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EDITORIAL

The TARGIT-A Randomized Trial: TARGIT-IORT Versus Whole Breast Radiation Therapy: Long-Term Local Control and Survival

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For assessing the efficacy of any cancer therapeutic approach, patients and clinicians want to know the chance of being free of disease as well as the likelihood of achieving long-term survival.

Single-dose targeted intraoperative radiation therapy (TARGIT-IORT) during lumpectomy for patients with early breast cancer can avoid the inconvenience and toxicity of whole breast radiation therapy (external beam radiation therapy [EBRT]) and results in reduced pain, a better quality of life,[1-6] a cosmetically superior outcome, and requires less traveling by the patient.[7] Scattered irradiation that accompanies EBRT has been shown to lead to second cancers (lung, esophagus, etc) and heart attacks, which are even more pronounced in smokers.[8-13] With the substantially lower doses to organs at risk, TARGIT-IORT minimizes such risk compared with EBRT.

In the large international TARGIT-A randomized trial (n = 2298),[14,15] as per the latest published results, breast cancer outcomes in patients randomized to TARGIT-IORT were comparable to patients randomized to whole breast

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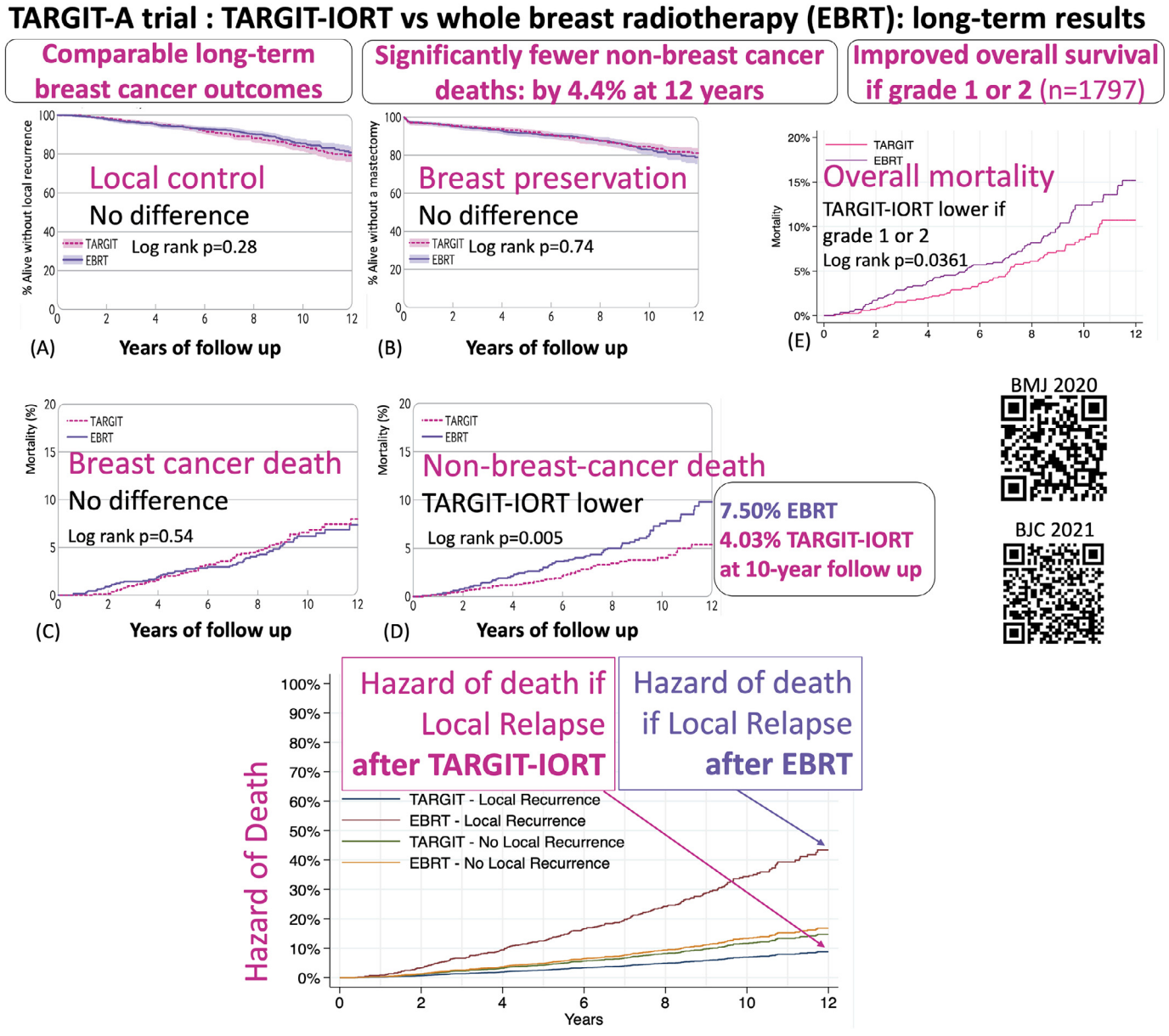

