Summary of comments on "Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence: The clinical and cost effectiveness of the INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer"

We ask that the NICE Committee give serious consideration to our comments on this Technology Assessment Report prior to making any recommendations based on it, as we believe it needs a major revision.

This Technology Assessment Report has focused on the two TARGIT publications (*The Lancet* 2010 and 2014) of which we are co-authors. On the whole, the report is comprehensive. However, it contains several important inaccuracies of fact and logic that have a significant impact on the conclusions to both the clinical effectiveness and economic analysis of the TARGIT technique using Intrabeam. **A few examples are as follows:**

1. **Main clinical endpoints.** The authors of the report correctly state that the TARGIT-A randomised controlled trial has demonstrated that TARGIT is non-inferior to EBRT and that the difference between the two groups is not statistically significant. That is, the TARGIT method of delivering radiotherapy is clinically not worse than the current standard of care. We are therefore puzzled as to why the authors later on claim that TARGIT is clinically less effective than EBRT. In reality, when TARGIT is given during lumpectomy, there is a 2.3% improvement in overall survival, p=0.12 vs. a 1% increase local recurrence p=0.31; the p value tells the probability that the difference is seen due to chance alone.
2. **Follow up.** We would also like to emphasise the natural history of breast cancer – the peak hazard of recurrence in 2-3 years after surgery and radiotherapy protects against recurrences only during the first 5 years of follow-up – so a longer follow up does not add to assessment of radiotherapy trials with regard to local recurrence.
3. **Comparability of groups.** The authors of the report attach significance to a *supposed* age difference of 0.5 years between the patients in the randomised groups. Firstly this difference is actually 0.275 years; mean ages: TARGIT 62.41 years SE 0.20, EBRT 62.69 years) and it is very difficult to see how this small and statistically non-significant difference could contribute to any of the differences in the outcomes. We are surprised that such arguments were used to dismiss the clinically and statistically significant reduction in non-breast-cancer mortality with TARGIT.
4. **Estimate of the number of patients suitable.** Rather than estimating the proportion of patients having breast conserving surgery that would be suitable for the TARGIT procedure i.e.,: $\frac{suitable\ for\ TARGIT}{suitable\ for\ lumpectomy}$ the authors have used data from a series of patients who were treated with a different intraoperative radiotherapy technique (not Intrabeam) and used the equation: $\frac{suitable\ for\ IORT\ as\ per\ some\ criteria}{number\ actually\ given\ IORT}$. The real proportion is nearer 56% rather than 16%. Therefore, the cost of Intrabeam per patient is significantly lower.
5. **Proportion of patients with recurrence after TARGIT who have mastectomy.** The authors have used 80% as the proportion of patients with recurrence who have a mastectomy, based on 'expert opinion' only, and incorporated it (0.8) in their cost-effectiveness calculations. In reality, in the TARGIT-A trial, only 50% of patients with recurrence after TARGIT during lumpectomy had a mastectomy– it is this value (0.5) that should be used.
6. **The cost of EBRT.** The authors' calculations do not include either the current standard (IMRT) nor the use of "respiratory gating" that is aimed to protect the heart and the lungs. It also does not include the high cost of travel (up to £150 per day) that is usually borne by the NHS in a large proportion of patients. These appropriate inclusions would more than double the estimates of EBRT cost. This is of course without counting the cost to the patient, which ultimately has a bearing on the national economy, or the higher current cost of a linear accelerator (1.5 to 2 million) rather than the older costs (1 million).

We are happy to work with the authors of the report to correct these inaccuracies, as the result could be a very useful and informative document assessing the use of the TARGIT treatment using Intrabeam.

