Multiple Technology Appraisal (MTA) INTRABEAM Photon Radiosurgery System for Adjuvant Treatment of Early Breast Cancer

Response by The Royal College of Radiologists (Faculty of Clinical Oncology)

The Royal College of Radiologists’ (RCR’s) role in oncology is to advance the science and practice of all aspects of oncology, educate the public on these issues and to set professional standards of practice. The RCR’s Clinical Oncology members and Fellows are the only medical professional group responsible for the delivery of radiotherapy to breast cancer patients in the UK and therefore wish to respond to this consultation and to express concerns under three main headings.

1. Recommendations drawn from a single trial (TARGIT A) reviewed in this MTA and confining the appraisal/recommendations to a single IORT facility (Zeiss Intrabeam device).

2. Concerns around the methodological flaws of this single study (TARGIT A trial).

3. The misrepresentation to/by the media of preliminary recommendations from the NICE appraisal findings at the start of the consultation period.

Background to External Beam Radiotherapy (EBRT) for breast cancer patients

Breast cancer radiotherapy has been one of the most thoroughly researched areas in oncology over the past 30 years. During this time sequential high-quality clinical trials, based on appropriate hypothesis generation, have been conducted and led to the evolution of an evidence-based practice which incorporates science, clinical probity, health economics and, additionally, has given high priority to patient acceptability and outcomes. Thousands of women have contributed to this programme of oncology research which embodies trial design advances and in which quality assurance is integral. This programme continues and assures patients that they are receiving the highest quality of care with proven clinical effectiveness, both in terms of cancer control and normal tissue effects, including cosmesis.

Against this background of high quality research the Clinical Oncology community, represented by the RCR, is concerned that the recommendations of this TA may facilitate patients being offered a treatment that has not been subject to the same rigorous scientific approach and that this may also destabilise and threaten the integrity of breast cancer research in the UK.

Areas of Concern regarding the Consultation document:

1. Recommendations drawn from a single trial (TARGIT A) reviewed in this MTA and confirming the appraisal/recommendations to a single IORT facility (Zeiss Intrabeam device).

   - The wording of the preliminary recommendation is tortuous and ambiguous, and its ability to cause confusion has been demonstrated by inappropriate media statements at the start of the consultation period.

   - As the Committee is aware of, and has acknowledged, criticisms of the TARGIT A trial, the RCR seeks explanation as to why any recommendation for the use of IORT should be
confined to the Zeiss intrabeam device. There are other devices which can deliver IORT in this setting and which are available in many centres without the investment in this specific equipment.

- The appraisal is based on a single RCT (TARGIT A) which does not meet the internationally recognised standard of five-year follow up for breast cancer trials addressing local recurrence. The TARGIT A trial reported with a median follow up of only two years and five months.

- The trial was designed on the premise that local recurrence rates were in the order of 6 per cent and this provided the basis for establishing a non-inferiority threshold of 2.5 per cent. This level of local recurrence is no longer accepted as appropriate and is more likely to be in the order of 2 per cent for the patient group in the trial. As a consequence, within the current parameters of the TARGIT A trial, and in the setting of inadequate follow up, this could allow a doubling of local recurrences, a doubling of the salvage mastectomy rate and a significant increase in reconstructive surgery procedures. This is well-described in the correspondence that followed in *The Lancet* following the TARGIT publication (Appendix 1).

- There are other published randomised trial data (ELIOT study¹) which report higher ipsilateral breast tumour recurrences and a higher mastectomy rate for patients treated with intraoperative rather than external beam radiotherapy after conservative breast surgery. There is over five years’ median follow-up and the five-year event rate favours EBRT by 0.4 per cent to 4.4 per cent.

- The PRIME II trial² provides further relevant randomised data in the setting of good prognosis breast cancer, in terms of evaluating IORT. Again, reporting with the standard five years follow up, there was a local relapse rate of 1.3 per cent for patients treated with adjuvant radiotherapy (external beam) and 4.1 per cent for the no radiotherapy arm of the trial. Patients included in this trial had good prognosis breast cancer, similar to those included in the TARGIT A trial, and this raises the possibility that the Intrabeam technique may offer an outcome similar to avoiding radiotherapy altogether.