Fig. 1. Long-term outcomes of the TARGIT-A trial (top panel, A to E) and contrasting hazard death in patients who develop local recurrence in the EBRT arm (43%) vs TARGIT-IORT arm (9%), the latter being no different from those who do not develop local recurrence in either arm (lower panel).

postoperative radiotherapy (EBRT).[14] No difference was found in survival without local recurrence, survival without having a mastectomy, survival without distant disease, or breast cancer mortality.[14] The local control was comparable irrespective of the tumor subtype[15] or when supplemental EBRT was not used. These are well illustrated in overlapping Kaplan-Meier curves drawn up to 12 years (Fig. 1[14] and Fig. 2[15]).

Deaths from other causes were fewer in the TARGIT-IORT arm by 41% (reduced from 7.5% to 4.0% at 10 years),[14] a statistically significant and clinically meaningful benefit.

In a subgroup analysis (with its usual caveats), overall survival was higher in the TARGIT-IORT arm by 4.4% at 12 years (Fig. 1)[14,15] in patients with grade 1 and grade 2 cancers (n = 1797), which make up the majority of cases.[15]

Importantly, prognosis after the rare local recurrence after TARGIT-IORT was much better than after EBRT. As seen in the lower left panel of Figure 1, the hazard of death was 43% for those patients who had recurrence in the EBRT arm, substantially higher than the 9% hazard after local recurrence in the TARGIT-IORT arm or those without local recurrence.[15]

Multiple prospective nonrandomized studies have published their results of using TARGIT-IORT, with similar outcomes in over 3000 patients treated with TARGIT-IORT from France, Germany, Denmark, Switzerland, and others.[16-21] By 2019, over 260 centers in 38 countries

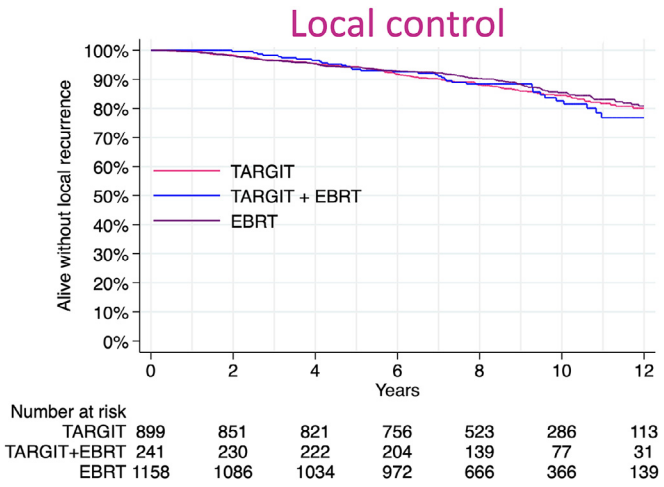

Fig. 2. Kaplan-Meier plot of local recurrence-free survival for patients randomised to receive EBRT (purple line) along with patients randomised to receive TARGIT-IORT separated by those who received additional EBRT (blue line), and those who did not (pink line). No statistically significant difference was found between EBRT and the two latter groups.

worldwide had treated over 45,000 patients with breast cancer with TARGIT-IORT (https://targit.org.uk).[22]

Ward et al[23] chose to look only at local recurrence, without accounting for deaths. But to develop a local recurrence, one needs to be alive. As a separate point, patients can and do die after local recurrence, especially after EBRT. As a consequence of this conceptual misunderstanding, we believe that their estimates are misleading.