Professor Jayant S Vaidya, On behalf of the TARGIT A Trialists' Group

Contributions to this document compiled by Professor Vaidya are from:
Professor Max Bulsara, Professor of Statistics, University of Notre Dame, Fremantle Western Australia
Professor Frederik Wenz, Professor of Radiation Oncology, University of Heidelberg, Mannheim, Germany
Dr Elena Sperk, University of Heidelberg, Mannheim, Germany
Dr Julian Singer, Consultant Radiation Oncologist, Princess Alexandra Hospital and NHS trust, Harlow, UK
Ms Chris Brew Graves, Clinical Trials Group, University College London.
Dr Norman Williams, Clinical Trials Group, University College London.

About: ["*Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence: The clinical and cost effectiveness of the INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer*"]
This is a comprehensive review that has focused on the two TARGIT publications in the Lancet in 2010[1] and 2014[2]
We would like to make the following comments as some of the authors of these papers.
The lengthy and otherwise authoritative appearance of this document can mask a few crucial inaccuracies that have a significant impact on the conclusion. We find that it does justice to neither the evidence about clinical effectiveness nor the economic analysis of the TARGIT technique. We found that these inaccuracies leads to a distortion of the available randomised evidence. Hence we felt the need to write this response.

We believe that clinicians and health-care policy makers should not deny suitable patients the opportunity to complete their treatment in one combined procedure (TARGIT) within a risk-adapted approach that not only reduces toxic effects and saves 20–30 visits to a radiotherapy centre, but also in many cases permits breast conservation rather than mastectomy.

Not all points may have been covered in this quick response.

1. **About the main clinical end points.** We agree with the authors that the TARGIT-A trial has demonstrated that TARGIT is non-inferior to EBRT and that there is no statistically significant difference in the primary outcome (local recurrence) for the whole trial and particularly when TARGIT is given during initial lumpectomy.
We are therefore puzzled how they can claim that TARGIT is clinically less effective than EBRT by using the 1% statistically **non-significant** difference between TARGIT and EBRT when TARGIT is given during lumpectomy when there is a 31% probability that this difference has arisen by chance alone (p=0.31).
It is not appropriate that they accept this difference in local recurrence as 'real', while they summarily reject the 2.3% difference in overall mortality which has only a 12% chance of having arisen by chance (p=0.12).

The following statement on page 4 of the abstract is not supported by data: "The review found that local recurrence was slightly higher following INTRABEAM than EBRT but the difference did not exceed the 2.5% non-inferiority margin providing INTRABEAM was given at the same time as BCS. Overall survival was similar with both treatments" – it should correctly read as follows:

"The review found that local recurrence was slightly higher following INTRABEAM than EBRT but the difference did not exceed the 2.5% non-inferiority margin providing INTRABEAM was given at the same time as BCS. Overall survival was slightly higher in the TARGIT arm of the trial, due to a statistically significant reduction in non-breast-cancer mortality".

Alternatively, as both these differences are not strictly "statistically significantly different", it should be said that "Between the two treatments, the differences in both local recurrence and in overall survival were not statistically significant."

This absolute difference in mortality is discounted by the authors, even though there is a 90% probability that

the difference is real (p=0.099). However, the absolute differences in local recurrence, all recurrence, and breast cancer death have been included by the authors in the model even though they are not statistically significant. These appear to be double standards. It is not appropriate to accept the slight (non-significant) difference in local recurrence and ignore the slight difference in survival, as clearly death is an important endpoint.

Similarly, the statement "Cost-effectiveness analysis indicates that INTRABEAM is less expensive but also less effective than EBRT because it is associated with lower total costs but fewer total QALYs" is contrary to the randomised evidence.

The correct statement should be : "Cost-effectiveness analysis indicates that INTRABEAM is less expensive but also as effective as EBRT because it is associated with lower total costs and no fewer total QALYs"

2. **Comparability of groups and ignoring the difference in survival:** We found it incredulous to read the authors' claim that the difference in age could have prejudiced the results of non-breast cancer mortality in favour of TARGIT because this group was allegedly younger. They estimate that this difference was 6 months. Firstly, the actual difference in the mean is only 3 months and the difference is not at all statistically significant. If this logic were to be extended, the fact that important prognostic factors such as nodal involvement, lymphvascular invasion, and ER and PgR negativity were all slightly more frequent in the TARGIT arm should be the attributable causes for any increase in recurrence in the TARGIT arm; and indeed if the difference in age were important it would also be detrimental to the patients in the TARGIT arm in terms of breast cancer. Therefore, if their argument is to be taken seriously, then the apparent difference in breast cancer recurrence should be explainable because of these baseline differences.