- The appraisal acknowledges that the risk of recurrence carries with it a burden to patients and their families who want to ensure they have the best chance of a future free from breast cancer. In the same section of the document, this statement is immediately followed by a patient group commenting on the frequency of hospital visits and potentially disruptive treatments, in terms of EBRT. Although the latter are very important issues, the former statement regarding concern of risk of recurrence and being offered the best chance of a future free from cancer would seem likely to dominate any argument for most patients, particularly in the modern era of delivering EBRT over a three week period. Furthermore, radiotherapy departments now offer increasing flexibility in terms of times of attendance which allows patients to incorporate their personal and professional activities.

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2. Concerns around the methodological flaws of this single study (TARGIT A trial)

- The Consultation document acknowledges most of the concerns held by the scientific and clinical community over the methodology and governance of the TARGIT A trial, but does not then seem to have given these issues full credence in the recommendations.

- The main criticism of the TARGIT A trial lies in the statistical analyses and it is of major concern that Professor Jack Cuzick has commented on these issues and voiced his opinion publicly in a *Lancet* publication (Appendix 2), also commenting that he had resigned from his position as Chair of the independent Data Monitoring Committee for the trial. The main statistical analyses criticisms can be summarised as follows:

  i. The median follow up of the trial is only two years and five months, which is inadequate for ensuring the estimate of risk recurrence is robust.

  ii. The analysis includes the presentation of results from three cohorts of patients with varying median follow-up. This flawed approach allows triple counting.

  iii. There is a linear risk of local recurrence for patients with tumours of the type entered into the TARGIT A trial - i.e. those with good prognosis tumour and a lower risk of recurrence. This means that there can be a year-on-year rise in local recurrence which necessitates the application of five-year follow-up (absolute minimum) to any recommendation for use of this approach.

  iv. There are errors in the analysis in terms of attributing causes of excess non-breast cancer mortality and the authors of the TARGIT study have made basic errors which are particularly apparent in the estimate of cardiac damage. These areas could lead to an estimate of standard breast RT risk to the heart being represented as approximately ten times the actual incidence. Again this is well explained in the correspondence in *The Lancet* (Appendix 3,4).

3. Misrepresentation to/by the media of preliminary recommendations from the NICE appraisal findings at the start of the consultation period.

- The RCR is concerned that the preliminary recommendations and findings of this appraisal were widely represented in the media at the start of the consultation period. This has obviously had an impact on patients who are currently approaching radiotherapy as part of their treatment for breast cancer, currently undergoing external beam radiotherapy or having had it in the past. It has also caused disquiet among professionals, both in terms of dealing with patient queries and in assessing the consequence of such a recommendation on the services they are able to offer patients.

- The release of this information at this inappropriate time makes it difficult to ensure that the remainder of the appraisal process is carried out without prejudice. The RCR is concerned that NICE does not appear to have taken steps publicly to deal with this situation, to provide assurance that the appraisal process will consider these events and ensure that the process retains credibility.

- The misrepresentation is explained by the response of an official body to the premature release of NICE findings in the media:

  NICE writes that:

  "...the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam was non-inferior to EBRT in terms of local recurrence. The Committee therefore
concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven."

On the CRUK website this is translated into:

"A clinical trial in 2013 suggested it [i.e. Intrabeam] was likely to be as effective as conventional radiotherapy".

In summary the RCR wishes to express its strongest concerns about both the conduct of, and preliminary recommendations from, this MTA, as detailed above. It urges NICE to reconsider its preliminary recommendations in keeping with the large body of expert clinical opinion, as expressed through the RCR's Clinical Oncology community.

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Radiotherapy for breast cancer, the TARGIT-A trial

Joanne S Haviland a, Roger A’Hern b, Soeren M Bentzen c, Timothy Whelan d, Judith M Bliss b

The investigators from the TARGIT-A trial1 claim to have established non-inferiority of intraoperative radiotherapy relative to external beam radiotherapy (EBRT) for breast cancer in terms of 5-year local recurrence. Assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point.

