NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

MTA Breast cancer (early) - Intrabeam IORT [ID618]

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

MTA Breast cancer (early) - Intrabeam IORT [ID618]

Contents:

Multiple Technology Appraisal (MTA)
INTRABEAM Radiotherapy System for the adjuvant treatment of early breast cancer [ID618]

Dear Appraisal Committee,

pursuant to the invitation to comment on the Appraisal Consultation Document (ACD) and evaluation report for the above appraisal we (manufacturer) would like to comment on the following:

- Has all of the relevant evidence been taken into account? **Yes**
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? **Yes, with some comments as stated below**
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS? **Yes, with a minor change suggested below**

We suggest the following changes to the draft guidance:

….

- …Clinicians should ensure that patients understand that less is known about the long-term outcomes of treatment with INTRABEAM … the data suggest that although the rate of local recurrence with Intrabeam could be slightly higher than with external beam radiotherapy there is a trend for a better survival rate with INTRABEAM **and**
- ...enter patient details into the UK routine cancer registries….

We suggest that to consider the following points for the interpretations of the evidence:

Page 10:
The Assessment Group also commented that patients in the EBRT group were slightly older at baseline (the Assessment Group calculated a mean age of 62.5 years for the EBRT group and 62 years for the Intrabeam group).

- the EBRT group and IB group were equally distributed, the age difference in mean age is 2.75 MONTHS (not 6 months as claimed by the HTA-NICE review) and it is not statistically significant.
- the shortfall of death in the IB group can be explained on the one hand with less side effects compared with EBRT (Darby et al.) on the other hand with immunological factors due to the influence on tumor biology of residual cancer cells and also EGF on cardiac disease (Beletti et al.)

Page 14:
Assessment Group noted that the manufacturer did not conduct a systematic review of economic evaluations

- A review of economic evaluations was done by the manufacturer, only the publication of Alvarado et al. was available and was listed in the data outline sent on October 7th 2013, also the ongoing trials have been listed in the data outline

in the UK most patients would have mastectomy after local recurrence

- Re-IORT is possible especially after Intrabeam treatment, in the future with longer life expectancy even elderly patients will prefer that option

not all patients who have mastectomy would also have breast reconstruction

- There will be a higher patients demand for breast reconstruction after mastectomy in the future

the average number of fractions with EBRT is 15 instead of the 23 fractions assumed in the manufacturer's model

- Some sites in the UK use still 23 fractions, also we based our model on the facts of the Targit trial, were 23 fractions were common also in the UK.
- With newer techniques (IMRT, Gating, SIB) the costs are higher than calculated in the AG model for EBRT, this would significantly change the ICERs for EBRT, therefore these techniques cannot be taken as argument for less side effects.

20 years used by the manufacturer was too short to reflect the entire follow-up period of the disease

- With a mean age of 60 we assumed a horizon of 20 years is more realistic than 30 or even 40 years (see also publication of Essermann et al.).

Page 16:
The Assessment Group noted that its clinical advisers suggested that the risk of local recurrence continues relatively linearly over the lifetime of the patient.

- Although the risk of local recurrence may continue linearly as proven by Cheng et al. meta-analysis, the peak of local recurrence is around 2.5 years. Importantly (Oxford Overview and Wickberg et al.) the effect of radiation on local recurrence is only seen in the first 5 years; the lines representing recurrences in the radiotherapy vs. no-radiotherapy group separate most in the first 2-3 years and do not separate after the first 5 years- they remain parallel. Thus radiotherapy is as ineffective as no-radiotherapy following the time after the first 5 years. Therefore the difference in recurrence rate at 5-years represents the difference at 10 and 20 years.

- The manufacturer model is based on the randomized Targit data with a superiority of non-breast cancer death for Intrabeam. Furthermore, fewer non-breast cancer were probably unmasked in this cohort of excellent prognosis patients (>98% were local-recurrence-free at 5 years) in whom only 36/3451 patients died from breast cancer (vs. 52 died from other causes) as stated above due to unmasked side effects of EBRT and probably due to inhibition of EGF factors through the effect of Targit on surgery wound fluids (Beletti et al.).

Page 17:
The Assessment Group did not apply a disutility associated with mastectomy based on the study by Robertson et al. (2012), which reported a higher utility

value for people who had mastectomy and breast reconstruction than the utility value from the COMICE trial for wide local excision.

- The utility of mastectomy w/o reconstruction is lower than wide local excision. Since the AG model calculates the costs for mastectomy w/o reconstruction, consequently these lower utility values should be calculated in the economy model.

the Assessment Group assumed that 16% of people diagnosed with breast cancer would be eligible to receive treatment with Intrabeam

- According to German investigation and conservative calculation 30.1 % (Sperk et al. Poster at German Senology congress 2014) of breast cancer patients would be suitable as per TARGIT-A inclusion criteria; Furthermore the remaining patients (60.6 % according to Sperk et al.) having lumpectomy can be potentially treated with TARGIT - Boost (which serves as a tumour bed boost) thus freeing up 1-2 weeks of EBRT) and consequently having impact on ICERs.

- Taking into account equal or slightly better QALY (including lower non-breast cancer death for IB as calculated in manufacturer model) and less costs compared to EBRT (including capital costs of EBRT) there is a higher ICER saved per same or better QUALY. Furthermore there is a better non measured but by patients group noted QOL: disruption of daily life, travel cost, time, inconvenience and productivity loss + ionizing radiation exposure to other organs in EBRT.

Page 19:
The results of the deterministic sensitivity analyses showed that the cost-effectiveness results were most sensitive to the probability of any other recurrence for both treatment groups.

- The difference in any other recurrence between both groups was very small, therefore the sensitivity to the probability of any other recurrence is mistaken. Any other recurrence (and breast cancer mortality) has been proven (Oxford overview 2011) to be unrelated to local recurrence when local recurrence is less than 10%. Also the number of total recurrences is very low in the Targit group compared to population statistics.

Page 21:
additional operating theatre time needed for Intrabeam could potentially create difficulties in meeting waiting time targets

- It is important to note that the additional time in the OR for the radiation can be used for RD-100i OSNA sentinel lymph node testing. Also the surgeons use the radiation time for writing OR reports or they switch to the next OR's doing another surgery and leaving the wound closure to residents. Thus no additional staff time is needed and Intrabeam radiation does not mean automatically that there are less OR procedures during a working day.

Page 22:

The Assessment Group and the professional groups also noted the ongoing FAST-Forward trial, which is investigating the potential to provide a shorter course of treatment with EBRT

- The FAST-Forward trial outcomes are unclear, thus the shorter course of EBRT can mean worse outcomes. Also it is not clear whether such a regimen is freeing up radiotherapy resources in the future. Furthermore, one would need to wait for the follow up of this trial to assess the effectiveness. We think it is not appropriate to deny today's patients an effective treatment for the sake of an unproven treatment that is still in development that might become available after another 5-10 years.

Page 24:
there were techniques allowing clinical oncologists to more accurately target the dose with EBRT such as using clips

- Despite the usage of clips (which can move) the geographical miss of tumor bed irradiation is still present and is especially of concern with onco-plastic techniques commonly used

- Brachytherapy for recurrence is an option but is more expensive than Intrabeam treatment

Page 25:
The Committee heard slightly differing opinions from the clinical specialists as to whether the cosmetic outcome from Intrabeam was superior to modern EBRT because EBRT outcomes have improved substantially in recent years.

- Newer EBRT techniques might have less side effects and improved cosmesis however they are more expensive resulting in worse ICER. Also there are interim data from the Canadian Rapid trial (Olivotto et al.) showing worse cosmesis. The TARGIT-A trial was conducted in centres of excellence and would have used modern radiotherapy techniques in the control arm which as indeed been found to have very low local toxicity and excellent local control.

- Older machines are still in use in the UK having side effects on critical organs, new investments are needed for improved devices

Page 28:
it considered 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 trial is not underpowered since even with a non-inferiority criteria based on recurrence rates less than 6 % recurrence, the 2232 patients would provide statistically give enough power. Furthermore the trial was closed after 3451 patients resulting in 9491 women-years of follow-up, therefore the non-inferiority is statistically proven.

Page 33:

the quality of the trial and particularly its generalisability to NHS clinical practice would still not provide conclusive evidence to establish the relative clinical and cost-effectiveness of Intrabeam compared with EBRT as delivered in the NHS.

- The trial has a good quality as stated also by the AG. The study included more than 700 German patients with a very high standard of EBRT treatment and clinical practice which can be compared to NHS quality requirements. Furthermore only centers of clinical excellence in France, Italy, Denmark, US and Australia were included.

- According to Australian and American preference trials, patients would accept the slightly higher recurrence for the sake of convenience of single dose intraoperative radiotherapy. In any case there is no statistically significant difference between TARGIT during lumpectomy (Prepathology) and EBRT (p=0.31).

Page 36:
although staff training was needed for Intrabeam, it did not necessarily imply an increase in the number of staff or staff time,

- a two day training course in included in IB machine cost provided by Targit Academy centers (London, Heidelberg, Cleveland)

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JCO July 8, 2013

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23rd July 2014

Dear [redacted]

Here are Breast Cancer Care's comments on the questions asked by the appraisal committee, about the Appraisal Consultation Document and the evaluation report appraisal on the MTA INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer.

Has all of the relevant evidence been taken into account?
To the best of our knowledge as a patient representative organisation, we believe all the relevant evidence has been submitted and discussed in great detail, taking into account all the issues identified.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
We are unable to comment on the cost effectiveness. However, we do believe the summary is a reasonable interpretation of the evidence presented and discussed by the assessment group, clinicians, clinical advisors and the appraisal committee.

We believe the summaries are a reasonable interpretation of the clinical evidence presented and discussed by the patient expert, clinicians and the appraisal committee.

Are the provisional recommendation sound and a suitable basis for guidance to the NHS?
Yes, as a patient representative organisation we welcome the provisional recommendation as sound and is a suitable basis for guidance for use in the NHS. We strongly agree with the need for the patients to be fully informed of potential risks prior to consenting to treatment and we believe that the continued collating of long term data after treatment should be mandatory, in order to learn fully the long term benefits/risks, such as those highlighted by the NCRI Breast Clinical Studies Group, Royal college of Physicians and Association of Cancer Physicians.

If you require any further information please contact me.

Kind regards

[redacted]
Clinical nurse specialist
[redacted]

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Mrs Bijal Joshi
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15 August 2014

Dear Mrs Joshi,

Appraisal Consultation Document – The Intrabeam Radiotherapy System for adjuvant treatment of early breast cancer

Breakthrough Breast Cancer is dedicated to improving and saving lives through breast cancer prevention, early diagnosis, more targeted treatments and better services for everyone affected by breast cancer. We welcome the opportunity to respond to NICE's appraisal consultation document for the Intrabeam Radiotherapy System for adjuvant treatment of early breast cancer.

Breakthrough Breast Cancer is delighted that NICE has provisionally recommended Intrabeam Radiotherapy for use on the NHS. We know that patients find travelling to and from hospital for conventional radiotherapy treatment highly disruptive to their own and their families' lives, especially if they do not have easy access to transport or live far away from the hospital. For these women, the option to receive their radiotherapy treatment at the same time as breast conserving surgery will be highly valuable. In addition, we have heard of examples of women for whom conventional radiotherapy is not appropriate and would usually have to have a mastectomy. Intrabeam radiotherapy means that these women can still receive radiotherapy treatment and can have breast conserving surgery rather than a mastectomy, which is preferable for many women.

In addition, at a time when the NHS faces significant financial pressures, this is a treatment that can save the NHS money and free up time and resource in radiotherapy clinics, something that should certainly be welcomed.

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Patron HRH The Prince of Wales

We agree with the conditions that NICE have placed on this guidance. As it is a new treatment, it is important that outcomes data continues to be monitored to ensure that we know about the long-term impact of Intrabeam. In addition, it is important that patients are made aware of the current lack of this data so that they are able to make an informed choice about their treatment.

It appears that all of the evidence has been taken into account and we were particularly pleased that the committee has listened to and taken on board the views of the patient expert who was nominated by Breakthrough Breast Cancer. NICE have always had a good track record of involving patients and we are pleased to see this continuing.

We urge the committee to issue final guidance recommending Intrabeam for use on the NHS. This is a treatment that can make a real difference to the lives of women with breast cancer as well as providing the NHS with significant cost savings. However, there are currently only six machines that can deliver Intrabeam in the UK so there is investment required to ensure that this is routinely available for all eligible women with breast cancer. We urge NICE to work with NHS England to ensure that this positive recommendation is implemented as soon as possible so that women with breast cancer can benefit from this new treatment.

Thank you for the opportunity to comment on this appraisal consultation document. If you have any questions or wish to discuss any of the points in our response, please do not hesitate to contact me by email at sallyg@breakthrough.org.uk or by phone on 020 7025 2433.

Yours sincerely

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Comments on ACD
On

The Intrabeam Radiotherapy System for adjuvant treatment of early breast cancer

FROM HEALTHCARE IMPROVEMENT SCOTLAND
15 AUGUST 2014

Comment provided to HIS by :
Consultant in Oncology, Western General Hospital, Edinburgh

1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?*

   No.

   There are a number of design and interpretation weaknesses in the TARGIT-A trial:

   1.1 Protocol violations. 100 of 1113 patients assigned to intrabeam did not receive their allocated treatment (Fig 3 Vaidya et al Lancet 2010;376:p.95). 61 received external beam irradiation, 31 received mastectomy and 8 received external beam only. 66 assigned to external beam did not receive it (10 given intrabeam, 4 intrabeam and external beam, 30 mastectomy and 22 wide excision only). The overall protocol violation rate is 7.4%.

   1.2 Patients who were found to have pathological risk factors for local recurrence after wide local excision and intrabeam treatment could be treated with whole breast external beam irradiation. There was no standardisation between centres on which pathological criteria were applied for patients to receive additional external beam. There may have been substantial selection bias in who received additional external beam irradiation and who did not. It could be that patients would have no higher a local recurrence rate with whole breast external beam irradiation than with the combination of intrabeam and external beam.

   1.3 The report states(4.4.1 last 4 lines) that 'If there were adverse histological features indentified in the cancer cells at final pathology after treatment within intrabeam and subsequent EBRT was recommended, a further external boost dose would not be needed. However there is no level 1 evidence showing that a boost of 20Gy with intrabeam is as effective as an electron boost, which has

been validated in EORTC boost vs no boost trial (Bartelink et al. J Clin Oncol 2007;25:3259).

