Breast Care
Editorial (accepted version)

Targeted intraoperative radiotherapy tumor bed boost during breast conserving surgery after neoadjuvant chemotherapy

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Kolberg and colleagues have recently published a series of papers[1-3], which for the first time give some idea of outcomes of TARGIT IORT as a tumour bed boost during lumpectomy after neo-adjuvant chemotherapy. The last of these series is published in the current issue of Breast Care. We would like to discuss these from two perspectives – neoadjuvant chemotherapy and TARGIT IORT.

Neoadjuvant chemotherapy

The generally accepted aims of neoadjuvant chemotherapy are to downsize an inoperable cancer, and to assess tumour response, particularly within 'window-of-opportunity' translational research clinical trials.

Whether it is better to give systemic therapy before or after surgery has been assessed in two large meta-analyses of randomised trials of neo-adjuvant vs adjuvant chemotherapy. In these meta-analyses, no difference in survival was found. However, they found a higher risk of loco-regional recurrence in patients randomised to receive neo-adjuvant chemotherapy before surgery when compared with adjuvant chemotherapy after surgery. The absolute increase in the risk of local recurrence was 3 to 5% at 5 years. The magnitude of the increased recurrence risk appears to be less with larger surgical excision after neo-adjuvant chemotherapy and it appears to be much higher when an operation is omitted altogether. The benefit of a smaller operation therefore should be balanced with the increased risk of local recurrence: at 5 years, about 3% absolute increase of local recurrence *vis a vis* a 6% increased chance of avoiding a mastectomy[4 5]. Early Breast Cancer Trialists group have performed a new meta-analysis with individual patient data from over 4500 patients and these data have been presented but not published. They appear to reinforce the findings of the previous two meta-analyses.

Therefore, if any of the benefits of NACT are to be realised, particularly the aim to convert a necessary mastectomy to breast conservation, an additional treatment to improve local control would be welcome. If such an intervention has systemic benefits it would be an additional bonus.

Systemic effect of TARGIT IORT

In the TARGIT-A trial[6-8], 3451 patients eligible for breast conserving surgery for breast cancer were randomly allocated to receive either risk-adapted TARGIT IORT or whole breast external beam radiotherapy (EBRT). TARGIT-IORT arm was found to be non-inferior to EBRT in terms of local control. In the analysis of deaths, there was no difference in breast cancer mortality, which was low in both arms of the trial. However, the trialists found a significantly lower non-breast cancer mortality for the TARGIT IORT patients (HR. 0.47; p = 0.0086) (Figure 1). The irradiation of the lung, oesophagus and heart during tangential field radiation of the breast has been repeatedly shown to cause fatal cancers[9 10] and deaths due to ischemic heart disease[11 12]. One would expect that TARGIT IORT should avoid such deaths. This view has been vindicated by a meta-analysis of randomised trials[13] of targeted radiotherapy/ partial breast irradiation) vs. whole external beam radiotherapy (EBRT). In this meta-analysis of over 4500 patients found that in the breast cancer populations where the breast cancer mortality is low (about 5%), the deleterious effect of whole breast radiation is unmasked and demonstrates an increased overall mortality – thus using targeted radiation rather than whole breast radiation in such patients leads to an improvement in overall survival albeit by a small absolute amount (Figure 2).