This analysis, including the non-inferiority test statistic, is therefore unreliable. The most appropriate measure of non-inferiority given available data uses the survival analysis of local recurrence rates. Based on the 5-year estimates for local recurrence of 3·3% (95% CI 2·1—5·1) after intraoperative radiotherapy and 1·3% (0·7—2·5) after EBRT, the estimated hazard ratio (HR) is 2·56. The standard error of the HR can also be estimated,2 suggesting an upper limit of 5·47 for its one-sided 95% CI. In view of the 1·3% local recurrence rate after EBRT, the local recurrence rate after intraoperative radiotherapy could therefore be as high as 7·1%, far exceeding the predefined non-inferiority limit.

The investigators present results for three cohorts of patients with varying lengths of median follow-up, claiming to portray the apparent stability of treatment effect estimates over time. The cohorts are nested within each other, thus patients with longest follow-up (who contribute most events) are analysed three times, generating a result of questionable validity. Median follow-up is only 2·4 years, and a substantial increase in observed duration of follow-up is needed before any analysis of non-inferiority of local recurrence risk can reliably inform clinical practice. The TARGIT-A trial1 remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.

We declare that we have no competing interests.

References


a Faculty of Health Sciences, University of Southampton, Southampton SO17 1BJ, UK
b Institute of Cancer Research Clinical Trials and Statistics Unit, Institute of Cancer Research, Sutton, Surrey, UK
c Division of Biostatistics and Bioinformatics, UMGCC Biostatistics Shared Service, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
d Department of Oncology, McMaster University, Hamilton, ON, Canada
Radiotherapy for breast cancer, the TARGIT-A trial

Jack Cuzick

The TARGIT-A trial (Feb 15, p 603) 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, which requires the upper (90%) 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 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.

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 criteria, 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.

I was chairman of the Data Monitoring Committee for the TARGIT trial previously but have resigned.
Radiotherapy for breast cancer, the TARGIT-A trial

John Yarnold a, Birgitte Vrou Offersen b, Ivo Olivotto c, Philip Poortmans d, Rajiv Sarin e

In reporting the testing of intraoperative radiotherapy against standard whole breast radiotherapy (WBRT), the investigators of the TARGIT trial1 claim an excess of non-breast cancer deaths are “almost certainly” due to the adverse effects of WBRT.2

We argue that causation is very unlikely. The risk of a major cardiac event increases by 7% per Gy of mean heart dose.3 Based on expected mean heart doses in the WBRT group of 1—5 Gy, radiotherapy cannot explain more than one of the 11 cardiovascular deaths. This is the case even if all eight cardiac deaths occurred in patients with left-sided cancers. Neither is it credible to attribute an excess of eight other, non-breast, cancer deaths in the WBRT group to radiotherapy. The NSABP B-04 trial4 followed 1665 patients for a median of 21·4 years after randomisation with or without locoregional radiotherapy after mastectomy, confirming a small excess (n=6) of primary lung cancer that took more than 10 years to emerge. The excess was attributed to large anterior axillary radiotherapy beams. No excess of lung cancers was noted in 1261 patients in the B-06 trial4 at a median of 19 years after randomisation with or without WBRT after lumpectomy. Lung cancer is the most common cause of death from other cancers in this context, but the TARGIT1 investigators provide no information about tumour site in relation to randomisation.

The difference in non-breast cancer deaths between randomised groups in the TARGIT trial is explained either by imbalances in risk factors or by under-reporting of non-breast cancer deaths in the test group.

We declare that we have no competing interests.

References

a Division of Radiotherapy and Imaging, Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton SM2 5PT, UK
b Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
c Division of Radiation Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada
d Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, Netherlands
e Advanced Centre for Treatment, Education and Research in Cancer, Tata Memorial Center, Mumbai, India
Radiotherapy for breast cancer, the TARGIT-A trial

Jay K Harness a, Melvin J Silverstein b c, David E Wazer d, Adam I Riker e f

Jayant Vaidya and colleagues 1 claim that TARGIT treatment results in increased survival since the number of non-breast cancer deaths are higher in the external beam radiotherapy (EBRT) cohort. The investigators cite higher incidences of cardiac toxic effects and deaths from non-breast cancers in the EBRT group as the major cause for the difference in overall survival, even though the TARGIT group currently has a higher, although not significantly breast cancer death rate (2·6% vs 1·9%, p=0·56).