Ward et al[23] derived an inaccurately estimated set of "pure" local recurrences, which they calculated from the data extracted from our graphs in the *BMJ* paper[14] on the long-term outcomes after intraoperative radiotherapy (TARGIT-IORT, which is given using the Intrabeam (Carl Zeiss) device during lumpectomy) for early breast cancer in the TARGIT-A trial.

They also assumed that risk-level for the cohort who received EBRT after TARGIT-IORT was the same as those randomized to EBRT, when in fact, this cohort included many more higher-risk cases (39% vs 20% node positive, 26% vs 15% lymphovascular invasion, 20% vs 10% positive margin, 24% vs 16% size >2 cm).[15] The assumption of lower risk in this subgroup has meant that their estimate of local recurrence in the rest of the TARGIT-IORT arm (that did not receive supplemental EBRT) was erroneously inflated.

Ward et al[23] calculated local recurrences by subtracting the overall survival probability from local recurrence-free survival probability. This method results in 2 separate and compounding errors.

First, it only counts those patients who were alive after local recurrence and does not account for the fact that some patients who had local recurrence subsequently died. As a consequence, they underestimate the local recurrence numbers. This underestimate is substantial, and mainly in the EBRT arm because the hazard of death after local recurrence was 43% in the EBRT arm and only 9% in the TARGIT-IORT arm (Fig. 1, bottom panel).[15]

Second, Ward et al[23] completely ignore deaths while plotting their estimated cumulative local recurrence rates. This would work well if everyone's follow-up was the same and no one died, but this of course is never the case because patients are never recruited all at the same instant in any trial. Censoring is the workaround for this problem. Censored patients' data are correctly used only until the point when last seen alive, with the assumption that they continue to have a risk of having local recurrence. But once patients are known to have died, this assumption is, of course, no longer true.

In the quest for finding "pure" local failure, Ward et al[23] inappropriately censor dead patients. This results in spurious figures, as patients are assumed to be at risk of local recurrence even after they have died. Their method therefore results in biased, misleading, and incongruous results, as illustrated in Figure 3.

In Figure 3, the right-hand graph (taken from Ward et al[23]) shows "1.7% people have local failure" in the EBRT arm. It implies that 98.3% are free of local failure. But the graph on the left shows that only 86% are actually alive at 10 years. Clearly, the right-hand graph, which implies that 98.3% are still alive without local recurrence, is unfounded and this method of estimating local failure is inaccurate.

In their article in *Lancet Oncology* (2021), Fojo and Simon[24] warn about this common mistake and emphasize that "censoring must be nonprognostic or noninformative, with individuals censored at any one time *having a prognosis identical to that of all other patients alive at that time but not censored.* Groups must be balanced both in terms of percentage of patients censored and the times of censoring."

Therefore, by censoring the dead, Ward et al[23] break these fundamental tenets, because death is informative, and its occurrence is unequal between the two arms of the trial. By artificially increasing the denominator, Ward et al[23] disproportionately underestimate the local recurrence rates in the EBRT arm due mainly to more deaths in the EBRT arm,