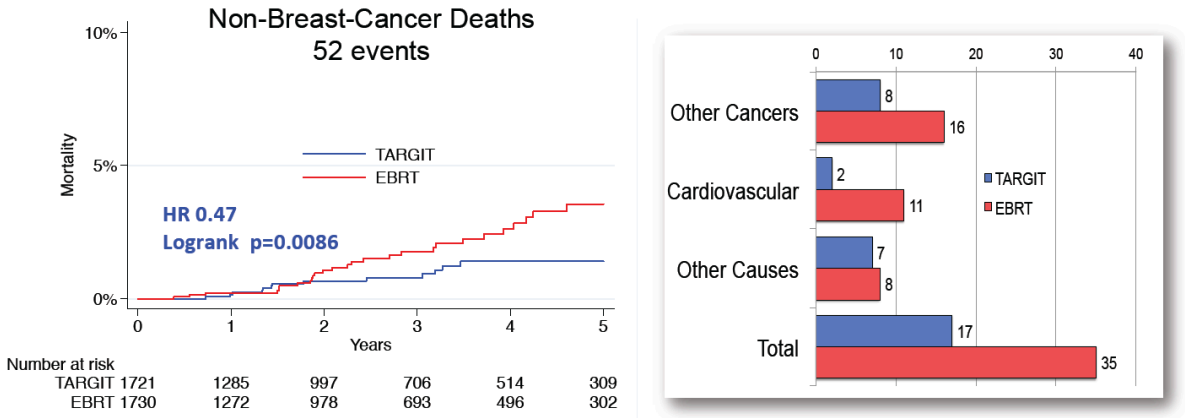


Fig. 1. Kaplan-Meier plot for deaths from causes other than breast cancer (17 vs 35) in the randomised TARGIT-A trial, showing a significantly higher risk of non-breast-cancer mortality with whole breast fractionated radiation given postoperatively over several weeks (EBRT), compared with a risk-adapted single dose radiation delivered to the tumour bed during the lumpectomy operation (TARGIT)[6-8]

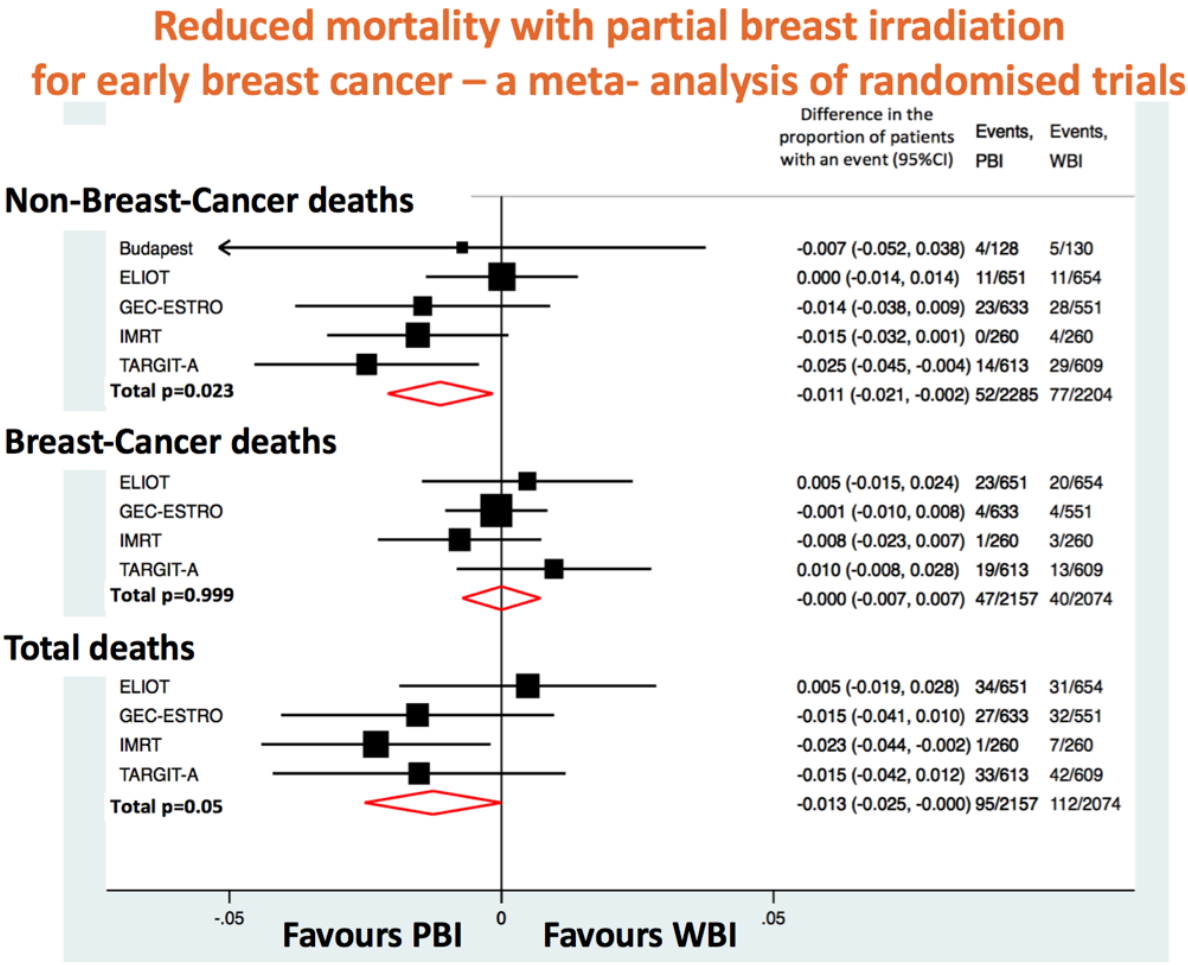
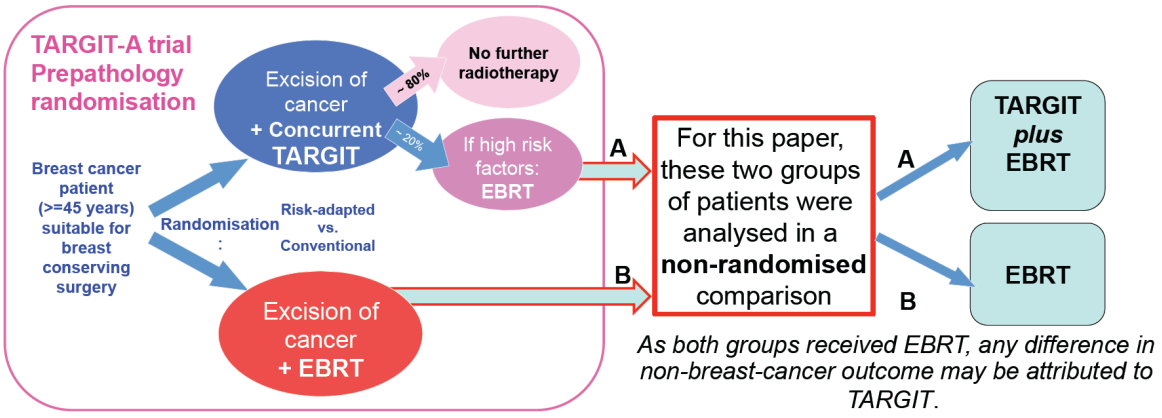