The data, with a 29-month median follow-up, show a total of 37 deaths in the TARGIT group, from all causes, and 51 deaths in the EBRT group, from all causes. The authors included deaths from stroke and ischaemic bowel disease as cardiac toxic effects. However, these diseases are caused by narrowing of the arteries (arteriosclerosis) or clot formation, which are unlikely to result from any purported radiation damage to cardiac vessels or valves caused by the EBRT breast treatment. Moreover, deaths from other cancers are not credible to attribute to the breast EBRT treatment. The latency period for induced cancers from breast treatment is well established to be at least 15—20 years. Even after developing a radiation-induced cancer, treatments should prolong survival for several further years, even if cure is not affected. Thus, it is impossible for the 12-year old TARGIT-A study 1 to affect other cancer deaths. If you include only cardiac deaths and breast cancer deaths, the difference between TARGIT and EBRT is only two patients, and is thus hardly significant.

The authors state that although cardiac deaths from radiotherapy typically do not manifest until 7—10 years after treatment (well outside the median follow-up of this study), a recent study 2 that included patients treated as late as 2001 shows that significant cardiac toxic effects are apparent within the first 4 years. Since 35% of the trial patients (1222 patients) had a median follow-up of 5 years, they claim that the study 2 supports the increased toxic effects with EBRT noted in the TARGIT trial. 1 This statement is supported neither by the science nor by any evidence the investigators present.

Darby's study 2 began in 1958 and ended in 2001, so most of their patients were treated with outdated radiotherapy techniques and equipment, and before the era when cardiac toxic effects from breast irradiation were fully appreciated. Furthermore, 76% of the patients in Darby's study 2 had radiation after mastectomy, which is known to result in higher doses to the heart, especially for left breast irradiation. The consensus is that modern radiation techniques should limit the cardiac dose to less than 2 Gy for left-breasted tumours, and to less than 1 Gy for right-breasted tumours. These small doses result in very low cardiac toxic effects. In Darby's study 2 the median heart dose for a cardiac event was 4·9 Gy, with heart doses as high as 25 Gy. The risk of cardiac toxic effects rose with increasing dose. All modern radiation treatment planning systems have constraints that limit the cardiac dose, so it is unlikely that any centre participating in the study would deliver high cardiac doses, and any EBRT breast radiation study should surely include the requirement to limit the dose to the heart for EBRT radiation. Furthermore, even with data from Darby's study, for doses limited to 3 Gy, the increased risk of death from ischaemic heart disease over 30 years is less than 1%—data that hardly support the TARGIT investigators' assertions. Although the authors state that data for comorbidities were not collected at the time of randomisation, the exclusion criteria listed on ClinicalTrials.gov excludes “Patients with any severe concomitant disease that may limit their life expectancy.” It should have been the responsibility of the participating centre to undertake such screening.
To prove their contention of reduced cardiac toxic effects with TARGIT, the authors should have taken four things into account. First, they should have calculated the heart dose for those patients who had a cardiac event. (There are only a total of eight EBRT patients so this would not be too burdensome). Second, they should have identified and presented in the paper whether the left or right breast was irradiated in those patients that died from cardiac toxic effects. Third, the authors should have identified the time after the completion of EBRT that the cardiac events occurred. Finally, they should have indicated whether deaths occurred in those who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths. 26 patients assigned to EBRT actually received TARGIT; were any of the eight deaths in the EBRT group in these 26 patients?

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.

References

a St Joseph Hospital Center for Cancer Prevention and Treatment and University of California, Irvine, Orange, CA 92868, USA
b Hoag Memorial Hospital, Newport Beach, CA, USA
c Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
d Departments of Radiation Oncology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA
e Advocate Cancer Institute at Advocate Christ Medical Center, Oak Lawn, IL, USA
f Department of Surgery, University of Illinois, Chicago, IL, USA