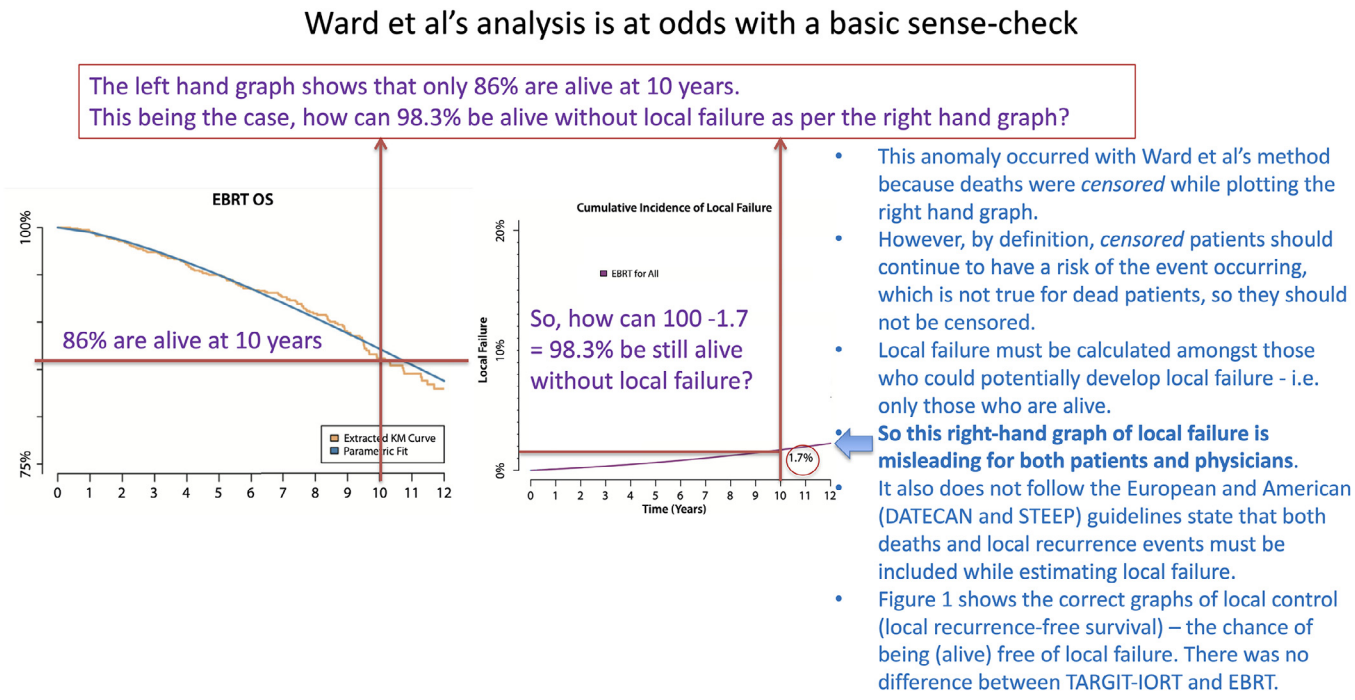

Fig. 3. Spurious results obtained by Ward et al because of inappropriate, informative and imbalanced censoring.

both overall and also after local recurrence. Therefore, there is an artificial increase in the efficacy of EBRT and an inflation of the difference between the two treatments.

The European Definition for the Assessment of Time-to-event Endpoints in CANcer trials[25] and the American Standardized Definitions for Efficacy End Points[26] (American) guidelines clearly state that death and local recurrence should both be included as clinical events for assessing local treatments for breast cancer. As these principles were not followed in Ward et al's methods, there is a discrepancy between their estimates and the actual raw data, even at the 5-year point when there is complete follow-up of 2298 randomized patients.[14]

Their parametric model estimate is higher than the actual local recurrence rate for TARGIT (true figure 2.11% artificially raised to 2.9%) and lower than the actual rate for EBRT (true figure 0.95% artifically reduced to 0.6%). Consequently, this mismatch artifically inflates the difference by 190%, that is, their estimate is wrongly inflated to 2.3%, which is nearly double the real value of 1.21%. This bias brings into question the validity of their model. Notably, the real chance of remaining free of local recurrence at 5 years, the relevant outcome from the patient's point of view, is identical for TARGIT-IORT and EBRT (94.15% vs 94.19%).[15]