   We truly do not believe that these minute differences that are not statistically significant contribute to any of the differences in the outcomes in this very large randomised trial.

   Death was a secondary end point in this trial. Breast cancer deaths are not different between TARGIT and EBRT but there is **already** a significant reduction in non-breast-cancer mortality, which leads to a trend for a reduction in overall mortality with TARGIT. Our data about fewer cardiovascular deaths is consistent with robust evidence using other large datasets that have investigated the cardiac toxicity of EBRT. There is a serious omission in the report about such evidence showing that there is a significantly increased risk of death from ischaemic heart disease due to EBRT - being highest in the first 5 years - and continuing for 25 years[3]. We find it shocking that the authors have summarily dismissed the clearly statistically significant difference (p=0.0086) in non-breast-cancer mortality that led to a trend in improved overall survival with TARGIT.

3. **The objective and scope:** The clear objective on page 9 (and page 26) is "**To assess the clinical and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour**" also, in the 2014 paper we have clearly said that we support the use of TARGIT only during lumpectomy therefore the figures used in the abstract should be those from the prepathology stratum and the clinical- and cost-effectiveness assessments should be based on the data from this stratum. The trial clearly showed that the postpathology stratum in which TARGIT was given after a median of 37 days after the initial lumpectomy by re-opening the wound (a very different intervention from what is stated in the objective) is not as effective and not non-inferior to EBRT, and we do not recommend its use. Including the data from this very different treatment approach rather than that which uses "TARGIT during surgical removal of the tumour" is clearly wrong. Using the Prepathology data alone would completely reverse the authors' conclusions.

4. **Use of correct parameters to assess clinical effectiveness and QALY**: We would like to point out that "any other recurrence" is not affected by the local interventions in question. Any other recurrence is not related to local recurrence nor does control of local recurrence impact on survival until the recurrence difference is more than 10% (which in case of TARGIT-A trial is 1 or 2% only)

If a global parameter that assesses the health of the patient with regard to the disease in question is required, then disease free survival should be used, as the authors have suggested.

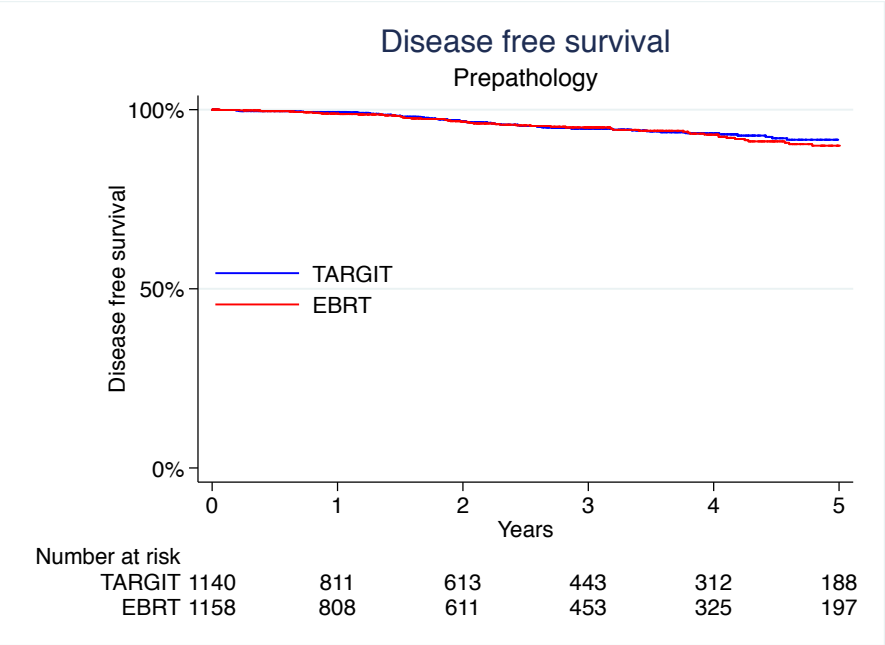
The values for disease free survival from the TARGIT-A trial are as follows. These are actual randomized data, not simply projections.