Fig. 2. Forest plots representing meta-analysis of difference in mortality between partial-breast irradiation (PBI) and whole-breast irradiation (WBI) with a random-effects model[14]. The trials included for non-breast cancer (Non-BC) mortality were the Budapest trial, TARGIT-A, ELIOT, IMRT, and GEC-ESTRO. 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.

An interesting sub-group analysis performed in the TARGIT-A trial[14] was for survival from causes other than breast cancer, comparing TARGIT followed by EBRT vs EBRT alone (Figure 3a). The group that were randomised to TARGIT but also received EBRT had a worse prognosis breast cancer (as defined by the protocol) but would not be expected to be different than the rest of the cohort in terms of other co-morbidity; as both groups received EBRT, any difference found in non-breast-cancer mortality could be attributable to the delivery of TARGIT IORT during lumpectomy.

Remarkably, there were no deaths from non-breast cancer causes in the TARGIT+EBRT group compared with 24 in the EBRT group 0/218 vs. 24/892, log-rank p=0.012. Although the numbers are small and the compared groups are not the randomised cohorts, these data suggest that avoidance of EBRT toxicity may not be the only reason for the fewer non-breast cancer deaths with TARGIT IORT, and the difference in mortality may also be attributable due to a *beneficial* systemic effect of TARGIT-IORT. It leads to the hypothesis that the local effect of TARGIT on the tumor bed by inhibiting the cancer-stimulating cytokines, may spill over to reduce inflammatory response to trauma and have significant long-term systemic beneficial effects, that might be protective against cardiac and cancer mortality[15].