1.4 There is the hazard of focussing on favourable subgroups (in this case the prepathology subgroup) rather than reporting on the whole study population highlighted by Professor Jack Cuzick (Lancet 2014 383:1716).

1.5 The local recurrence rate in the intrabeam arm of TARGIT A trial is 3.1%. This is likely to rise when the trial reaches a median follow up of 5 years. This may approach the 4.1% local recurrence rate seen in the no radiotherapy arm of the PRIME 2 of women =/> 65 years with hormone receptor positive T1-2 (=/< 3cm) early breast cancer treated by wide local excision and endocrine therapy +/- postoperative radiotherapy. (Kunkler IH, Williams LW, Jack W, Canney P, Prescott RJ, Dixon MJ. The PRIME 2 trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥65 years with early breast cancer managed by breast conservation. Presented at: the 36th Annual San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX. Abstract S2-01).

If proper weight had been given to the above and, in particular to the guidance of the professional bodies who had advised the committee that follow up the TARGIT A trial was inadequate, intrabeam would not have been recommended as a treatment option.

2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? *If not, please explain.*

No.

The comparator in the TARGIT trial for cost effectiveness for whole breast irradiation was 50 Gy in 25 fractions over 5 weeks whereas the standard in most of Scotland is 40 Gy in 15 daily fractions over 3 weeks.

3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? *If not, in which areas do you consider that the summaries are not reasonable interpretations*?

No.

3.1 In 4.4.5 (lines 1-4) the NICE committee noted comments received from professional groups that the length of follow was too short to reliably demonstrate the clinical effectiveness of intrabeam compared with EBRT. I think that this is a reasonable consensus among most breast oncologists. The NICE committee states (4.4.5 lines 8-10) that the results of the TARGIT-A should be interpreted with caution because the length of follow up was less than 5 years for the full trial population.

3.2 Despite its statement in 4.4.12 (lines 16-18) that 'the committee recognised it role of not recommending treatments if the benefits to patients are unproven or if the treatments are not cost effective' it allows intrabeam as an option for treatment. I do not think there is sufficient evidence at present to justify

including intrabeam treatment for breast conserving treatment for early breast cancer and that further follow up is needed for the TARGIT-A trial.

3.3 The committee (4.4.12 lines 30-35) 'concluded that individual patient preference was important and agreed with the clinical specialists and the patient expert that patients should be fully informed of the evidence and the treatment options available, the lack of information about long-term outcomes with intrabeam and the risks and benefits associated with the technology'.

I agree that patient preference is important but patients should be offered options that are evidence based. The committee states (4.4.9, lines 10-12) that it 'understood that some patients were willing to accept slightly higher risk of local recurrence as long as the absolute risk remained low and the treatment had other benefits which they considered important'. However few patients would be prepared to choose to choose a treatment unless it had a strong evidence base for being clinically effective. In addition the committee notes in the draft assessment report (Picot et al, 2014, page 33 para 3, lines 9-11) that it is unknown whether English patients would be prepared to accept a higher risk of local recurrence. There is a similar lack of information among Scottish patients, although most patients I think would want the risks of local recurrence to be as low as possible.

3.4 The committee concluded (4.4.2, last 4 lines) that intrabeam given as the same time as surgery provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed and represented an alternative treatment option for people for whom EBRT is not suitable. That is true in theory but there is no evidence that it is any more effective than undertaking a wider than standard local excision with greater margins omitting postoperative whole breast irradiation.

3.5 Psychological distress of radiotherapy. It is stated that 'the patient expert explained that when a patient is diagnosed with breast cancer, she thought of many radiotherapy sessions over a number of weeks can cause emotional distress and anxiety and is highly disruptive to daily living.' While that may be true for some patients, it is not true for the majority and many are relieved to receive a course of external beam radiotherapy, despite its inconvenience, because of the high level evidence from the Oxford overview of it reducing the risk of first recurrence by 50%. No such reassurance can be given for intrabeam.

3.6 Cost effectiveness.

The data on the cost effectiveness of intrabeam is weak. No formal health economic analysis was conducted as part of the TARGIT A trial. In their review of the economic data submitted by Carl Zeiss in their NICE assessment report, Picot et al state in 5.3 (p.81, lines 6-9) that ' a systematic review of any relevant cost-effectiveness models was not conducted. Very limited information on the model was presented in the main submission document and whilst further details were contained within the Excel model, these too were limited'. There is clear selection bias in the omission from the economic data the results of the less favourable post pathology stratum. The model only met half of the requirements for methodological and quality (Picot et al, p 82 final para). None of these drawbacks are mentioned in the committee's statements about the cost effectiveness of intrabeam (section 4.4.10).

4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?*

The answer to both questions is no.

The committee seems to have ignored the advice of professional bodies that the follow up of the TARGIT A trial is too short to demonstrate its clinical effectiveness and the comments of an internationally recognised statistician Professor Jack Cuzick on focussing reporting on favourable subgroups rather than the whole trial population (see my comments in 1.4). There is poor quality evidence on the cost effectiveness of intrabeam and its impact on quality of life.

Allowing intrabeam to be an NHS treatment option without a sound basis for its clinical effectiveness is inappropriate. Patients need to be reassured that it is effective and considering it as a treatment option is premature. The advice that should have been given is that further follow up of the TARGIT A trial is needed and a decision on recommending it for treatment made in the light of longer term follow up data.

5. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? *If not, how do they differ in Scotland?*

The patient pathways are the same and same issues of treatment options are applicable.

6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? *If so, please describe what these changes would be.*

If the provisional recommendations were adopted, many fewer patients might be offered external beam irradiation after breast conserving surgery for early breast cancer.

7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? *If yes, please explain why this is the case.*

The guidance is not valid for the reasons stated above.

8. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment.

If Intrabeam was found to be clinically effective it could certainly be considered a treatment option in early breast cancer. However I think the conclusions of the guidance are not justified by the current evidence. NICE should give proper weight to the professional bodies that have advised it that the clinical effectiveness of Intrabeam is not yet established. The guidance should be revised recommending further follow up of the TARGIT A trial, further critical review of

the issues relating to the design and interpretation of the results and a review undertaken at a later date.

independent cancer patients' voice
www.independentcancerpatientsvoice.org.uk

We are breast cancer patient members of Independent Cancer Patients' Voice – a patient advocate group run and lead by patients whose aim is to bring the patients' voice to the cancer research community.

We have watched with interest that high quality research has shown that radiotherapy can be safely reduced from 6 to 3 weeks and we welcome the use of a more targeted, and more specialised, radiotherapy as it is clearly better for patients.

Continuing research may show that it is safe for patients some with no affected lymph glands, to avoid any radiotherapy but this will need many years of collecting follow-up data before it can become standard practice.

We have followed the development of intraoperative radiotherapy with great attention.
Whilst we do not want to get embroiled in the politics of this, there are a number of issues that are of great concern to us as patients.

- We are concerned that the current publicity does not make clear that NICE approval of intra-operative radiotherapy is not applicable to all types of breast cancer. Although the NICE quote as printed expresses caution about early breast cancer, even this does not mention different types of breast cancer?

- We were very worried by the press statement that came out last week and the impression that was given that radiotherapy in its current method would no longer be carried out. The Daily Mail (used the term "tens of thousands of women will benefit" This is totally irresponsible journalism and is not helped by the rather woolly statements put out by NICE.

- Current and potential patients need to be fully informed partners in their treatment decisions and to understand that collection of follow up data is needed for many years to assess safety of any treatment.

- Patient choice is important of course but forcing Trusts to spend money on this sort of equipment up and down the country on as yet insufficient evidence, will affect patient choice somewhere else, and may result in considerable wastage down the line if the 10 year results show problems.

However, in some parts of the world where daily attendance for radiotherapy is impossible due to distance etc, one-off intra-operative radiotherapy could be both safer and more effective than no radiotherapy?

Patients need a balanced view on this. Intrabeam may well be the future – but the future is not here yet.

V Trustee (on behalf of ICPV Members)

7 August 2014

Response to Appraisal Consultation Document (ACD) for Multiple Technology Appraisal of INTRABEAM Photon Radiosurgery System for Adjuvant Treatment of Early Breast Cancer from the Institute of Physics and Engineering in Medicine (IPEM)

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The use of INTRABEAM for IORT represents a radical approach to breast cancer management, and one that is not without controversy. Therefore clear guidelines from NICE should clarify the evidence currently available, and provide a pragmatic approach for future implementation.

Clinical effectiveness

The committee highlighted that non-inferiority of this technique at 5 years has not been proven, since the median follow up is much less. In addition, the excess of cardiac deaths is unlikely to be due to differences in radiation dose[1]. However, the counter-suggestion that differences were due to age between the two cohorts also appears to be unfounded. Further follow up is required, and it would be helpful if the TARGIT trial could publish data on the original cohort of 2232 patients with follow up for five years (expected to have occurred in April 2013[2]), and also on the mean heart doses delivered to the external beam arm of the trial. However, as the recurrence rates are low in absolute terms, the committee concluded that this technique should be offered as an option for adjuvant treatment of early invasive breast cancer, given the strong patient preference, so long as these uncertainties are clearly explained and patients are entered into a registry for further data collection. Such a register has already been started at the Royal Free Hospital, and should be mandated on a national scale. It should also be emphasised that only selected patients are appropriate for this treatment, and clear guidelines made available to all patients.

Cost effectiveness

Detailed and thorough modelling was performed by SHTAC, which showed that the effectiveness and costs were the same for INTRABEAM IORT and EBRT in 15 fractions, within the uncertainties of the model. Often IORT has been advertised as much cheaper than conventional options, but this first UK-specific analysis shows there is little difference between the two. There was some debate about the inclusion of capital costs in the analysis. However, tariffs for EBRT have included the capital costs of a linac, since there is no longer centralised funding for this equipment. In a recent NIHR report (HTA 2010[3]), the costs of prostate radiotherapy were calculated from a detailed breakdown of the resources required, and the values closely reflected current tariffs.

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[1] It is also notable that differences were only seen in the pre-pathology arm, whereas the EBRT treatment (control arm) should be identical in both strata. This suggests confounding factors are the reason for the difference, rather than differences between IORT and EBRT.

[2] Vaidya et al. *Lancet* (2010) stated a median follow up of 26 months in May 2010. The full cohort of 3351 patients had a median follow-up of 29 months in June 2012, so would be expected to reach 5 years follow up in Jan 2015.

[3] Hummel et al. *Health Technology Assessment* (2010) 14:47 . Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation: Appendix 6.

In addition, since there are very few INTRABEAM units currently available in the UK, an NHS trust would have to consider the capital expenditure as part of their costs. Therefore, it is reasonable to include capital costs on both sides, and INTRABEAM is not cheaper than EBRT when these are included.

Implementation

There are four potential models for implementation of this technique across the UK:

1) Large acute cancer centre - Treatments are delivered on site at an existing large radiotherapy centre. This has the advantage of greater resources available to support the technique, but there may be more demand for theatre time and a heavy routine workload.

2) Small existing radiotherapy centre - a smaller centre may have more flexibility to accommodate this new technique, but may also have fewer staff and so commissioning time may be prolonged. Also, the cost equality of INTRABEAM was for a centre delivering at least 100 treatments per year to a catchment area of in excess of 1 million, so it may be better to concentrate units in large and geographically diverse centres.

3) Small district hospital supported by existing radiotherapy centre - staff would travel to the district hospital from the radiotherapy centre increasing resources from the latter, but allowing greater access for the patients to their local hospital. The same considerations for throughput also apply however. An MPE should be closely involved (see below).

4) Privately run service (as “any qualified provider” to an NHS hospital) - a portable service is offered to some private centres with a different intraoperative device[4]. If such a service was available for INTRABEAM, then it could be used by NHS hospitals, without having to invest in their own capital equipment.

Whatever model is followed there will need to be a period of equipment commissioning, staff training and initial clinical implementation. It is recommended that this should be at least 3-6 months after the equipment is delivered, and at least 6-12 months from the publication of the guidance. In addition, funding of this new technology should include dedicated staff for commissioning and initial installation. Although in the long term the resources required may be the same as for conventional (EBRT) treatment, in the short term extra physics staff will be needed to establish the service. Recruitment and training of these staff should be factored into the implementation time. It is also suggested that radiographers are used to provide the routine service. If the service is at a remote site, then one registered clinical scientist and one radiographer should be present. If on the same site, then two radiographers may be used as the operators, as long as a registered clinical scientist is available on site if needed. In all situations, a Medical Physics Expert (MPE) “must be closely involved in every therapeutic medical exposure” (IRMER 2000 legislation). In practice this means they should be contactable during treatment, either on- or off-site.

David Eaton and Claire Birch
on behalf of IPEM *12th August 2014*

Approved by Wendy Waddington (Director of Science, Research and Innovation Council)

[4] http://www.dha.co.uk/IORT/iort.html

Multiple Technology Appraisal (MTA): INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer

Response on behalf of the Radiotherapy Clinical Reference Group

Summary of Response

- The Radiotherapy CRG's view is that the clinical effectiveness of IORT is, as yet, unproven and that the NICE recommendation has been based on a single, immature, methodologically flawed study
- The cost effectiveness analysis does not reflect likely developments in UK breast radiotherapy practice over the next 5-10 years.
- The training costs and capital required to implement the guidance as it stands have been underestimated and would be a costly financial risk for the NHS and divert funding for existing services.
- This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices.
- The Radiotherapy CRG does not consider the NICE recommendations to be a suitable basis for guidance to the NHS
- The Radiotherapy CRG does not support the use of the INTRABEAM for the delivery of IORT in the adjuvant treatment of early breast cancer outside of well designed and conducted clinical trials.

Clinical Effectiveness

- The appraisal has been based on a single RCT (TARGIT A) with inadequate follow up.

In this good prognosis group of patients with breast cancer, it is the clear dominant clinical and professional opinion that a minimum of 5 years of follow up should be expected before any changes to policy are implemented. The TARGIT trial has reported with a median follow up of the whole cohort of only 2 years and 5 months.

- Local recurrence is higher with IORT

At the initiation of the TARGIT study local recurrence rates were commonly reported of approximately 6% and it was on this basis a non-inferiority threshold of 2.5% was determined. With advances in treatment an expected local recurrence rate would be about 2%. The results of the TARGIT A trial allow for an absolute increased risk of local recurrence of 2.5% to be classified as non-inferior. In practical terms, with inadequate follow duration available now, this would allow a doubling of the risk of local recurrence for patients. Given the most likely salvage treatment would be mastectomy this would be of huge consequence for patients. It effectively allows a doubling of the failure rate for breast conservation strategy for patients. There is wider evidence of higher mastectomy rates for partial breast irradiation with the ELIOT trial and other older and US insurance based registration studies. The appraisal consultation document states that 'the committee therefore concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven' (4.4.6). The Radiotherapy CRG's view is that a

recommendation for IORT as a treatment option should not be made until the mature results of the TARGIT trial are published and non-inferiority is proven.