Ward et al's hypothetical data yield even stranger results at 10 years. Their upper 95% confidence limit is 4.3% for their 1.7% estimate of local recurrence rate with EBRT. So the upper 95% confidence *interval* is 4.3 *minus* 1.7 which is 2.6. Normally, the upper and the lower confidence intervals (1.96 times the standard error) are equally above and below the point estimate. Therefore, the lower 95% confidence limit has to be 1.7 *minus* 2.6, which is *negative* 0.9%. A negative local recurrence rate! The same anomaly is present for their 5-year estimate (their lower 95% CI is a local recurrence rate of 0.6 *minus* 1.3, which is *negative* 0.7%). Ward et al seem to simply truncate these negative values to 0%. Even if one accepts unusually asymetric 95% confidence limits, their lower 95% CI estimate of 0% for 5- and 10-year local recurrence rate in 1158 medium-risk patients with breast cancer is clearly unrealistic (in the TARGIT-A trial, 83% [1898] patients were <70 years, 20% [443] had grade 3 cancers, 19% [426] were estrogen or progesterone receptor negative, and 22% [488] had involved nodes).[27] When such unrealistic estimates and confidence limits are generated by Ward et al's model, there can be little confidence in that model or its results.

The real data are that at 5 years, 2.11% versus 0.95% of the initially recruited women had local recurrence with TARGIT-IORT and EBRT (an increase of 1.16%), but 3.68% versus 4.84% women died (a reduction of 1.16%).[14]

The Kaplan-Meier estimates for local control (ie, chance of being free of local recurrence) at 5 years were 94.15% (92.6-95.4) and 94.19% (92.6-94.4) for TARGIT-IORT and EBRT,[15] and breast preservation was 92.32% (90.59-93.74) and 91.64% (89.85-93.12).

Over the 19 years of follow-up (median follow-up 9 years), the real raw data show that in the whole trial of 2298 patients, there were 25 (2.2 %) more invasive local recurrences but 21 (1.8%) fewer deaths in the TARGIT IORT arm compared with the EBRT arm.[14]

With a long-term follow-up (maximum 19 years, median 8.6 years), analysis of the actual data shows that there was no statistically significant difference between TARGIT-IORT and

EBRT in terms of the chance of being free of any local recurrence (hazard ratio [HR], 1.13; 95% CI, 0.91-1.41; $P = .28$), of remaining mastectomy free (HR, 0.96; 95% CI, 0.78-1.19; $P = .74$), of remaining distant disease free (HR, 0.88; 0.69-1.12; $P = .30$), or of breast cancer mortality (HR, 1.12; 0.78-1.60; $P = .54$).[14] The local control was comparable between TARGIT-IORT and EBRT,[14] irrespective of the tumor subtype,[15] and even when supplemental EBRT was not used.[15] Overall survival was improved with TARGIT-IORT for patients with grade 1 or grade 2 cancers (HR 0.72 (0.53-0.98), $P = 0.0361$)[15]

The correct results for the proportion of patients who did not have local failure, that is, those who were free of local recurrence at 10 years, were as follows: TARGIT arm (those who received supplemental EBRT: 82.6%; those who did not receive supplemental EBRT: 84.5%) and EBRT arm (85.5%; log-rank P value = .51; Fig. 2).

We acknowledge that local recurrence has been a popular traditional endpoint and has been used in many important studies. However, the pitfalls when estimating it are being increasingly recognized.[24–27] Deaths during follow-up cannot be ignored while estimating local recurrence, as the patient does of course needs to be alive to have the potential for local recurrence. If deaths are simply ignored, the results no longer represent what actually happens to patients, even more so when deaths form the more substantial proportion of events or are unequal between the treatments being compared. We strongly believe that presentation of the data should reflect what actually happens. The outcomes should be clinically relevant and should provide realistic information for our patients. Such complete and accurate information (Figs. 1 and 2) is essential for both patients and physicians to decide what kind of treatment will suit them best.

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