality.

Regarding the trials we could not include in the meta-analysis, we could not obtain the actual number of events in the Christie Hospital trial, whose last report was published 23 years ago. Importantly, the overall mortality in two of the excluded trials was very high and breast cancer mortality was 20% to 30% (9, 10), as compared with <2% in the included trials. This low breast cancer mortality seems to be one of the reasons for the non−breast cancer death difference becoming evident in modern trials, and such a difference may not have been detectable when breast cancer mortality was high as in these older trials anyway. Finally, overall survival in the Budapest trial was higher in the partialbreast radiation therapy arm than in the wholebreast radiation therapy arm (94.6% for PBI vs 91.8% for WBI). We could not include these figures because the absolute numbers of events for overall survival and breast cancer survival were not available. If these events had been included, it would have strengthened the results rather than diluting them.

When the results of the Canadian RAPID, NSABP-B-39, and IMPORT-LOW trials are available, we plan to combine their data with longer-term results of the trials already included to assess how they affect these meta-analysis findings in the near future.

It would have been useful to assess whether there was any difference between left- and right-sided cancers, but these data were not available. However, the ratio of cardiac risk for left-sided cancers to right-sided cancers is only 1.34 (17). With modern radiation therapy designed to reduce cardiac dose, the absolute difference between sides is likely to be even lower and undetectable with few events. In fact, the finding of an overall reduction in non−breast cancer and total mortality suggests that such reduction may even be larger in patients with left-sided breast cancers.

Individual patient data were not available for this analysis. However, the absolute numbers of events for each randomized arm—at a similar time point—were available and can be used to answer the main question: How many patients died at a median follow-up of 5 years? It should be noted that for the TARGIT-A trial, data from only the initial 1222 patients whose median follow-up was 5 years have been used for this meta-analysis.

Previous literature has suggested other-cause mortality after WBI only appears many years after irradiation. However, the 5-year breast cancer mortality in early trials is up to 60%; thus it is likely that a small 1% to 2% difference in early non−breast cancer mortality would be masked. In the modern era of very low breast cancer death rates, we may be unmasking this true effect. Furthermore, several studies have recently shown that sensitive instruments can detect cardiac effects of radiation therapy within days (18); within months (19); and as shown in a large Oxford overview, certainly within the first 5 years (17).

This meta-analysis has used modern data to address this long-standing issue. It suggests that PBI does appear to avoid deaths from other causes. The need to avoid even very small harmful effects of treatment is vital today because the overall survival and survival of patients with T1N0 breast cancer are now nearly identical to women without breast cancer (20).

When WBI is being discussed as part of breast-conserving therapy, the option of using partial-breast radiation therapy, along with the data showing the small yet significant reduction in non−breast cancer mortality, should be discussed with appropriate patients before surgery is performed.

We would like to conclude with two statements regarding which there should be no controversy: (*1*) use of PBI does not compromise breast cancer or overall mortality; and (*2*) the possibility that use of PBI instead of WBI may reduce overall mortality can no longer be ignored or ridiculed—it must be taken seriously. We remain cautious and, given the long time-frame for outcomes in this favorable population, seek longer follow-up of all the studies.

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