- The TARGIT A trial methodology

The appraisal consultation document does not fully reflect the concerns regarding the methodological flaws of the TARGIT A trial raised by the expert members of the appraisal committee. The statistical method of the trial was questioned substantially with the resignation of the chair of the Data Monitoring Committee and subsequent critical correspondence within the Lancet

- Positive margins

There is uncertainty about what are safe options of treatment if the pathology, post immediate IORT, demonstrates positive circumferential margins.

- Current EBRT is safe and effective

Breast radiotherapy using forward planned Intensity Modulated Radiotherapy (IMRT) is very safe and effective treatment offering both a low local recurrence rate and successful breast conserving option with minimal risks. Modern techniques of external beam radiotherapy have a substantially lower risk relating to cardiac events and other side effects. It should be noted that there was no quality control of the EBRT delivered within the TARGIT A trial.

Partial breast irradiation (PBI) reduces irradiation of normal tissue, potentially lowering late normal tissue effects and improving quality of life. IORT is only one of a number of techniques for delivering PBI. PBI can be delivered simply by all radiotherapy centres in the UK using EBRT and the results of the UK IMPORT LOW study testing whole breast radiotherapy vs PBI are awaited.

Cost Effectiveness

- The EBRT comparator is not future proofed for UK breast radiotherapy practice.

A large UK randomised trial (FAST FORWARD), has completed accrual, testing 15 fractions over 3 weeks versus 5 fractions over just 1 week. If this were to show non-inferiority, it would be likely that 5 fractions would become the UK standard of care within the next 5-10 years and would significantly impact the cost effectiveness modelling in favour of EBRT. One week of radiotherapy would also counterbalance important arguments made about patient experience, convenience, travel times and QOL put forward in favour of IORT. The potential future combination of hypofractionation with PBI using EBRT offers an alternative to IORT that all UK radiotherapy centres could deliver without additional investment in infrastructure.

- Omission of radiotherapy has not been considered in the economic model

In any informed discussion with patients in this low risk group could equally include the omission of radiotherapy. This has been tested in a number of RCTs including the UK PRIME II study. This study shows a local recurrence risk of 4.1% at 5 years with no radiotherapy. This is not fully considered in the appraisal.

- Pathway assumptions based on the TARGIT trial underestimate the use of axillary radiotherapy

For significant numbers of patients where greater prognostic information will not inform decision making about systemic treatment options, it is clear from the AMAROS trial that axillary

radiotherapy is an equivalent option in terms of local control compared to axillary clearance but with less oedema side effects following on from axillary nodal sampling. The trend is towards the use of more radiotherapy in conjunction with breast conserving therapy. Significant numbers of patients will have axillary nodal irradiation as a subsequent treatment and so arguments about saving 15 visits of social and psychological impact for breast radiotherapy do not apply in this group. .

- Impact on surgical pathways

Expert physics advice to the Radiotherapy CRG is that necessary routine quality assurance for the Intrabeam device requires 30-45 mins prior to each theatre session. Typically standard operation times are prolonged by 45-60 mins for the required treatment (beam on) time (30 minutes) and applicator placement, preparation and clear up (30 minutes). This will significantly impact on theatre throughput and capacity.

- The workforce requirements for the safe delivery of IORT have been underestimated

The radiotherapy CRG is clear that delivery of IORT should be by an appropriately trained multi-professional team including clinical oncologists, radiographers, surgeons and physicists. Two operators under IRMER would be required for checking/setting up purposes. Radiotherapy should be prescribed by a clinical oncologist. The costing of extra surgical lists, reduced theatre throughput as well as extra medical physics, radiographer and clinical oncology time are simplistic and do not place them in the context of NHS practice.

The radiotherapy CRG supports the routine national collection of high quality data on clinical outcomes and this will require additional resource that has not been considered in the model.

- The cost analysis underestimates equipment requirement

If multiple patients are treated with IORT in a single theatre session there is a likelihood that the same applicator size may be required. The applicator cannot be used without re-sterilizing and therefore it is likely that additional applicators would be required.

- Clinical input into the economic model

The Radiotherapy CRG note that NICE have developed a de-novo economic model. What was the level of expert clinical advice taken about the assumptions in economic and clinical pathways? Given the complexity of the subject and uncertainties was this robust? For example the need for axillary radiotherapy was not modelled.

Implications for Implementation into NHS Practice

- Inequity of Care

Rightly patient choice has been a priority in this appraisal. However, there is a risk of an undue weight being applied in many areas in the evaluation on hope and expectation rather than on evidence. Of course patients would rather avoid extra visits for radiotherapy but if the alternative is a potential doubling their risk of mastectomy is this a successful strategy? Many years of clinical trials and improvements in surgery and radiotherapy have made breast conserving options a very safe and predictable one.

In a balanced discussion of treatment options a significant proportion of patients will decline a treatment which potentially doubles their risk for local recurrence. Whilst there are patients for whom IORT will be an attractive option, most patients will opt for the treatment offering highest probability of disease control which is EBRT.

This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices.

- Wider use of IORT will have detrimental effects on surgical pathways

The consequence of wider use of IORT has not been taken into account in the surgical pathway with longer operating times, reduced throughput and potential impact on Cancer Waiting Time Targets. Current pressures on CWT compliance suggest that increased demand and pressure early in the treatment pathway may be undeliverable. Radiotherapy 31 day waiting times are no longer a critical problem.

Surgical referral pathways would also require reconfiguration as the radiotherapy is delivered at the time and place of surgery. It is unlikely that IORT would be available at every radiotherapy centre and the impact for patient choice about surgeon and place of surgery needs to be taken into consideration. There is a risk of fragmentation of services with IORT being delivered outside an integrated care pathway.

National Institute for Health and Care Excellence

INTRABEAM Radiotherapy System for the adjuvant treatment of early breast cancer [ID618]

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for (Breast cancer (early) - Intrabeam targeted intraoperative radiotherapy) [618]

Nurses caring for people with Breast Cancer have reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below:

i) **Has the relevant evidence been taken into account?**

One of our reviewers feels that with modern oncoplastic breast cancer surgery, the intrabeam radiotherapy may not compatible. Our members have highlighted the importance of remodelling the breast disc at surgery to leave an attractive looking breast. Concerns have been raised that the Intrabeam probe has to be inserted directly into the 'hole' that is made by the surgeon – leaving a scar above the tumour. This means a larger visible scar may be left.

RCN members concerns focus on the cosmetic outcome for women; a (potential) long term reminder of their treatment each time they look at their breast

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

iv) **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?**

The Intrabeam Radiotherapy System for the adjuvant treatment of breast cancer: NICE Appraisal Committee's preliminary recommendations

Comments of behalf of the NCRI Breast Clinical Studies Group, Chair of NCRI Clinical & Translational Radiotherapy Research Working Group, Royal College of Physicians, Association of Cancer Physicians and Joint Collegiate Council for Oncology

The main purpose of this document is to draw attention to major concerns as to the scientific validity of the analyses, which has led to a large multidisciplinary body of UK breast cancer experts to express concern that we could well observe an excess risk of local breast cancer relapse in women treated with Intrabeam over the next 10 years. As a result, we have major reservations and consider guidance supporting the adoption of this technique for routine practice on the basis of incomplete data to be premature.

Background and general comments

Well designed trials with many years of follow up have firmly established breast conservation and whole breast radiotherapy as a safe alternative to mastectomy

Radiotherapy is currently part of standard treatment for the many thousands of women with early breast cancer who receive breast conservation surgery. The benefits and adverse effects of radiotherapy have been well documented by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis of >10,000 patients randomised into trials of breast conservation surgery (BCS) with and without radiotherapy over the last 30 years [1]. The 2011 EBCTCG systematic overview estimates that radiotherapy after BCS reduces the relative risk of any first cancer relapse by 52% and breast cancer mortality by 18% across all risk groups [1].

Falling absolute relapse rates raises the possibility of partial breast radiotherapy or avoidance of radiotherapy for subgroups at low and very low risk of recurrence

In the last decade, earlier detection, and improvements in the multidisciplinary team approach to patient management (radiology, surgery, pathology, adjuvant systemic treatment and radiotherapy) has dramatically improved outcomes for women with breast cancer [2] and overall the *absolute* long-term risk of local relapse following BCS and radiotherapy is very low. This raised the hypothesis that specific subgroups with predicted low risk of recurrence could be treated with partial breast radiotherapy or avoid radiotherapy completely, with acceptable long-term recurrence rates and minimal side effects. As a result, several randomised controlled trials were developed to address this hypothesis.

Long-term follow up is required to establish the efficacy of partial breast radiotherapy and complete avoidance of radiotherapy

In the same way that BCS and whole breast radiotherapy was established as a safe alternative to mastectomy for selected patients, trials of partial breast radiotherapy or avoidance of radiotherapy require long-term follow up information regarding both recurrence rates and toxicity before practice can be confidently changed. Studies have shown that in contrast to higher-grade breast cancers, lower grade tumours tend to have a similar rate of recurrence in the 5-10 years following diagnosis as the first 5 years [3,4]. In addition, radiotherapy side effects can continue to develop over many years following completion of treatment [5]. As a result, the majority of UK breast radiotherapy trials are planned with a first analysis of efficacy at 5 years, but follow up is continued until 10 years post-treatment [6-8]. Many partial breast

radiotherapy trials are still in follow up, such the as the UK IMPORT LOW study, which tested partial breast radiotherapy using external beam radiotherapy (EBRT) against whole breast radiotherapy with both arms utilising the current UK standard dose and fractionation [7]. The trial closed in 2011 and the five-year results will be presented in 2016/17.

The only large randomised trial, other than TARGIT, to report 5-year recurrence rates is the intraoperative radiotherapy (IORT) ELIOT study. 1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between 2000 and 2007 [9]. After a medium follow-up of 5.8 years (IQR 4.1–7.7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had had an ipsilateral breast tumour recurrence (IBTR) ($p<0.0001$). The 5-year event rate for IBRT was 4.4% (95% CI 2.7–6.1) in the intraoperative radiotherapy group and 0.4% (0.0–1.0) in the external radiotherapy group (hazard ratio 9.3 [95% CI 3.3–26.3]). The local recurrence rates continued to rise in a linear fashion for both study arms for those patients follow up beyond 5 years. The relapse rate was higher in the IORT arm compared to TARGIT, despite the effectively higher dose to a larger volume of breast tissue.

In addition, a study investigating avoidance of radiotherapy has been published in abstract form. The PRIME II trial randomised 1479 good prognosis breast cancer patients (defined as aged ≥65 years with primary invasive cancer ≤3cm, grade 1/2, node negative with clear margins following BCS). Recent early results shows 1.3% and 4.1% local relapse rates by 5 years with and without radiotherapy [10]. The authors state that mature 10-year data will be presented in due course, which will add to the growing body of evidence suggesting that avoidance of breast radiotherapy in certain subgroups of patients is a reasonable treatment option. It is likely that further studies will be required in order to show definitively which subgroups patients can safely avoid radiotherapy.

Patient choice is paramount, but this most be informed and based on high quality trials with adequate follow up

Patients have an obvious right to make choices about their treatment, but treating clinicians must be able to discuss the pros and cons of any therapy including no treatment at all, based on good evidence. At present, there is insufficient evidence to offer partial breast radiotherapy or no breast radiotherapy as standard care within the NHS [11]. Given the short median follow up of the TARGIT study of only 2 years 5 months, the evidence reported is too premature to allow informed discussion regarding the long term efficacy and safety of Intrabeam. This sentiment is reflected in the statement from patient's groups published in the NICE Appraisal Committee's preliminary recommendations:

"Patient groups highlighted that although early breast cancer is treatable it might recur and spread to other parts of the body. They noted that the psychological burden of the disease is high for the patient and their family and that people want to ensure that the have the best chance of a future free from cancer."

Our NCRI patient advocates have made the following statement:

"Current and potential patients need to be fully informed partners in their treatment decisions and to understand that collection of follow up data is needed for many years to assess safety of any treatment. Patient choice is important of course but forcing Trusts to spend money on this sort of equipment up and down the country on as yet insufficient evidence, will affect patient choice somewhere else, won't it, and may result in considerable wastage down the line if the 10 year results show problems."

Specific comments regarding TARGIT trial and NICE Appraisal Committee's preliminary recommendations

1. Lack of validity of TARGIT-A analysis

There are major criticisms of the statistical analyses, which affect the validity of the presented results. i.e. Intrabeam cannot be considered to be non-inferior to external beam radiotherapy (EBRT). In summary:

(i) Survival analysis has been used to test inferiority of local recurrence, but the median follow-up for the trial is only 2 years and 5 months. This is insufficient to provide robust estimates of risk of recurrence.
(ii) Comparison of binominal proportions has also been used to test inferiority of local recurrence, but due to the inadequate follow up, the number of relapses is likely to be considerably less than expected with a median follow up of 5 years.
(iii) The authors try to address the issue of inadequate follow up by presenting results for 3 cohorts of patients with varying lengths of median follow-up: it is stated that the results illustrate the stability of the treatment effect over time. This is flawed as the cohorts are nested within each other and so in effect, the patients with the longest follow-up have been analysed three times.

These points have also been made by Professor Jack Cuzick former Chair of the TARGIT Independent Data Monitoring Committee who has since resigned [12].

In addition, as the median follow up is only 2 years 5 months this figure *does not* represent a true 5-year local recurrence rate. It must also be noted that these patients with lower risk of recurrence (typically lower grade, and oestrogen receptor positive) have a linear risk of local recurrence, which can rise steadily year on year as previously stated [3,4]. Therefore, these 5-year local recurrence rates are misleading and almost certainly under represent the real risk at 5 years.

The Intrabeam device delivers a very low dose (5 Gy) compared to standard EBRT, and to just a 1 cm rim around the tumour bed. This could be considered as sub-therapeutic compared with whole breast EBRT. Therefore, it is probable that the results from the use of Intrabeam (which do demonstrate a recurrence risk which is twice as great as standard EBRT) may be closer to the recurrence risk following no radiotherapy at all. It is probable that the true 5-year recurrence rates (all patients reaching 5-year follow up) with TARGIT may mirror the results from PRIME II: 1.3% and 4.1% local relapse rates by 5 years with and without radiotherapy.

