Approximately 80% of the breast tumor recurrences originate at the site of the original disease. These data suggest that the majority of breast tumor recurrences result from residual foci of disease from the original index tumor that approximate the site of the original surgery.

Thus is clear that giving radiation only to a volume of 1-cm radius around the tumor site would also be an ineffective strategy.
Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick. For LIAC HWL the recommended settings would be 60 mm diameter applicator, 12 MeV energy and 21 Gy prescribed at 3 cm. The effective irradiated volume inside 90% isodose is a cylinder with a diameter about 50 mm and a depth of 32 mm, for a total volume of about 63 cm$^3$.

The treatment time with electrons takes 100 seconds.
Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick. **Intrabeam** using a 25 mm applicator and 20 Gy at the surface of the applicator. The volume treated within the 90% isodose is less about 2.1 cm$^3$. The volume treated within the 50% isodose is less than 7.1 cm$^3$.

**The low energy X rays treatment takes between 35 and 50 minutes.**
TARGIT – A study : main criticisms

The TARGIT-A study has been criticized above all for:

- MEDIAN FOLLOW-UP
- STATISTICAL ANALYSIS
- PROTOCOL DEVIATIONS
- POST-PATHOLOGY STRATUM
- NON-BREAST CANCER DEATHS
- CONFLICT OF INTEREST
- RELATIVE BIOLOGICAL EFFECTIVENESS OF LOW-ENERGY PHOTONS
Radiotherapy for breast cancer, the TARGIT-A trial

The TARGIT-A trial (Feb 15, p 603)^3 Is a good example of trying to make data fit a pre-existing hypothesis; there are several major deficiencies in the analysis. Paramount among these deficiencies is the misuse of the non-inferiority criterion,^7 which requires the upper (50%) CI to be below a predefined value (here 2.5%). This criterion clearly fails when the appropriate 5-year Kaplan-Meier estimates are used, which, in fact establish a 2% superiority of external beam radiotherapy (p=0.04) and a CI extending beyond 2.5%. Table 3 of the Article^6 uses crude rates that are substantially diluted by patients with short follow-up (only 611 (18%) patients had a 5-year follow-up). The effect is even clearer if locoregional recurrence or all recurrence is used, as in previous radiotherapy trials.^4

Another common but well known danger is to focus attention on the most favourable subgroup. The protocol clearly states that the primary analysis population includes all randomised patients. However, the report concentrates on the prepathology group. No correction for multiple comparisons or test for heterogeneity between groups is provided, and the data available suggest that it would not be significant. More should be said about all randomised patients.

Although a small increase in recurrence with a simpler therapy might well be acceptable in many circumstances, the present attempt to argue for virtually no difference by misuse of the non-inferiority criterion, focusing on the most favourable subgroup and not including all events affected by external beam radiotherapy does not give an objective assessment of this treatment modality.

Prof. Cuzick, who wrote these cogent words, was the Chairman of Data Monitoring Committee for the TARGIT-A trial previously but he have resigned.

The protocol clearly states that primary analysis population includes all randomised patients. The study focuses on the most favorable subgroup defined prepathology group; but more should be said about all randomised trial: the investigators from TARGIT-A trial claim to have established non-inferiority of IORT relative to EBRT for breast cancer in terms of 5-year local recurrence.

The 5-year follow-up is not available for all patients because only 611 (18%) of 3451 have reached this point; it means that this analysis, including the non-inferiority test statistic, is therefore UNRELIABLE.
TARGIT-A STUDY
DEBATE:
MEDIAN FOLLOW-UP

The length of median follow-up for three cohorts of patients is different and considering that the cohorts are nested within each other, the patients with longest follow-up are analyzed three times generating a result of questionable validity.

The median follow-up is **only 29 months** and an increase duration of follow-up is necessary before any analysis of non-inferiority for the clinical practice.

Haviland et al. conclude this letter with the following words: **The TARGIT-A trial remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.**
Javant Vaidya and colleagues report an increased risk of non-breast cancer deaths with external beam radiotherapy (EBRT) compared with intraoperative radiotherapy, highlighting the difference in cardiac events in the two treatment groups. Although the log-rank statistics show a significant difference in non-breast cancer deaths in the EBRT group, these deaths included stroke, bowel ischaemia, and other events unrelated to breast irradiation. Therefore, the number of cardiac events is small, and to suggest that the risk of cardiac death differs between EBRT and intraoperative radiotherapy would be premature.

Additionally, since the median follow-up of most patients was less than 5 years, it would be unexpected that these cardiac deaths were attributable to radiotherapy. If cardiac mortality from radiotherapy occurs, existing studies suggest it would occur 10-20 years after radiotherapy treatment. During this early follow-up, differences in baseline cardiac risk factors between study groups could account for this difference in cardiac deaths. Furthermore, in a study by Darby and colleagues, the 95% CI for cardiac events for patients who received less than 2 Gy of radiotherapy ranged from 9-33 and included zero. This finding emphasises the uncertainty, or at least very low risk, of an absolute increased risk of cardiac disease from radiotherapy treatment.