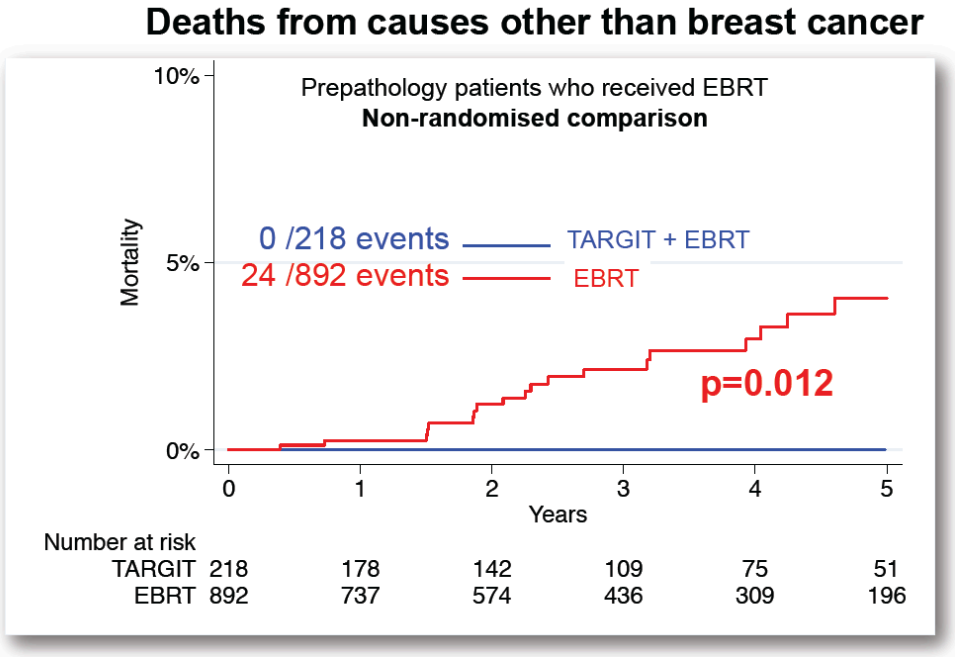


Fig. 3. Non-randomised comparison between those who received TARGIT + EBRT and those who received EBRT for deaths from non-breast-cancer causes: (above) schema of the analysed cohorts of patients; and (below) Kaplan–Meier plot depicting deaths from causes other than breast cancer in prepathology patients who received EBRT – non-randomised comparison[8,14-15].

Testing of this hypothesis within a randomised trial will occur in the TARGIT-B trial. In this trial, patients who are younger than 45 or at high-risk of relapse, including those rendered suitable for breast conservation by pre-operative administration of neoadjuvant chemotherapy, are randomly allocated to receive a tumour bed boost either by TARGIT IORT during lumpectomy or by the traditional external beam radiotherapy. While an improvement in local control is the primary aim the specified second aim of this trial is to assess whether a TARGIT IORT boost has any effect on breast cancer and non-breast cancer survival.

Neoadjuvant chemotherapy + Surgery including TARGIT IORT

Kolberg and colleagues have reported the results of consecutive patients receiving TARGIT-IORT during lumpectomy after NACT. As a comparator control, they used consecutive patients treated in the previous year without TARGIT-IORT, and have taken efforts to ensure that the two groups are matched in all other aspects in this non-randomised study. To ensure that the follow up period is similar, they have truncated the follow up for the historically older cohort.

In their first of the three papers they reported that patients having oncoplastic breast conserving surgery after neo-adjuvant chemotherapy along with intraoperative TARGIT-IORT Boost, experienced similar local control, but statistically significantly better survival outcomes than those who received a postoperative EBRT boost (overall survival 96.7% vs. 81.7%, hazard ratio 0.19, log rank p = 0.016, and distant-disease free survival 95.1% vs. 69.0, HR 0.23, log rank p = 0.012)[2]. In the two subsequent papers, they tried to ascertain if there is any impact of tumour biology on this effect – by analysing the data in three different subgroups - ER+ PgR+ Her2 neg, Her2 positive, and triple negative tumours. The results were numerically similar, but did not reach statistical significance, most likely due to paucity of events; it is arguable that such an analysis of impact of tumour factors should normally be performed using a Cox proportional hazard model.

While these non-randomised data are not enough to prompt a change in practice, they are reassuring that despite the short physical range of radiation field of TARGIT IORT, its effectiveness is at least as good as an externally delivered tumour bed boost and it may have a bonus of systemic beneficial effects. Therefore, at the very least these data give a strong support to clinicians and patients to participate in the TARGIT-B trial.

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