2. Intrabeam does not increase QALYs

The provisional report states that:
"…concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT."

There is no proven benefit to the patient (other than anecdotal) in terms of quality of life for Intrabeam and the slightly lower costs add little benefit to the NHS. Quality of life scores with modern EBRT are in general very high and the majority of people are able to continue with normal daily activities during and after EBRT [13].

3. No evidence that Intrabeam mode of delivery is advantageous

The preliminary recommendations state that:
"The Committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed…"

As stated previously, a very low dose of radiation is delivered to a 1 cm rim around the excision cavity: there is no evidence that this is advantageous compared with standard EBRT that treats the whole breast. In patients at higher risk of recurrence (not candidates for Intrabeam), the tumour bed is treated with an additional boost. This is guided by surgical clips implanted into the tumour bed at the time of surgery under direct vision and is recommended by the Association of Breast Surgeons as best practice [14]. Migration of these clips is extremely uncommon and use of clips to guide EBRT has been shown to be highly accurate [15]. It is not appropriate to recommend a treatment for NHS use on the basis of an unproven 'potential' benefit.

4. Intrabeam is not the only alternative for patients unable to have standard whole breast EBRT

The preliminary recommendations state that Intrabeam represents an alternative to patients for whom whole breast EBRT is unsuitable, e.g. those who cannot raise their arm and that the only other treatment option would be mastectomy. Firstly, this situation is extremely uncommon given the modern EBRT immobilisation devices that provide good arm support. Secondly, mastectomy is unusual in this setting for patients at low risk of recurrence. Alternative options are already available for patients include treating with partial breast EBRT with either photons or electrons with the arm down (using standard dose and fractionation) or avoiding radiotherapy completely, based on PRIME II results. Although both of these treatments are non-standard at present and would require close follow up, they do provide alternative treatment options.

5. Treatment with a combination of Intrabeam and EBRT causes greater side effects

Around 15% of patient within TARGIT-A required a combination of Intrabeam and whole breast EBRT due to adverse histology following breast conserving surgery. The provisional guidelines state:

"If there were adverse histological features identified in the cancer cells at final pathology after treatment with Intrabeam and subsequent EBRT was recommended, a further external boost dose would not be needed."

However, the combination of Intrabeam and whole breast radiotherapy has been shown to produce high levels of late normal tissue fibrosis: in the sub-analysis (Arm A IORT vs. Arm A IORT + WBRT vs. Arm B WBRT), fibrosis had a cumulative rate of 5.9 versus **37.5** versus 18.4 %, respectively at 3 years [16]. This high level of toxicity raises concerns about the use of Intrabeam as a boost treatment in combination with whole breast radiotherapy compared with an EBRT boost [17].

6. Lack of appropriate research governance for the TARGIT trial

We have serious concerns over the conduct of the TARGIT trial as follows:

(i) Lack of effective regulatory research framework, which allowed submission of the final manuscript for publication despite the strong disapproval of the Chair of the Independent Data Monitoring Committee, Professor Jack Cuzick, who expressed concerns that the manuscript distorted the findings of the study

(ii) Errors by the TARGIT authors in applying the research findings of Professor Sarah Darby and colleagues and thus wrongly attributed causes of excess non-breast cancer mortality to standard external beam breast radiotherapy

Summary

It is the opinion of the Breast CSG and other UK breast cancer experts that the TARGIT-A analysis is too limited and thus the efficacy of Intrabeam radiotherapy is currently unproven. In addition, it has not been proven to increase QALYs, has little if any cost savings for the NHS, its mode of delivery has not been shown to offer an advantage, it is not the only alternative other than mastectomy for patients unable to have whole breast EBRT, and treatment in combination with EBRT causes unacceptable toxicity. Until further mature data has been presented it should not be recommended as standard care to patients outside the context of an ethically approved research study.

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CHIEF EXECUTIVE OFFICER RICHARD EVANS

THE SOCIETY AND COLLEGE OF RADIOGRAPHERS

Our ref: NICE/INTRABEAM/CB&SJ

8th August 2014.

Dear Sir

Multiple Technology Appraisal (MTA): INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer

Response on behalf of the Society and College of Radiographers

The Society and College of Radiographers is pleased to be able to provide a detailed response to the above consultation. We are very concerned by the recommendations within this guideline and equally concerned that the recommendations from this draft appear to have reached the national press ahead of a final decision from NICE. This has the potential to falsely raise patient expectations. We are concerned about this and the process.

For information the Society and College of Radiographers has fully contributed to the NHS England Radiotherapy Clinical Reference Group and the Radiotherapy Board responses, and this response summarises our views from the Society and College of Radiographer, including the NHS England Radiotherapy Clinical Reference Group response.

Summary of Response

- The Society and College of Radiographers view is that the clinical effectiveness of IORT is, as yet, unproven and that the NICE recommendation has been based on a single, immature study.
- The cost effectiveness analysis does not reflect likely developments in UK breast radiotherapy practice over the next 5-10 years (see notes below*).
- The training costs and capital required to implement the guidance as it stands have been underestimated and would be a costly financial risk for the NHS and divert funding for existing services.
- This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices.
- The Society and College of Radiographers does not consider the NICE recommendations to be a suitable basis for guidance to the NHS
- The Society and College of Radiographers does not support the use of the INTRABEAM for the delivery of IORT in the adjuvant treatment of early breast cancer outside of well designed and conducted clinical trials.

We have included below some very specific comments related to points within the document and include following these three points, the summary to which we contributed to as an affiliated organisation of the NHS England Radiotherapy Clinical Reference Group.

*The time estimated to deliver the treatment has been discussed in this consultation document; however we feel this is underestimated as in reality the time taken to deliver the treatment varies depending on the size of the applicator. Realistically the size of the applicator will always be 3cm or above, and the beam on time can be any time between 25-40 minutes (for the 5cm applicator). This does not take into account the time it takes for the surgeon to choose the applicator, do the purse string suture, drape the machine, as well as dismantling the equipment afterwards. In reality the whole process adds about an hour to the surgical procedure whereas radiation delivery time in the consultation has been estimated as 20-30mins in total.

**We have particular concerns in circumstances where this equipment is purchased and used in hospitals where there are not any onsite radiotherapy facilities. This potentially introduces difficulties in ensuring an adequate 'radiotherapy pathway of care' for patients receiving their radiotherapy using this equipment. In these circumstances there will be an absence of an oncology trained health care professional such as a clinical oncologist or therapeutic radiographer when the therapeutic dose of radiation is delivered and therefore there will not be the expertise to ensure adequate radiation records should the patient require additional radiotherapy using External Beam Radiotherapy and the management of radiotherapy side effects could be compromised. Centres using IORT within the ongoing trial have attempted to create a pathway that follows the relevant MDT so guaranteeing that the radiotherapy centre is informed and aware of these patients and thus ensuring adequate provision with regard to these aspects of care.

*** We would also like to bring to your consideration that the NHS England Radiotherapy Clinical Reference Group is currently in the process of additional comprehensive radiotherapy service mapping to inform work within NHS England and that the data from this work must be taken into considered before being able to make the assumptions on page 21 regarding the likelihood of the introduction of Intrabeam in freeing up existing radiotherapy capacity.

With very best wishes

Charlotte Beardmore Acting Director of Professional Policy
Sarah James Professional Officer in Radiotherapy.

Multiple Technology Appraisal (MTA): INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer

Response on behalf of the NHS England Radiotherapy Clinical Reference Group

Summary of Response

- The Radiotherapy CRG's view is that the clinical effectiveness of IORT is, as yet, unproven and that the NICE recommendation has been based on a single, immature, methodologically flawed study

- The cost effectiveness analysis does not reflect likely developments in UK breast radiotherapy practice over the next 5-10 years.

- The training costs and capital required to implement the guidance as it stands have been underestimated and would be a costly financial risk for the NHS and divert funding for existing services.

- This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices.

- The Radiotherapy CRG does not consider the NICE recommendations to be a suitable basis for guidance to the NHS

- The Radiotherapy CRG does not support the use of the INTRABEAM for the delivery of IORT in the adjuvant treatment of early breast cancer outside of well designed and conducted clinical trials.

Clinical Effectiveness

- The appraisal has been based on a single RCT (TARGIT A) with inadequate follow up.

In this good prognosis group of patients with breast cancer, it is the clear dominant clinical and professional opinion that a minimum of 5 years of follow up should be expected before any changes to policy are implemented. The TARGIT trial has reported with a median follow up of the whole cohort of only 2 years and 5 months.

- Local recurrence is higher with IORT

At the initiation of the TARGIT study local recurrence rates were commonly reported of approximately 6% and it was on this basis a non-inferiority threshold of 2.5% was determined. With advances in treatment an expected local recurrence rate would be about 2%. The results of the TARGIT A trial allow for an absolute increased risk of local recurrence of 2.5% to be classified as non-inferior. In practical terms, with inadequate follow duration available now, this would allow a doubling of the risk of local recurrence for patients. Given the most likely salvage treatment would be mastectomy this would be of huge consequence for patients. It effectively allows a doubling of the failure rate for breast conservation strategy for patients. There is wider evidence of higher mastectomy rates for partial breast irradiation with the ELIOT trial and other older and US insurance based registration studies. The appraisal consultation document states that ‘the committee therefore concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven’ (4.4.6). The Radiotherapy CRG’s view is that a recommendation for IORT as a treatment option should not be made until the mature results of the TARGIT trial are published and non-inferiority is proven.

- The TARGIT A trial methodology

The appraisal consultation document does not fully reflect the concerns regarding the methodological flaws of the TARGIT A trial raised by the expert members of the appraisal committee. The statistical method of the trial was questioned substantially with the resignation of the chair of the Data Monitoring Committee and subsequent critical correspondence within the Lancet

- Positive margins

There is uncertainty about what are safe options of treatment if the pathology, post immediate IORT, demonstrates positive circumferential margins.

- Current EBRT is safe and effective

Breast radiotherapy using forward planned Intensity Modulated Radiotherapy (IMRT) is very safe and effective treatment offering both a low local recurrence rate and successful breast conserving option with minimal risks. Modern techniques of external beam radiotherapy have a substantially lower risk relating to cardiac events and other side effects. It should be noted that there was no quality control of the EBRT delivered within the TARGIT A trial.

Partial breast irradiation (PBI) reduces irradiation of normal tissue, potentially lowering late normal tissue effects and improving quality of life. IORT is only one of a number of techniques for delivering PBI. PBI can be delivered simply by all radiotherapy centres in the UK using EBRT and the results of the UK IMPORT LOW study testing whole breast radiotherapy vs PBI are awaited.

Cost Effectiveness

- The EBRT comparator is not future proofed for UK breast radiotherapy practice.

A large UK randomised trial (FAST FORWARD), has completed accrual, testing 15 fractions over 3 weeks versus 5 fractions over just 1 week. If this were to show non-inferiority, it would be likely that 5 fractions would become the UK standard of care within the next 5-10 years and would significantly impact the cost effectiveness modelling in favour of EBRT. One week of radiotherapy would also counterbalance important arguments made about patient experience, convenience, travel times and QOL put forward in favour of IORT. The potential future combination of hypofractionation with PBI using EBRT offers an alternative to IORT that all UK radiotherapy centres could deliver without additional investment in infrastructure.

- Omission of radiotherapy has not been considered in the economic model

In any informed discussion with patients in this low risk group could equally include the omission of radiotherapy. This has been tested in a number of RCTs including the UK PRIME II study. This study shows a local recurrence risk of 4.1% at 5 years with no radiotherapy. This is not fully considered in the appraisal.

- Pathway assumptions based on the TARGIT trial underestimate the use of axillary radiotherapy

For significant numbers of patients where greater prognostic information will not inform decision making about systemic treatment options, it is clear from the AMAROS trial that axillary radiotherapy is an equivalent option in terms of local control compared to axillary clearance but with less oedema side effects following on from axillary nodal sampling. The trend is towards the use of more radiotherapy in conjunction with breast conserving therapy. Significant numbers of patients will have axillary nodal irradiation as a subsequent treatment and so arguments about saving 15 visits of social and psychological impact for breast radiotherapy do not apply in this group. .

- Impact on surgical pathways

Expert physics advice to the Radiotherapy CRG is that necessary routine quality assurance for the Intrabeam device requires 30-45 mins prior to each theatre session. Typically standard operation times are prolonged by 45-60 mins for the required treatment

(beam on) time (30 minutes) and applicator placement, preparation and clear up (30 minutes). This will significantly impact on theatre throughput and capacity.

- The workforce requirements for the safe delivery of IORT have been underestimated

The radiotherapy CRG is clear that delivery of IORT should be by an appropriately trained multi-professional team including clinical oncologists, radiographers, surgeons and physicists. Two operators under IRMER would be required for checking/setting up purposes. Radiotherapy should be prescribed by a clinical oncologist. The costing of extra surgical lists, reduced theatre throughput as well as extra medical physics, therapeutic radiographers and clinical oncology time are simplistic and do not place them in the context of NHS practice.

The radiotherapy CRG supports the routine national collection of high quality data on clinical outcomes and this will require additional resource that has not been considered in the model.

- The cost analysis underestimates equipment requirement

If multiple patients are treated with IORT in a single theatre session there is a likelihood that the same applicator size may be required. The applicator cannot be used without re-sterilizing and therefore it is likely that additional applicators would be required.

- Clinical input into the economic model

The Radiotherapy CRG note that NICE have developed a de-novo economic model. What was the level of expert clinical advice taken about the assumptions in economic and clinical pathways? Given the complexity of the subject and uncertainties was this robust? For example the need for axillary radiotherapy was not modelled.

Implications for Implementation into NHS Practice

- Inequity of Care

Rightly patient choice has been a priority in this appraisal. However, there is a risk of an undue weight being applied in many areas in the evaluation on hope and expectation rather than on evidence. Of course patients would rather avoid extra visits for radiotherapy but if the alternative is a potential doubling their risk of mastectomy is this a successful strategy? Many years of clinical trials and improvements in surgery and radiotherapy have made breast conserving options a very safe and predictable one.

In a balanced discussion of treatment options a significant proportion of patients will decline a treatment which potentially doubles their risk for local recurrence. Whilst there are patients for whom IORT will be an attractive option, most patients will opt for the treatment offering highest probability of disease control which is EBRT.

This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices.