Therefore, the increased risk of non-breast cancer events, including cardiac toxic effects, reported in this Article should be interpreted with caution. In view of the short follow-up period, small number of cardiac events, and scarce information regarding cardiac risk factors at baseline in the study groups, we declare that we have no competing interests.

Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.

On the basis of the previous critique (an increased risk of non-breast cancer deaths with EBRT), Wazer et al. wrote that the TARGIT-A authors should have indicated the 4 following things:

1. the heart dose for those patients who had a cardiac event;
2. if was the left or right breast irradiated in every specific case;
3. the time after the completion of EBRT where the cardiac events occurred;
4. whether deaths occurred in those patients who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths.

No one of the listed things were reported. In fact, this critique ends as «Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.»
TARGIT-A STUDY DEBATE: NON INFERIORITY OF POSTPATHOLOGY STRATUM

An other point to pay attention is about the POSTPATHOLOGY STRATUM: the patients that received a second surgical procedure for no reason other than the application of the radiation therapy.

The follow-up of the TARGIT-A trial, defined as preliminary and immature, is much too short to draw any conclusions about local recurrence rates.

1. Anyway the TARGIT –A authors adfirm that the most local recurrences occur in years 2 and 3, but this do not imply that local recurrences after this time will not occur.

2. For a very low-dose penetration to a depth of 1 cm, the rate of in-breast recurrences has to be observed extremely carefully in the long term. The median time to true local recurrences is somewhere between 40 months and 65 months but out-quadrant relapses occur later than that.

**THUS, IT’S CLEAR AND EVIDENT TO AVOID THE USE OF INTRAOPERATIVE RADIOThERAPy AS A SINGLE SHOT OUTSIDE A CLINICAL TRIAL UNTIL THE LONG-TERM FOLLOW-UP DATA FOR NON-INFERIORITY WILL BE AVAILABLE.**

Such conclusion published in 2010 has led to the ASTRO updated recommendations (september 2016) on IORT with low energy X rays.

This correspondence begins: «We congratulate Jayant Vaidya and colleagues for their important contribution....the radiation doses uses in TARGIT-A are substantially lower than historical standards»

The standard dose with EBRT for the treatment of breast cancer is 50-66 Gy. In the TARGIT-A study they affirmed that the dose delivered in the experimental group is only 5-7 Gy at 1 cm depth.

If it assumes that the relative biological effectiveness for such low-energy photons is twice that of higher energy photons, THE BIOLOGICALLY EQUIVALENT DOSE USED IN TARGIT-A WOULD STILL CONVERT TO ONLY 24 Gy: LESS THAN HALF THE RADIATION DOSES USED WITH ACCELERATED PARTIAL OR WHOLE BREAST IRRADIATION.

IT MEANS THAT THE RADIATION DOSE USED IN TARGIT-A MIGHT HAVE SUFFICIENT TO DELAY, NOT PREVENT LOCAL RECURRENCES.

As written by Cuzick et al., TARGIT trialists used a non-inferiority test statistic based on binomial proportions; each subject with 1 month or 5 years follow-up contributed the same to the denominator. In particular, the subjects with very short follow-up are counted as not having a local recurrence.

Haviland et al. concluded this comment «The TARGIT trialists can and should provide a proper analysis of LR rates at 5 years (with CI) to enable an unequivocal assessment of noninferiority». They reported that the TARGIT protocol would have included all randomized patients and focusing on the prepathology subgroup was clearly post hoc after seeing the results. The dangers of restricting results to subgroups are well known.
As reported by Haviland et al., the TARGIT-A International Steering Committe is composed for the majority by professionals who cooperate and cooperated with Zeiss.

In fact, they reported that “Vaidya, Baum, and Tobias are experienced enough to know that these arrangements are perceived as real conflicts of interest. The TARGIT-A trial needs to mature in better shape.”
TARGIT STUDY: A FLAWED STUDY

EDITORIAL

A Flawed Study Should Not Define a New Standard of Care

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The final judgment on the TARGIT A study is, thus, that expressed by Wazer et al.:

“The TARGIT-A trial has many methodologic and analytic flaws that deeply undermine the scientific validity of its claims. In the interest of all women with early breast cancer, clinicians and policy makers must carefully assess the actual state of our current knowledge associated with this modality and recognize that many more questions need to be addressed before we can declare that we have arrived at a new standard of care.”

All these criticisms have lead to the ASTRO 2016 APBI guidelines update
On the basis of the published evidence and the mature results obtained thanks to the 5.8 years follow-up of the ELIOT trial, it has been recognized the efficacy of performing the IORT with electrons compared to the 29 months follow-up of the TARGIT-A trial (the reference study of IORT with low energy x-rays).

The ASTRO society stated the following recommendations [1]:

- IORT with electrons (IOeRT) can be used in the clinical practice outside of a clinical trial for the suitable group of patient;

- IORT with low energy x-rays can never be used outside of a clinical trial. As ASTRO commented on web site [2] : “Low-energy X-ray IORT should be used only in the context of a prospective registry or clinical trial and restricted to women with invasive cancer who are considered otherwise suitable for partial breast irradiation.

This recommendation reflects the short, 2.4-year median follow-up of existing trial data”.