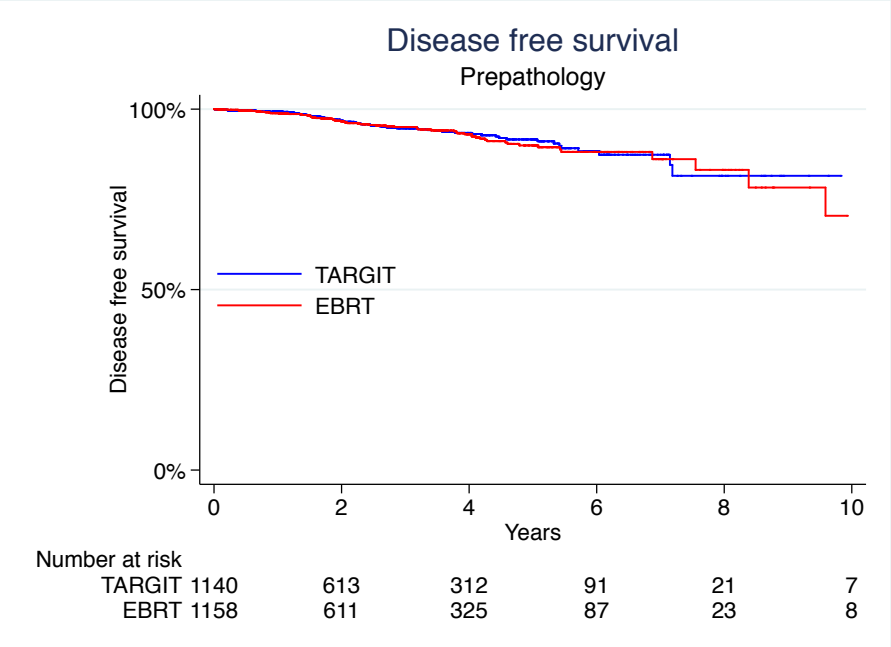
For the whole trial and for Prepathology stratum, the Disease Free Survival is not different with TARGIT compared with EBRT (p=0.78 and p=0.68 respectively).

The K-M estimates for Disease Free survival for the whole trial are as follows:
P value for difference = 0.78
at 5 years TARGIT 90.5% (88.1-92.5) vs. EBRT 91.0% (88.6-92.98)
at 10 years TARGIT **77.7% (65.5-86.8) and EBRT 71.5% (49.8-85.1)**

The K-M estimates for Disease Free survival for the Prepathology stratum when TARGIT is given during surgical removal of cancer are as follows **(a per the objective of this report):**
P value for difference = 0.68
at 5 years TARGIT 91.6% (88.7-93.8) vs. EBRT 90.1% (86.8- 92.6)
at 10 years Disease Free survival figures are TARGIT **81.3% (71-88) and EBRT 71.2% (49-85)**

The authors' suggestion that QALY or clinical effectiveness is worse with TARGIT is contrary to the randomised evidence from the TARGIT-A trial. The graphs below show the disease free survival up to 5 years and 10 years.





5. **The economic analysis** and the comparison between EBRT and TARGIT presented by the authors leaves some room for improvement.