- Wider use of IORT will have detrimental effects on surgical pathways

The consequence of wider use of IORT has not been taken into account in the surgical pathway with longer operating times, reduced throughput and potential impact on Cancer Waiting Time Targets. Current pressures on CWT compliance suggest that increased

demand and pressure early in the treatment pathway may be undeliverable. Radiotherapy 31 day waiting times are no longer a critical problem.

Surgical referral pathways would also require reconfiguration as the radiotherapy is delivered at the time and place of surgery. It is unlikely that IORT would be available at every radiotherapy centre and the impact for patient choice about surgeon and place of surgery needs to be taken into consideration. There is a risk of fragmentation of services with IORT being delivered outside an integrated care pathway.

To Dr. Jane Adam and the NICE Appraisal Committee:

It is marvellous that you have granted provisional approval for Intrabeam-IORT. I could not be more delighted - or more grateful. And I could not be more sure that your decision is the right one. But I am very aware that final approval has yet to be given.

The Evaluation Report seemed to me – and I am new to such documents - to be extremely thoughtful and comprehensive. Of course I must confine myself to what Intrabeam-IORT offers the patient. You ask if all the relevant evidence has been taken into account? Even I can see that at least two figures - the suggested number of prospective patients of 126 (p.18) and 16% of women diagnosed (p.22) - are somewhat low and therefore not accurate. This of course is very important because of the financial implications.

To my layman's eye, the only other source of concern was the need expressed for a national register. To set one up specifically would surely be both complex and expensive, and could hold up the use of Intrabeam-IORT in the NHS. This would be a cruel loss for women who might otherwise benefit very soon. I very much hope that this can be easily resolved – a workable solution might be to use the existing (and excellent) National Cancer Registration Service?

I was surprised to learn of the criticisms made by detractors of Intrabeam-IORT. Having read several of their comments I would like to make my own, if I may, in response to any you might have received.

I find it very disturbing – and very strange – that the criticisms are all about the delivery system. They address only the possible problems and (arguable) risks of this. There is talk of economic modelling, staffing resources, extra

theatre time….. But there seems to be no appreciation of the benefits of Intrabeam-IORT for the user.

Why has the patient point of view not been acknowledged by the critics? There is no reference by them anywhere that I can see (and forgive me if I have missed something) to quality of life; to the saving of stress in relationships; to work and careers uninterrupted; to leisure activities still pursued…
Are they unaware of – or indifferent to – these issues?

The answer, of course, is that for the Intrabeam-IORT patient, there is either no downside or so little as to be negligible. So - nothing for the critics to get their teeth into. No terrible stories of pain and suffering and ongoing medical problems resulting from radiation damage; no recounting of days and months spent waiting for treatment. With Intrabeam-IORT, these are eliminated.

Yet still the critics criticize. So I have to ask, is medicine here for the good of the patient, or are we patients just canon-fodder for battling specialists? I would hate to think the latter was true.

I am concerned that so much negative emphasis is being put on the length of follow-up time in the TARGIT-A trial: two years five months is repeatedly cited.

TARGIT-A was a large study and of their 3,451 patients, 1,222 had a follow-up time of five years. Many are now between seven and twelve years from their surgery and Intrabeam-IORT treatment, with no recurrence.

I was horrified to read that the suggestion that Intrabeam-IORT, with its long clinical testing and the current take-up rate worldwide, should not be permitted for use in the UK.

The argument I read claims that 'the EBRT comparator is not future proofed.' Apparently there is another promising treatment which has just started its first clinical trial and may be available at some unspecified time.

There may indeed be many wonderful new systems yet to be developed in the future – one can only hope and trust that there are. But the women for whom Intrabeam-IORT is hopefully now to be used are all over 45, and very many far older than that. For them, that future, with whatever marvellous treatment it may possibly hold, simply does not exist. They need what we have now, this minute. Sadly, the lives of these women are *not* future-proofed.

You ask if the provisional recommendations provide a suitable basis for guidance to the NHS.

I totally appreciate the need for the wording of the caution to patients from clinicians that less is known about the long-term outcomes and that the rate of local recurrence with Intrabeam could be higher than with EBRT.
However, it is my understanding that the outcomes for the relevant period are already known because radiation appears to limit the chance of cancer coming back in the breast mainly in the first five years. After that there is a small chance of the cancer returning but this happens at the same rate in those given radiotherapy as in those who had just a lumpectomy.

Could I suggest that while delivering this warning of risk – as of course they must – clinicians make sure their patients are also aware of the three main benefits that made TARGIT so important for me and so many other women?

First, that because Intrabeam-IORT delivers soft x-rays to the wound site immediately the tumour has been removed, there is no time for cancer cells to regroup. With EBRT,

weeks and often months elapse after surgery while the wound heals, while chemotherapy may be used, and then finally radiation is delivered. During all that time, if Intrabeam-IORT is not given, wound fluid provides the perfect environment for cancer cells to proliferate.

Second, that in the unlikely event of recurrence in a different part of the same breast, Intrabeam-IORT could be used again on the same breast. (EBRT cannot be repeated on the same breast because the tissues will not tolerate it. In the case of recurrence following EBRT, mastectomy - or Intrabeam-IORT - would be the only recourse. So this latter option is an additional bonus of the treatment.)

Third, that patients receive the reassurance that unlike EBRT, there is no risk of Intrabeam-IORT adversely affecting and damaging other organs – heart, lungs, oesophagus. This because of precise targeting of the tumour site alone, and the use of soft x-rays.

You ask about any adverse impact on any patient with a particular disability or disabilities.
In this instance, surely the reverse is true: Intrabeam-IORT, with its speed, accuracy and simplicity, is so user-friendly it would seem to offer even more advantages to suitable candidates with almost any physical or indeed mental disabilities. I see your Report notes the possibly limited ability of some patients to comprehend the details. But I cannot think this would be any more of a problem than explaining current practice?

One final point: I do believe that with their decision, NICE have made a carefully considered step into the future of medical technology. I hope there is a way to reach out to all the clinicians who should be involved in providing this for their patients. I've read that it can take up to ten years for any new protocol (treatment or drugs) to be fully

implemented. Too long! For the 30,000 women being diagnosed with early breast cancer every year, Intrabeam-IORT cannot come soon enough.

Below I have added brief case histories of just a handful of the women successfully treated with Intrabeam-IORT. If I carried on, I can assure you I would get more of the same responses. I now know for instance of several professional women in New York and Israel who have had this treatment in the last three years: there's an interesting (and growing) group of TARGIT fans around these days….

First, may I just recap the story of my cousin, who I mentioned at the first meeting? She is my age, a retired GP in Devon. Her breast cancer was discovered around the same time as mine, very similar, and she had standard EBRT. Her regime involved a 60 mile round trip to hospital daily for five weeks. We last talked when the Committee had just released their provisional decision.

She then confessed what I did not know - she had abandoned her radiation treatment after three weeks: she could no longer tolerate it, or face the journey and the exhaustion. And she is a doctor!
She says she now lives in dread of her next check-up.

How many other patients have made similar potentially damaging decisions?

Case Histories for Intrabeam-IORT

Individuals are not identified here. All are delighted to be included and if the Committee wishes it, are happy for their names to be given. All are well, free of disease, never relapsed.

Patient P, 60, surgery 2010:
'I found TARGIT myself – I read about it in the Ham and High. (Hampstead & Highgate Express.) Professor Tobias and Professor Vaidya put my name forward for the trial (TARGIT-A.) I jumped up and down in the air when they said yes.

I had a lumpectomy on the left side on the Thursday and I left hospital on Friday. Even straight afterwards I was glowing – my family said I looked as if I'd been on holiday. I felt fine: I was at the gym that Sunday - I did an hour on the treadmill and the bike. And I continue to go there as I always have, four times a week.'

Patient R, retired civil servant, surgery 2009 and 2011:
'I was treated at the Royal Free. I had TARGIT both times. Nothing ventured, nothing gained: if people don't go into trials, you don't move forward. The first time, I went in at 9 am, was back on the ward at 2 pm and at 4 o'clock I went home and cooked salmon for dinner. I felt a bit hot over the weekend but I was up and running.

Two years later they found cancer on the other side. That time I was in at 9.30 am and at 3.30 pm they said, you can go home. In and out in a day, both times. I told Professor Vaidya, I feel a fraud, I'm all done and dusted, I can go out, do whatever I want.
Friends said, how can you have been treated and have your operation all in a day? It's impossible.'

Patient J, 78, surgery 2008:
'The treatment is brilliant, actually brilliant. I'm very fairskinned and redhaired so I would have burned more than others with standard radiation. But with TARGIT I had no side-effects of any kind, and I'm still checked every six months.

I do think, thank God I didn't have breast cancer when I was younger – before this treatment was available – that would have altered my whole lifestyle. Now I don't give it a second thought. And this treatment should instill such confidence in younger women.'

Patient C, surgery 2007:
'The operation was easy – the worst thing was the core biopsy. Afterwards, nothing hurt. I wasn't sore, the site never hurt at all. 24 hours and I went home. I was delighted not to have a long period of radiation – that means your whole life is tied to it.'

Patient A, international academic, surgery 2014:
'I have thyroid cancer of many years standing and had radical neck surgery with many problems the previous year (2013.) Professor Tobias told me I couldn't have EBRT because of radiation overlap. TARGIT was brilliant. I went in on Thursday and by Saturday morning I was fit to leave. I had a slight pain in the armpit but the breast itself was completely free from pain. Spectacular bruising – but no pain! I was fit to do anything by the next day and was already working.

Two days after leaving hospital, on the Monday, I went downstairs to where the roofers had left a mess on the front step after doing a repair. I was out there with a Stanley knife on all fours on a baking hot day, scraping hardened asphalt for two hours – that's a measure of how I felt. There was nothing I couldn't do.'

ends

[redacted]

10 March 2015

Janet Robertson
Associate Director, NICE Technology Appraisals Programme

Dear Ms Robertson

Thank you for the email sent on 16 February and the attached letter. As discussed over the phone, we are sorry we might have misunderstood the request made at the meeting.

We were under the impression that all the requested graphs needed to be prepared using newly unblinded data. At the meeting, it was clear that unblinding is not required. Therefore, we only submitted the only statistic that was ***not*** previously published – viz. the difference between the Kaplan-Meier curves.

Thank you for arranging a meeting between yourself, Ms Pilar Pinilla-Dominguez, Professor Max Bulsara, and me on 3 March 2015. As discussed during this meeting, we were delighted that you were happy with the complete set of analyses that we had prepared.

Ms Pinilla-Dominguez was happy that we had supplied the integrated difference between the KM curves, but requested that we also supply the difference in the values for the 5-year KM estimates and the 95%CI as well, although she and you confirmed that the committee recognizes that:

- The right hand end of the curve is the one with the most uncertainty and with the widest confidence intervals.
- In the presence of censoring the K-M point estimate at a particular time point e.g., 5 years are not a simple binomial proportions, and treating them as such introduces a bias resulting in a wider confidence interval. Therefore it is inappropriate to apply the simple formula normally used to calculate the SE (and CI) of a difference between binomial proportions, viz., $\sqrt{SE1^2 + SE2^2}$ to calculate differences between such point estimates.
- These values, i.e., 5-year point estimates, should not be used to calculate the confidence interval of the difference or for testing non-inferiority.
- These values are being requested mainly for completion and will not be wrongly used to assess non-inferiority.

Having provided all the requested analyses, you felt that raw data need not be provided. We emphasized that the TARGIT-A trial investigators were very willing to supply the raw data as long as all the governance, consent, custody, data access and security issues are looked after appropriately. However, we understood that it is not necessary to supply the raw data because all the analyses requested by the committee were satisfactorily supplied.

We have now modified our response. In the following pages, we have added all the graphs and statistics requested by the committee – as of the data lock on 25 June 2012, in addition to the blinded analysis including new events until 1 October 2014.

In response to the recommendation in the draft recommendation, we have also included at the start of this document, a diagram to help patients make a shared decision along with their consultant.

We hope this is satisfactory and hope that the committee find this document helpful.

Best wishes
Professor Jayant S Vaidya, Professor Max Bulsara, Professor Jeffrey S Tobias, Professor Frederik Wenz, Dr Norman Williams and Professor Michael Baum

CONTENTS

Executive summary

1. This document gives all the additional analyses requested by NICE from the TARGIT-A trial investigators/ authors.
2. Following the initial request, NICE and the TARGIT-A trial investigators met on 9 December 2014. TARGIT-A investigators gave a response on 18 December.

   NICE responded on 16 February 2015, which was followed by a meeting on 3 March to discuss and confirm that all the required analyses were being included.
3. It is well established that the peak hazard of recurrence is in the first 2-3 years. Most importantly, the effect of radiotherapy on local recurrence is limited to the first 5 years, with most of the radiotherapy effect being seen in the first 2-3 years.

   The results in the TARGIT-A trial were obtained despite the fact that the eligibility criteria and cases in the TARGIT-A trial were not limited to very-low-risk cases.

   With over 1200 patients with a median follow up of 5 years as published in the Lancet, the TARGIT-A trial has sufficient data to change clinical practice.

4. Kaplan-Meier Curves

a. The Kaplan-Meier curves for local recurrence, survival without local recurrence, overall survival, breast cancer survival and disease free survival all demonstrated that the lines TARGIT and EBRT representing with their 95% CI overlap each other.

b. On the other hand, the 95% CI for TARGIT and EBRT curves for non-breast-cancer survival do not overlap, demonstrating the previously published statistically significant difference.

5. Absolute difference between Kaplan-Meier curves

a. The appropriate method of calculating the difference between Kaplan-Meier curves was by using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves.

b. For the primary outcome of local recurrence, the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years,

i. for the whole trial is 0.62% (95%CI +0.007 to +1.24)and

ii. for the Prepathology stratum is 0.3% (95% CI -0.4% to +1.03%).

6. **Data from further follow up**

   As of October 2014, the number of patients with a *minimum* follow up 5 years in the whole trial is 1116. For the Prepathology stratum it is 776, with 15 new events of local recurrence in addition to the previous 16. We were told that unplanned unblinding for new analysis is not necessary. Therefore, we have provided a blinded analysis: In the most plausible hypothetical scenario, weighted against TARGIT the new local recurrences might be distributed as TARGIT 10: EBRT 5. In this case, the difference between the binomial proportions of the two arms would be 0.83 (90%CI 0.0 -1.6) (95% CI -0.1-1.8), $P_{noninferiority}$= 0.00038 and TARGIT would remain non-inferior to EBRT.