   Modern External Beam Radiotherapy (EBRT) practices in the UK are not taken account of in the authors' model. These incur a higher cost.
   A typical patient with breast cancer today has the following costs:

Radiotherapy planning for breast		£867 to 1095
Delivery of radiotherapy 15 fractions	15 x £130 =	£1950
Electron boost planning		£504
Delivery of 8 fractions boost	8 x £108 =	£864
Total		**£4,185 to £4413**

   This appears to be already much more than the supposed cost as per the authors
   In addition,

- Many radiation centres, which care for the patients' safety and aim to reduce toxicity, add extra lead shielding to reduce cardiac toxicity. This involves more medical physics cost.
- EBRT now also involves 4D respiratory gated breath hold techniques "stop and shoot" techniques for left sided breast cancers , to minimise cardiac dose. These add cost for every one of the 15 fractions
- If 50 Gy in 25 fractions are used instead of 40 gy in 15 fractions (as may be required in 5-10% of cases), then it is proportionately more expensive
- Patients are seen weekly for a consultation with doctor or radiographer to assess skin toxicity- the cost of this is not included in the model
- The current cost of a linear accelerator is £1.5 to 2 million and only the older <=£1 million cost appears to have been used in the calculations. The cost of replacement does not appear to be included
- The costs associated with travel/parking/accommodation were not included within the EBRT arm. These expenses might range from £50 – 100 per patient per fraction delivered and therefore add a substantial increase in the total cost e.g., 100 x 21 = additional £2100. In a large proportion of patients these costs are directly bourne by NHS (hospital transport). If not borne by the NHS directly, travelling costs are a very large expenditure both financially and in time for the patient and this must be taken into consideration and added to the total cost for EBRT.
- Ideally, we should not be using tariffs as we all know they are not a true reflection of price/cost; tariffs are

simply reimbursements and for full HE data we ought to use cost.

There also appears to be an overestimate (by multiple times) of the cost of training and delivery of Intrabeam. One wrong assumption is that the surgeon is present in the operating theatre when radiotherapy is being delivered (33 minutes). Normally he/she is doing other unrelated work in a different room which immediately reduces the estimated cost per treatment by 40%.

Esserman et al[11] applied a Markov modeling technique to simulate the early and late adoption of the results of the TARGIT A trial in terms of QALYs and resources gained or lost. Using the worst-case scenario of a increased of 10% in local recurrence rate at 10 years – (in reality is only 1% difference at 5 years) they concluded that the opportunity cost of using EBRT is $1.7 billion if we waited another 5 years before adopting the TARGIT technique for appropriate patients.

In reality, there is no significant difference (statistically or clinically), in the local recurrence or disease free survival between TARGIT and EBRT but there is a significant difference in local toxicity and other-organ toxicity favouring TARGIT. So there should be no doubt in anyone's mind that not only is TARGIT clinically effective and cost-effective, but it would be significantly be less toxic to the patient and less expensive to the NHS and the tax-payer.

These are the obvious oversights and we have not been able to go into great detail in the short time available to us. We shall be delighted to work with the authors to improve the accuracy of their model.

6. **Regarding follow up of the TARGIT-A trial.** "Longer term follow-up data from the TARGIT-A trial".
It may appear tempting to speculate that in the future a difference in local recurrence will become apparent and the difference in mortality that is already seen will disappear, but neither our data nor previous trial results support this speculation. This suggests a lack of understanding about the complex natural history of breast cancer and robust literature about the toxic effects of EBRT on other organs such as the heart. Continuing to ignore these data can potentially put a large proportion of breast cancer patients at a significant disadvantage.

Statistically, it is inappropriate to use median follow up on its own without taking into account the absolute number of patients. Biologically, the temporal distribution of local recurrence shows that the first 2 to 3 year period covers the peak hazard of local recurrence after surgery[4] (see figure A – figure 2 from reference[5]). More importantly, various local therapy trials (surgery and radiotherapy) have repeatedly shown that the effect of local therapy such as surgery or radiation is mainly seen in the first 5 years, with the peak of the hazard being bracketed by the first 2-3 years. The lines representing local recurrence between radiotherapy and no-radiotherapy in Kaplan-Meier plots remain virtually parallel after 5 years in the NSABP B06[6] (see figure B left), NSABP B04[7], and the Oxford Overview[8] (latter two not shown). The conclusion of the 25 year follow up of the Swedish trial of radiotherapy vs. no radiotherapy[9] was explicit: "*Radiotherapy protects against recurrences [only] during the first 5 years of follow-up…*". Whatever difference was going to be seen at 25 years was already seen at 5 years, with most of it already seen at the 2-3 year median follow up of the trial (see figure B right). TARGIT-A trial has a substantial number of patients (n=1222) patients with a median follow up of 5 years and 2232 patients had a median follow up of nearly 4 years.

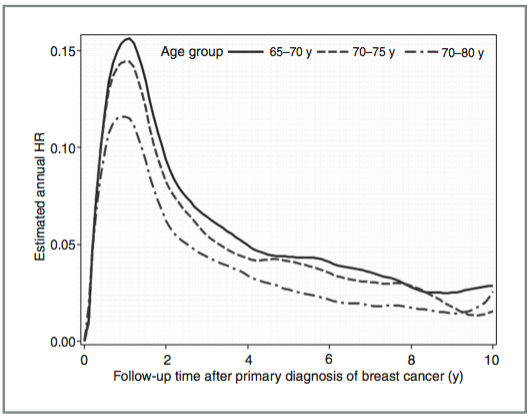


Figure 2. Smoothed hazard functions by age group for first recurrence among women after primary breast cancer treatment. The HRs describe showed hazard of recurrence for each 1-year interval.

FIGURE A- from Cheung et al[5]

As per authors' admission the number that was needed with enough statistical power to prove non-inferiority in the TARGIT-A trial is much smaller (page 54), because of the vanishingly low risk of recurrence. In 2010, we calculated that this number is 585 (table 6 of reference[1]). Clearly we have many more patients than that with a 5 year follow up.

Figure B

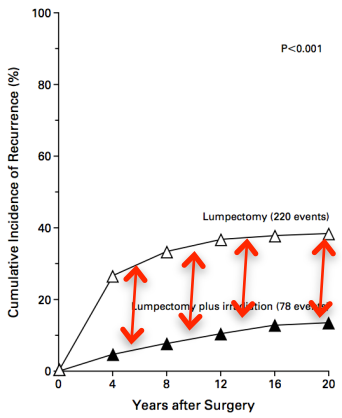
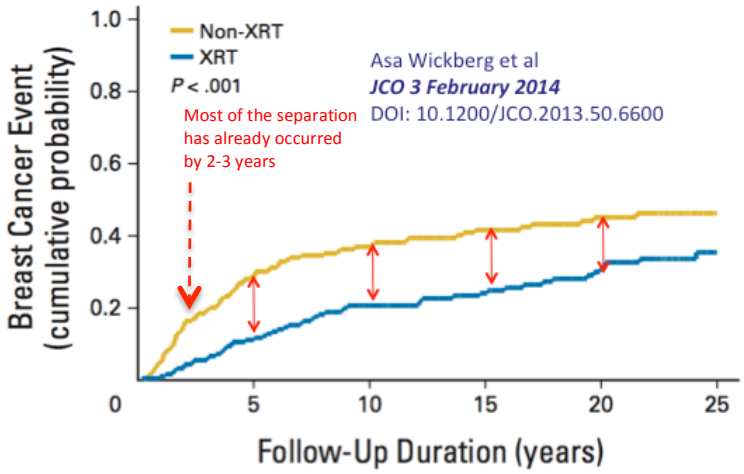
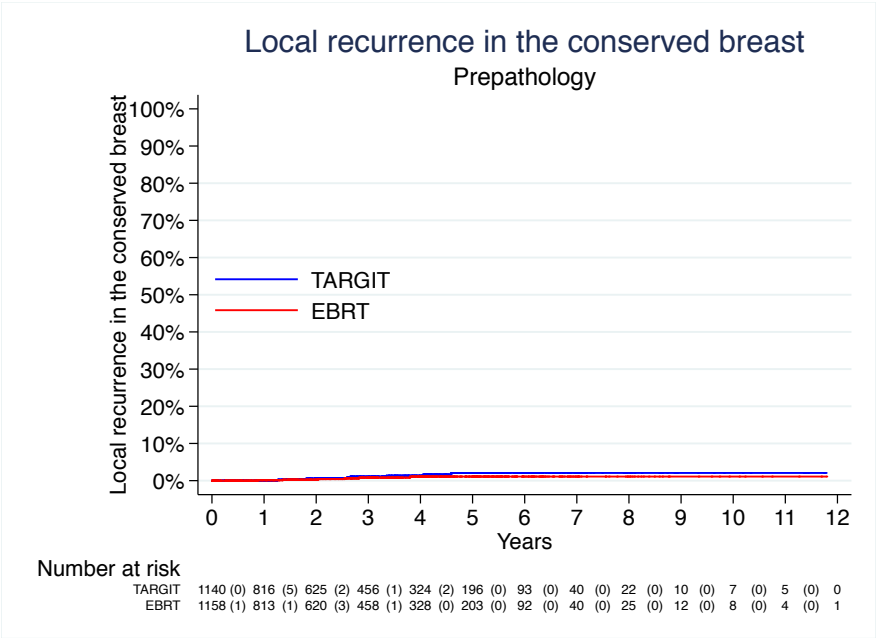


Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.
The data are for women whose specimens had tumor-free margins.



The biological rationale that adequately explains these observations are covered by Retsky et al[4] and further explored in greater detail with their relevance to the interpretation of the results of randomized trials by Baum in 2013[10]. Finally Esserman and her colleagues reiterate the overwhelming volume of data describing the hazard rate peak for local recurrence at 2-3 years after surgery and go on to explain a decision model framework that strongly recommends the adoption of results of RCTs when the median follow up comfortably brackets this point (as with the TARGIT trial)[11].

7. **Highly inappropriate extrapolation of our data projected out to 40 years (page 93).** As seen from other trials, follow up after first 2-3 years adds little information about local treatment of breast cancer and nothing after first 5 years. The 10-year Kaplan-Meier plot of local recurrence in the TARGIT-A trial confirms this as well, as seen below: (these are actual randomised data – not just a projection)



7. **Completely wrong proportion used to estimate the number of patients suitable for TARGIT with INTRABEAM**. (page 104 and in the economic model) For calculating this, the authors have used data from a study describing a series of patients who were treated with a different intraoperative radiotherapy technique. Rather estimating the proportion of patients undergoing breast conserving surgery that would be suitable for the TARGIT procedure i.e., : $\frac{suitable\ for\ TARGIT}{suitable\ for\ lumpectomy}$, the authors have used data from a series of patients who were treated with a different intraoperative radiotherapy technique (not Intrabeam) and used the equation: $\frac{suitable\ for\ IORT\ as\ per\ some\ criteria}{number\ actually\ given\ IORT}$. This study calculated how many of such patients who were all treated with IORT would have been considered 'suitable' as per ASTRO criteria (NB the ASTRO criteria were created before the results of randomised trials were published and were based solely on an educated guess about which patients might be suitable). In any case the proportion of patients treated with IORT using ELIOT technique that are in the ASTRO 'suitable' group has nothing to do with the proportion of patients undergoing breast conserving surgery that would be suitable for the TARGIT procedure. So the authors have used this very proportion - the value of 16%! Firstly, the proportion of TARGIT-A trial patients in the ASTRO 'suitable' group is in reality 38%. But more importantly, in the large German centre database of 1108 patients, 628 patients (56.7%) would be suitable for the TARGIT procedure (*Elena Sperk and Frederik Wenz, Mannheim, Germany – personal communication*). This is the value (56.7%) that should be used while calculating the utility of TARGIT in clinical practice. We should remember that those patients who are not suitable for TARGIT-A as standard treatment would be suitable for randomisation in the UK NIHR –HTA funded TARGIT-B trial. Using the correct proportion of patients suitable for TARGIT would immediately reduce the cost of TARGIT treatment per patient significantly.