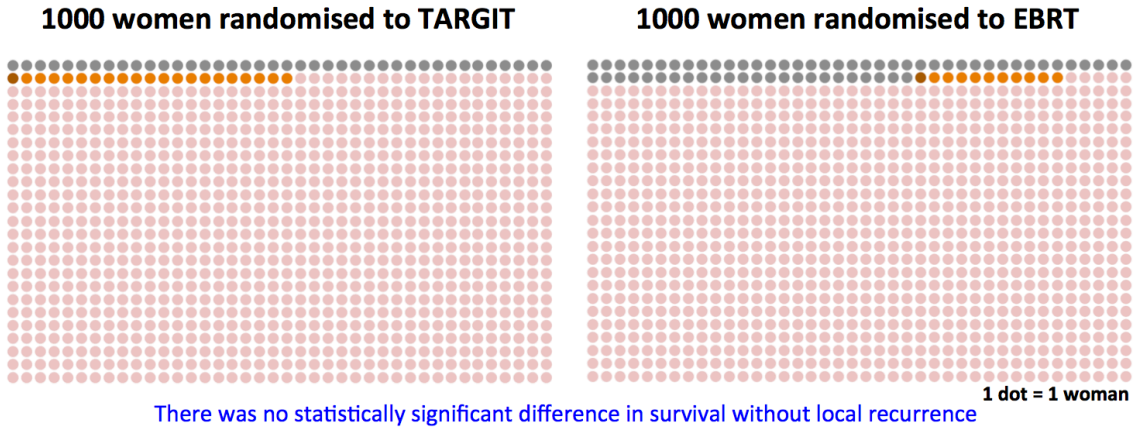
7. Please note that as published in the Lancet, that there is no significant difference between TARGIT and EBRT by conventional logrank test (p=0.31) and TARGIT was non-inferior to EBRT using the standard test for non-inferiority ($P_{noninferiority}$<0.00001)

8. **In conclusion:** Using three quite separate statistical methodologies, the TARGIT-A trial has demonstrated that the risk-adapted approach using single dose TARGIT IORT given during lumpectomy provides breast cancer control that is not inferior to several weeks of conventional radiotherapy.

9. The pictogram to help patients and doctors to make a shared well-informed decision is provided on page 4.

1. A pictogram to help patients and doctors to make a shared, well-informed decision

What happened to women with early breast cancer, treated with TARGIT during lumpectomy compared with those treated with EBRT, over the first 5 years?



There was no statistically significant difference in survival without local recurrence

1000 women randomised to TARGIT	1000 women randomised to EBRT
939 women alive without local recurrence	925 women alive without local recurrence
20 women alive after treatment of local recurrence	10 women alive after treatment of local recurrence
1 woman died after local recurrence	1 woman died after local recurrence
40 women died	64 women died

TARGIT-A international multi-centre trial included 3451 women randomised to receive TARGIT or EBRT. These figures are created by applying 5-year Kaplan-Meier estimates of survival without local recurrence to 1000 women having breast conserving therapy in the two trial arms. Distant or regional disease not shown: there was no difference seen between TARGIT and EBRT.

2. Summary of discussion following the meeting held on 9 December 2014

18 December 2014

To
Dr. Jane Adam MBBS, MRCP, FRCR
Chair, Appraisal Committee
National Institute for Health and Care Excellence

Dear Dr. Adam,

Thank you very much for meeting us to discuss the new findings from the TARGIT-A trial. The notes in the following pages represent a brief summary of our discussions and our response to the main question you wanted answered.

Although the committee reminded us that it is solely concerned with the potential application of this technique in the UK, we have taken the liberty of attaching a recently published paper originating from several centres in France. This study clearly concludes that over 50% of patients with early breast cancer would be suitable for TARGIT. The 50% value is consistent with the estimate that we had cited in our original response- it was from Germany - that 56% of patients would be suitable for TARGIT, rather than the value of 16% as calculated by the assessment group.

You made it clear that NICE committee's remit was *not* to give guidance to doctors about practising clinical medicine. NICE is there to facilitate the availability of new treatments and make decisions about which are made available in the NHS. However, it has become only too evident to us that there is a totally mistaken and all-pervading perception that formal stated approval by NICE is necessary before TARGIT IORT can be offered to any patients in the UK (NHS or private). Therefore, we are concerned that if the well considered draft recommendation of July is reversed:

a. Clinicians will not be able to offer this treatment to suitable UK patients - even though randomised Level 1 evidence is available.
b. UK patients could only choose between weeks of conventional radiotherapy, or travel to Europe (e.g., Italy, France, Germany, Poland) or USA for the treatment.
c. Patients unable to have EBRT would need to be recommended mastectomy: no other choice.

If the committee confirms its recommendation, it would mean that clinicians will be allowed to offer this UK-designed, individualized, less-expensive treatment (with supporting level I randomised evidence of safety and efficacy) to suitable and selected patients after due discussion with the patient and the hospital breast multidisciplinary team, on a par with patients in over 200 facilities in USA, Europe and around the world.

Yours sincerely

Professor Jayant S Vaidya, Professor Max Bulsara, Professor Jeffrey S Tobias
Professor Frederik Wenz, Dr Norman Williams and Professor Michael Baum

2. Summary of discussion following the meeting held on 9 December 2014 … contd

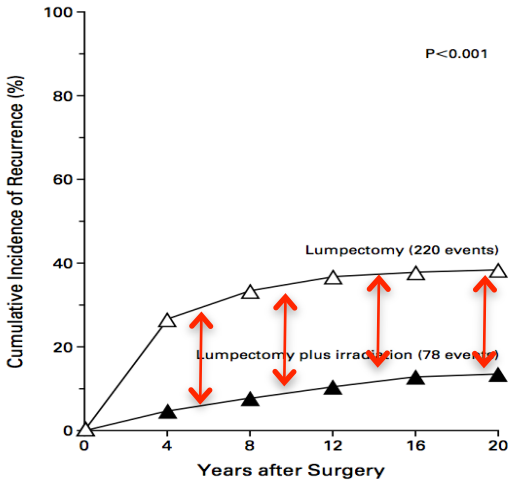
We were asked to give updated results of the TARGIT-A trial beyond what was published recently in The Lancet[1 2].

During the meeting on 9 December 2014, we briefly explained how breast cancer surgery has evolved from being very radical (e.g., radical mastectomy and axillary clearance) to more individualized and precise (lumpectomy and sentinel node biopsy).
Even though randomised evidence supported less radical treatment, there was strong initial opposition to its adoption only a few decades ago. TARGIT-A trial has provided evidence that radiotherapy does not also need to be radical and should be a more precise and individually optimised. The opposition to its adoption appears to be similar that shown by strong proponents of radical mastectomy to those who wanted to spare women this mutilating operation. Some important and relevant points about the natural history of breast cancer have been elucidated via the results of several randomised clinical trials:

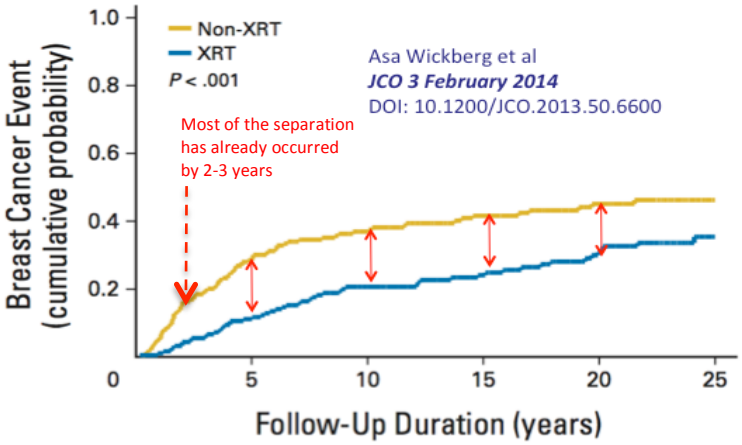
a. The peak hazard of recurrence is in the first 2-3 years and more importantly, the effect of radiotherapy on local recurrence is limited to the first 5 years, with most of the radiotherapy effect being seen in the first 2-3 years[3-6]. This is clearly seen from the figures below. Thus, local recurrence occurring between 5 and 25 years is no more frequent even in non-irradiated patients compared with those who had received radiotherapy[3-6].

These figures demonstrate how the reduction in local recurrence by radiotherapy occurs only in the first 5 years – most of the effect already seen in the first 2 – 3 years.

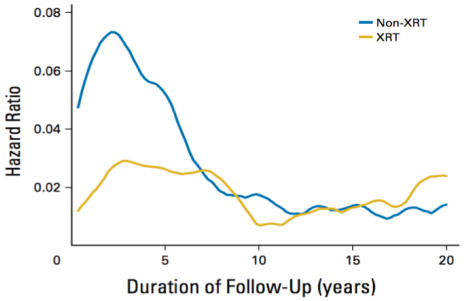
Top figure is Kaplan-Meier plot from the landmark NSABP B06 trial of radiotherapy vs. no radiotherapy after lumpectomy by Fisher et al[3];

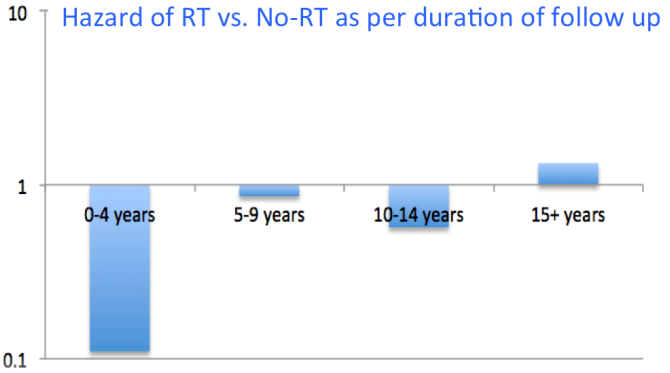


The bottom figure is the Kaplan-Meier plot taken from the Swedish trial of radiotherapy vs. no radiotherapy after lumpectomy with a 25 year follow up by Wickberg et al[5]



The left figure and the data for right figure is from the Swedish trial of radiotherapy vs. no radiotherapy by Wickberg et al[6]





Therefore the available follow up of the TARGIT-A trial gives information that is enough to use it in clinical practice.

b. When the reduction in local recurrence because of radiotherapy is less than 10%, there is no discernible benefit on survival from breast cancer.

c. The detrimental effect of conventional whole breast radiotherapy on non-breast-cancer deaths (e.g., from cardiac/other cancers) becomes more important when deaths from breast cancer are few and this effect starts in the first few years.

d. It has been suggested that TARGIT treatment is as good as 'no-radiotherapy'. The table below gives results of randomised trials testing the effect of completely omitting radiotherapy. As can be seen clearly in the table below, one in every 17 to 25 of even the

	CALGB	BASO 2	PRIME 2	TARGIT-A Prepathology
Number	636	1135	1326	2298
Age	>=70	>=65	>=65	>=45
T Size	<=2cm	<=2cm	<=2cm	Small T2, preferably<=3.5cm
Grade		Grade 1	Grade 1 or Grade 2	No restriction
Nodes	Negative	Negative	Negative	No restriction
LV invasion		Negative	Negative	No restriction
ER status	Positive	Positive	Positive	No restriction
5-year local recurrence (LR)	4% vs 1% Stat Sig.	6% vs 2% Stat Sig.	4.1% vs 1.3% Stat Sig.	2.1% vs. 1.1% overall 1.4% vs. 1.1% if ER pos. **Both *not* statistically significant**
5-year LR in experimental arm	1 in 25	1 in 17	1 in 25	1 in 48 overall 1 in 71 if ER positive

most stringently selected low-risk patients would have a local recurrence if radiotherapy were omitted[7-9]. On the other hand when TARGIT is given during lumpectomy local recurrence is rare - 1 in 48, which reduces to 1 in 71 when just a single selection criterion (ER positive) is applied.

2. Summary of discussion following the meeting held on 9 December 2014 … contd

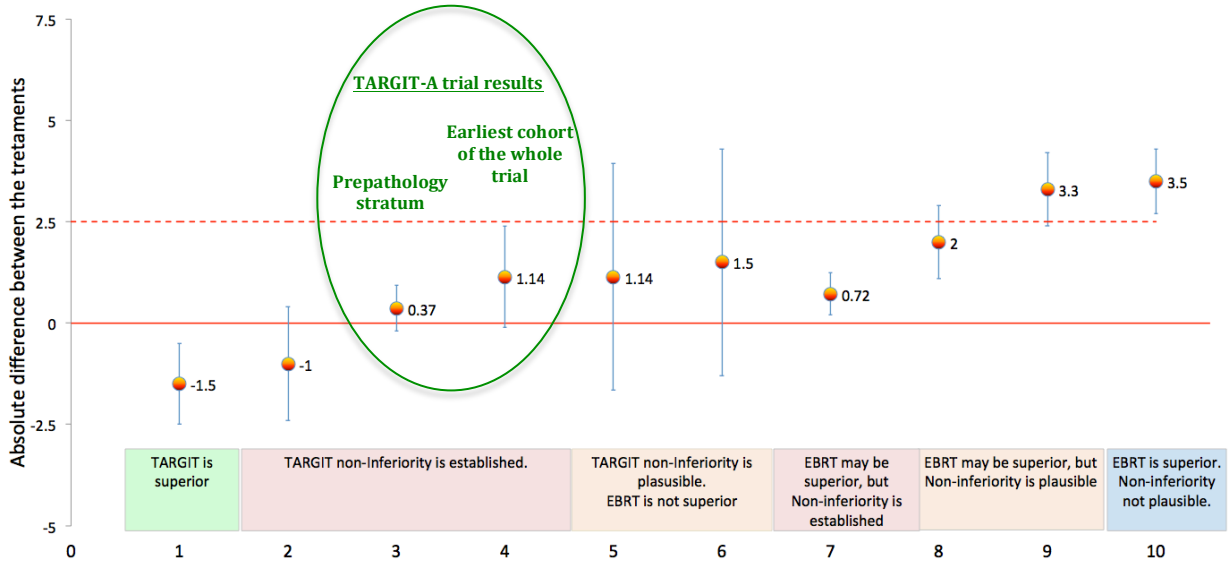
e. Importantly, the TARGIT-A trial eligibility was not limited to a "good prognosis" cases. In fact, 85% of patients in the TARGIT-A trial were younger than 70 years of age and there were a large number of patients in each of the adverse prognostic groups such as node positive (n=502), ER or PgR negative (n=554) or grade 3 (n=459), >2cm (n=397); over 60% of cases in the TARGIT-A trial would be considered 'unsuitable' or 'cautionary' by the ASTRO criteria for partial breast irradiation[10]; only 17.5% of patients in the TARGIT-A trial Prepathology stratum would have been eligible for the PRIME 2 trial – all others (82.5%) had 'worse' prognosis cancers.