8. **Proportion of patients with recurrence after TARGIT who have mastectomy.** The authors have used 80% as the proportion of patients with recurrence who have a mastectomy, based on 'expert opinion' only, and have used this (0.8) in their cost-effectiveness calculations. In reality, only 50% of patients with recurrence after TARGIT had a mastectomy in the TARGIT-A trial – it is this value (0.5) that should be used.

9. **The p value cut-off** for the LOG RANK test was pre-specified for local recurrence to be 0.01 as this was the second such analysis. The authors have confused this with the $P_{non\text{-}inferiority}$ on page 44. Clearly the cut off is not meant for $P_{non\text{-}inferiority}$ – for which the conventional 0.05 cut off should be used – as it is the first time the test has been performed. Thus, contrary to the statement in the document on page 44, for the whole trial non-inferiority remains established for even the earliest cohort of 1222 patients with a median follow up of 5 years.

10. **The need for TARGIT in the UK** The authors have stated that "Overall, 57% of women received radiotherapy within 60 days and 92% within 90 days of their final surgery" and admitted that meeting the 31 day goal for radiotherapy is very difficult. This again underscores the need for TARGIT.

11. **Use of TARGIT elsewhere in the world.** TARGIT has been used in over 8000 patients worldwide. It is standard of care for appropriate patients in many centres of excellence and NHS hospitals in Europe and USA. This fact should not be ignored.

We are happy to work with the authors of the report to correct these errors, as the result could be a very useful and informative document assessing the Intrabeam technology.

Professor Jayant S Vaidya MBBS MS DNB FRCS PhD

Professor of Surgery and Oncology and Consultant Surgeon
Scientific Director, Clinical Trials Group
Head of Bloomsbury Campus, Division of Surgery and Interventional Science
University College London

References

1. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *The Lancet* 2010; **376**(9735): 91-102.
2. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *The Lancet* 2014 (e-pub 11 Nov 2013); **383**(9917): 603-13 DOI:10.1016/ S0140-6736(13)61950-9.
3. Darby SC, Ewertz M, McGale P, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *New England Journal of Medicine* 2013; **368**(11): 987-98.
4. Retsky MW, Demicheli R, Hrushesky WJ, Baum M, Gukas ID. Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer. *APMIS* 2008; **116**(7-8): 730-41.
5. Cheng L, Swartz MD, Zhao H, et al. Hazard of recurrence among women after primary breast cancer treatment - a 10 year follow up using data from SEER-Medicare. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2012; **21**(5).
6. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *NEnglJMed* 2002; **347**(16): 1233-41.
7. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *NEnglJMed* 2002; **347**(8): 567-75.
8. Early Breast Cancer Trialists' Collaborative G. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *The Lancet* 2005; **366**(9503): 2087-106.
9. Wickberg A, Holmberg L, Adami HO, Magnuson A, Villman K, Liljegren G. Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014; **32**(8): 791-7.
10. Baum M. Modern concepts of the natural history of breast cancer: a guide to the design and publication of trials of the treatment of breast cancer Eur J Cancer. 2013 Jan;49(1):60-4. . *European Journal of Cancer* 2013; **49**(1): 60-4.
11. Esserman LJ, Alvarado MD, Howe RJ, et al. Application of a decision analytic framework for adoption of clinical trial results: are the data regarding TARGIT-A IORT ready for prime time? *Breast cancer research and treatment* 2014; **144**(2): 371-8.