   The results in the trial were obtained despite the fact that the eligibility criteria and cases in the TARGIT-A trial were not limited to very-low-risk cases.

f. In a non-inferiority trial if the difference between the treatments being tested (and its upper confidence limit) is less than a pre-set non-inferiority margin, the treatments are considered non-inferior even if the difference is "statistically significant" using a log-rank test The pre-specified non-inferiority boundary of 2.5% absolute difference in local recurrence *is very conservative* and validated in patient preference studies[11-13]. At this boundary, TARGIT is non-inferior to EBRT ($P_{noninferiority}<0.00001$). See figure below.

   Furthermore, we have recommended that TARGIT should be used during the initial lumpectomy, as in the Prepathology stratum (NB not subgroup), where the difference between the two treatments was undoubtedly not statistically significant (p=0.31).

The meaning of non-inferiority: Ten **examples** of different scenarios that might occur in a randomized trial testing non-inferiority between two treatments. The dots represent the absolute difference, and lines the confidence intervals.
The green circle includes two of the trial results: on the left is the TARGIT prepathology stratum (difference 0.37%) and on the right is the Earliest cohort of the whole trial (n=1222) which has the median follow up of 5 years (difference 1.14%) (see Table 3 of the main paper)[1 2].



Analysis requested by the Committee

3. Whole study population: Local Recurrence

a. Local recurrence:

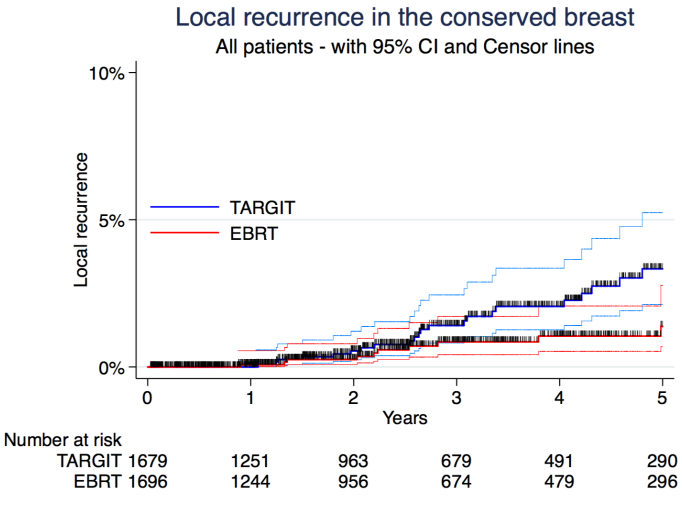
i. The absolute number of local recurrence events (n)

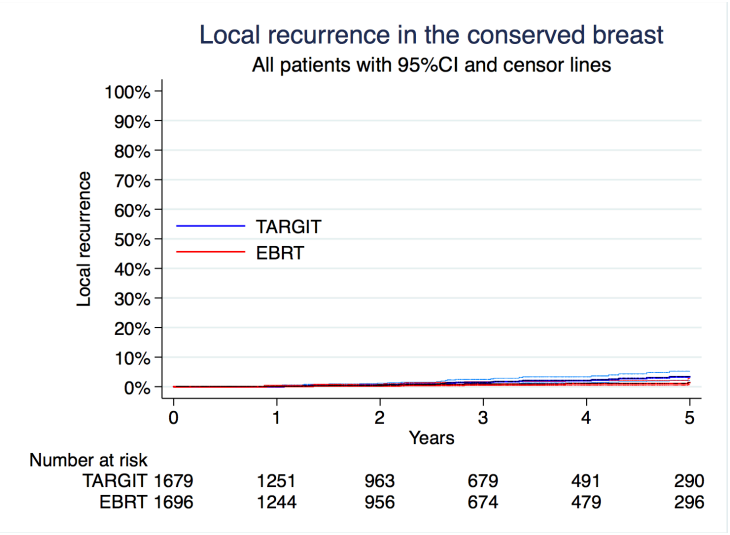
Whole study population	TARGIT	EBRT
Number of local recurrence events	23	11

ii. A Kaplan-Meier analysis including all patients using the most up-to-date follow-up data from TARGIT-A for each treatment group showing the cumulative risk of local recurrence over time using the latest available follow-up data. Please supply 4 figures for this survival analysis showing the following: [The numbers of patients at risk of local recurrence in each treatment group at yearly intervals should be reported below the plot]

1. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, with tick marks indicating censoring and 95% confidence intervals around the curve for each treatment group.

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines
Censoring ticks: small black vertical lines at the point of last follow up, withdrawal or death



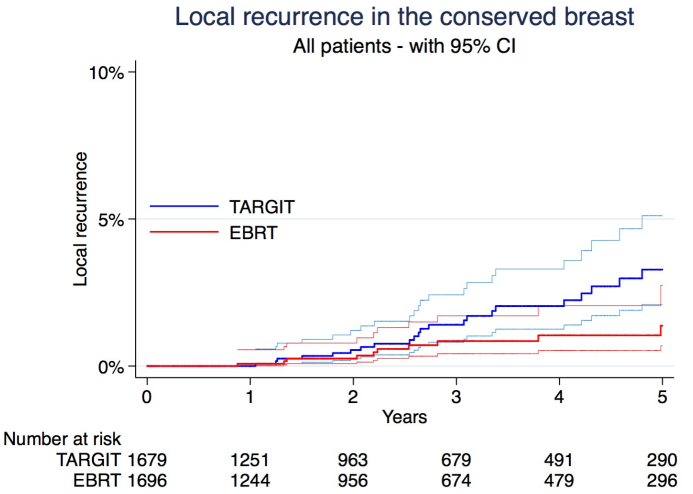


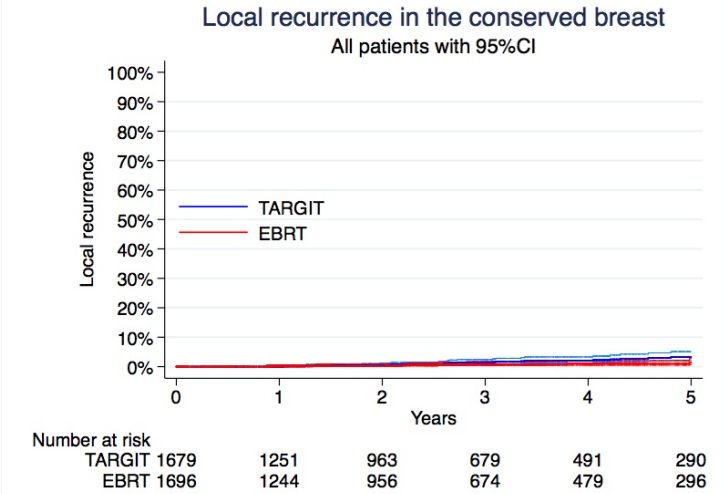
(Left: magnified y-axis, Right: full y-axis)

3. Whole study population: Local Recurrence … contd

2. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, without tick marks indicating censoring but with 95% confidence intervals around the curve for each treatment group.

   95% CI of TARGIT– two light blue lines
   95% CI of EBRT – two light red lines

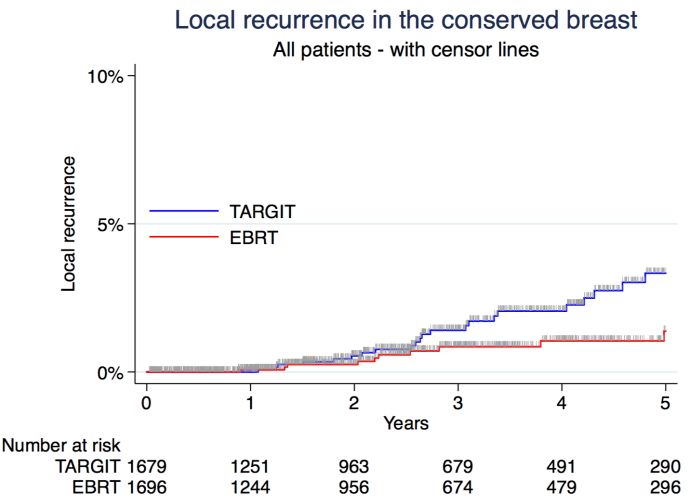


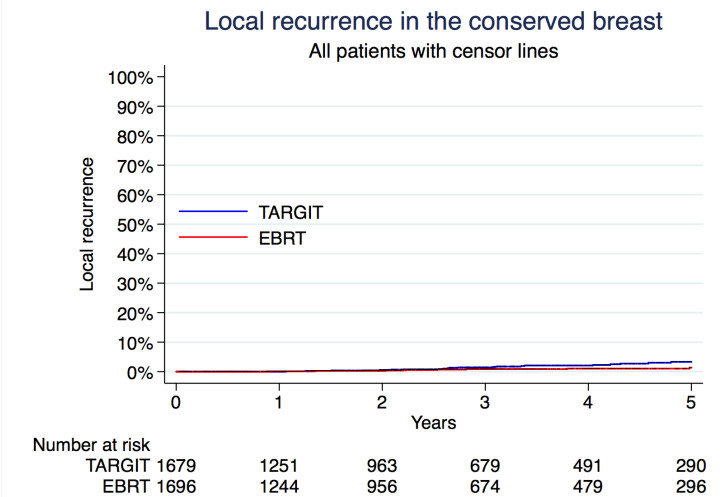


(Left: magnified y-axis, Right: full y-axis)

3. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, with tick marks indicating censoring but without 95% confidence intervals around the curve for each treatment group.

   Censoring ticks: small black vertical lines at the point of last follow up, withdrawal or death

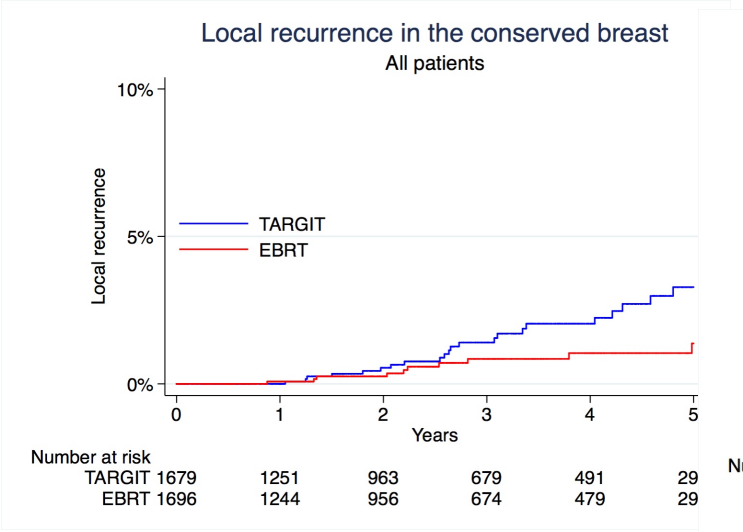


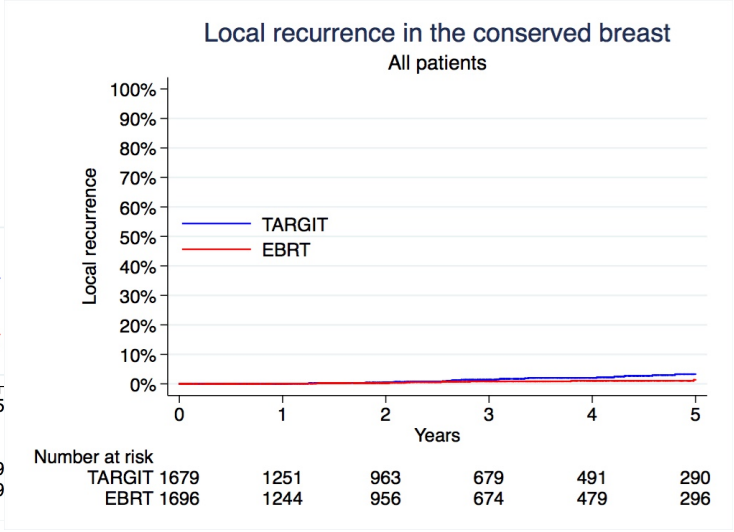


(Left: magnified y-axis, Right: full y-axis)

3. Whole study population: Local Recurrence … contd

4. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, without tick marks indicating censoring or 95% confidence intervals around the curve for each treatment group

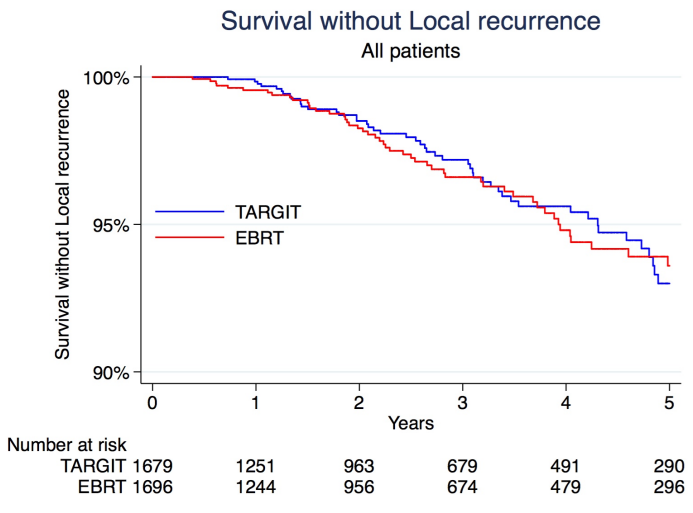


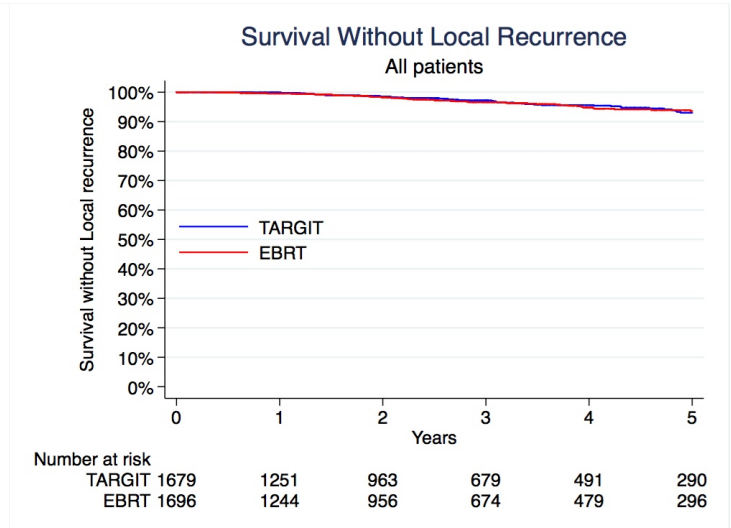


(Left- magnified y-axis, Right full y-axis)

5. Kaplan-Meier curves of cumulative survival without local recurrence.

The following Kaplan-Meier plot is **the true representation** of how patients with breast cancer would fare in the first 5 years of their life following treatment with TARGIT or EBRT, with respect to local control. Censoring is done at the point of last follow up or withdrawal[11 12].
For any patient her chance of being alive without local recurrence can be read off this plot.
The 5-year survival without local recurrence:
TARGIT: 93.1% (90.8 – 94.9) EBRT: 93.8% (91.7 – 95.4), p value = 0.81.





(Left: magnified y-axis, Right: full y-axis)

3. Whole study population: Local Recurrence … contd

ii. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of local recurrence between treatment groups and the 95% confidence interval around that difference. (Note: please present the 95% confidence interval, rather than the 90% confidence interval which has been reported previously).

- In the paper, we reported the 90% CI of the *difference in binomial proportions* – not of the difference in KM estimates*. The difference between binomial proportions of local recurrence for TARGIT and EBRT were:

  Difference = 0.72% (90% CI 0.15 – 1.30) (95%CI *0.05 – 1.40)*

- In the presence of censoring, the K-M point estimate at a particular time point e.g., 5 years are not a simple binomial proportions. Therefore, it is inappropriate to apply the simple formula normally used to calculate the SE (and CI) of a difference between binomial proportions, viz., $\sqrt{SE1^2 + SE2^2}$, to calculate differences between such point estimates.

- Furthermore, when looking at KM curves, the right hand end of the curve is the one with the most uncertainty and with the widest confidence intervals. These values, i.e., 5-year point estimates, should not be used to calculate the confidence interval of the difference or for testing non-inferiority.

Professor Max Bulsara, Professor Jayant Vaidya, Ms Pilar Pinilla-Dominguez and Ms Janet Robertson met on 3 March 2015. It was agreed that the above points were absolutely valid and it was accepted that the difference in 5-year K-M estimate are not to be used for assessing non-inferiority, but are provided for completion:
For local recurrence the difference is
2% (95%CI -0.14 - 4.14) (90%CI 0.18 - 3.82)
For survival without local recurrence the difference is
0.64% (95%CI -2.09 – 3.37) (90%CI -1.69 – 2.97)

It was agreed in this meeting that the appropriate method of calculating the difference between Kaplan-Meier curves is by using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17]:

The difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years is 0.62% (95%CI +0.007 to +1.24)

***NB: For non-inferiority testing the convention is to use 90% CI rather than 95%[13-16]**

4. Whole study population: Survival

b. Survival (Whole trial)

iii. The absolute number of deaths (n)

Whole study population	TARGIT	EBRT
Number of deaths	37	51

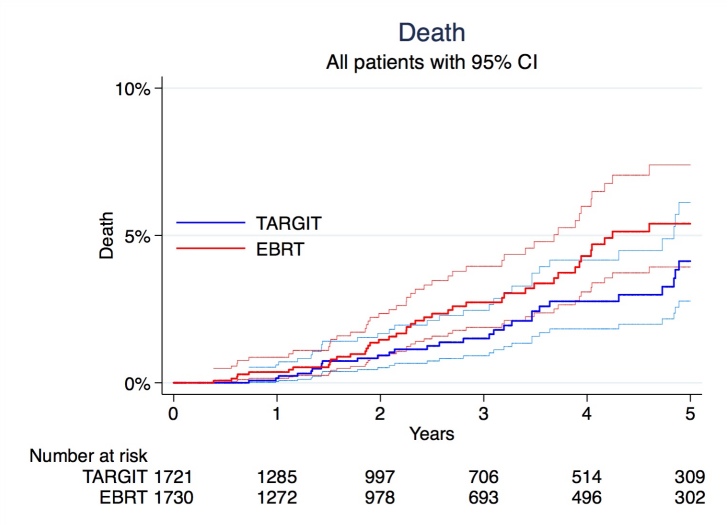
iv. The number of patients with different causes of death (n).

Whole study population, causes of death	TARGIT	EBRT
Breast Cancer	20	16
Other cancer	8	16
Cardiac	2	8
Other Vascular	0	3
Other	7	8

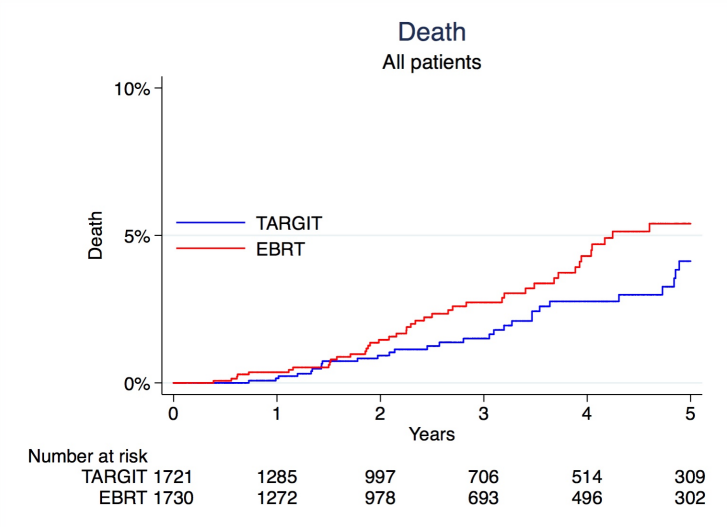
v. Kaplan-Meier curves (including all patients) for each treatment group showing the cumulative risk of overall mortality. Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



4. Whole study population: Survival … contd

vi. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of overall mortality between treatment groups (Intrabeam and EBRT) in the whole study and the 95% confidence interval around that difference.

NB. The caveats mentioned on page 12 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is (*minus)* -1.38% (95%CI -3.67 – +0.91) (90%CI -3.3 - +0.57)

Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years is -0.85% (95% CI -1.75 to +0.04)

4. Whole study population: Survival … contd

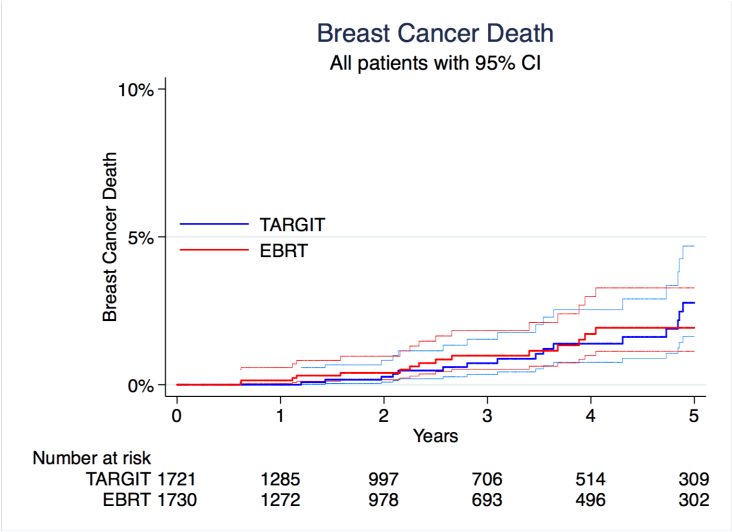
c. Breast cancer mortality (whole trial)

vii. The absolute number of breast cancer deaths (n)

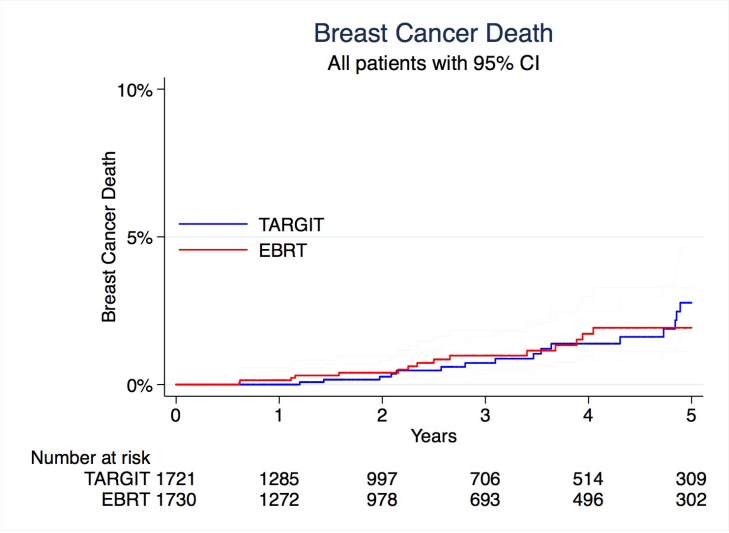
Whole study population	TARGIT	EBRT
Number of breast cancer deaths	20	16

viii. Kaplan-Meier curves (including all patients) for each treatment group showing the cumulative risk of breast cancer death.
Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group
95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



ix. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of breast cancer mortality between treatment groups (Intrabeam and EBRT) in the whole study population and the 95% confidence interval around that difference.

NB.The caveats mentioned on page 12 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is 0.67% (95%CI -1.01 – +2.35) (90%CI -0.76 - +2.10)

Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years is 0.15% (95% CI -0.71 to +0.42)

4. Whole study population: Survival … contd

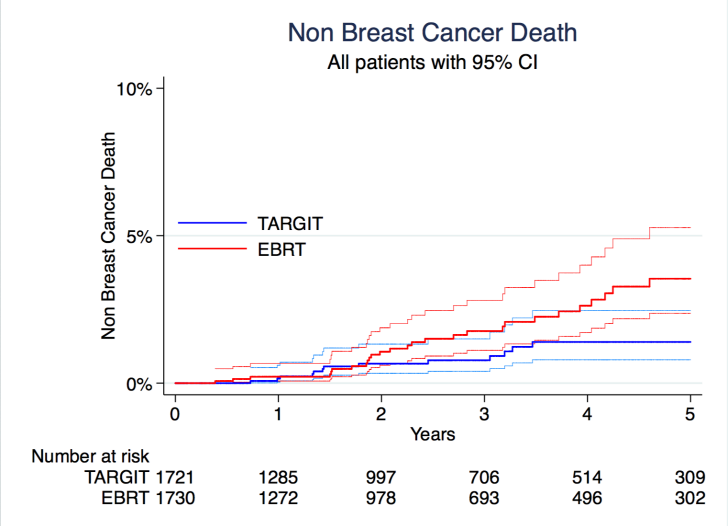
d. Non-breast cancer mortality (whole trial)

x. The absolute number of non-breast cancer deaths (n)

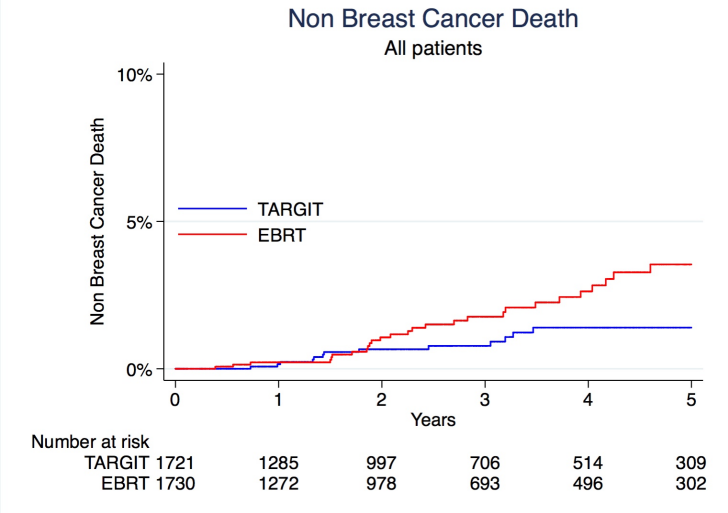
Whole study population	Intrabeam	EBRT
Number of non-breast cancer deaths	17	35

xi. Kaplan-Meier curves (including all patients) for each treatment group showing the cumulative risk of non-breast cancer death. Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group
95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



xii. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of non-breast cancer mortality between treatment groups (Intrabeam and EBRT) in the whole study population and the 95% confidence interval around that difference.

NB.The caveats mentioned on page 12 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is
(*minus)* -2.08% (95%CI -3.70 – -0.46) (90%CI -3.46 - -0.70)

Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years is -0.72 (95% CI -1.42 to -0.02)

4. Whole study population: Survival … contd

e. Tabulation of the number of patients with at least 5years of follow-up data

Whole study population	Intrabeam	EBRT
Number of patients with at least 5years of follow-up data (as of 25 Jun 2012)	309	302
Number of patients with at least 5years of follow-up data (as of 1 Oct 2014)	**1116** **Detailed New Analysis below (p27)**	

5. Prepathology stratum – Local recurrence

Pre-pathology stratum

a. Local recurrence:

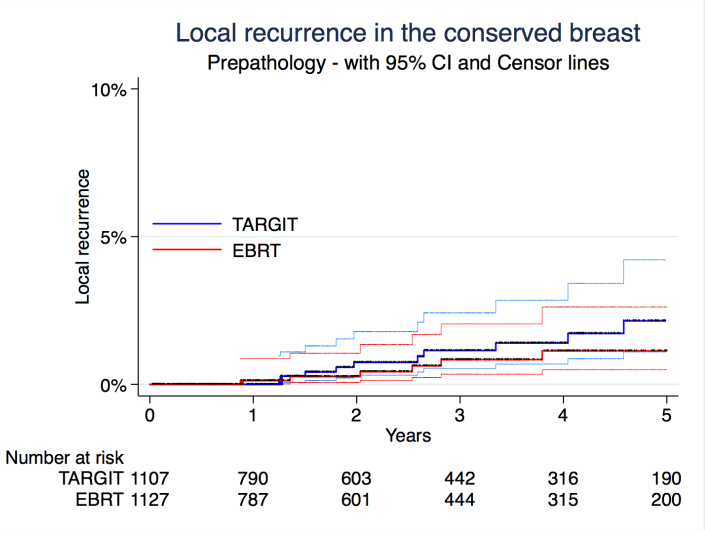
i. The absolute number of local recurrence events (n)

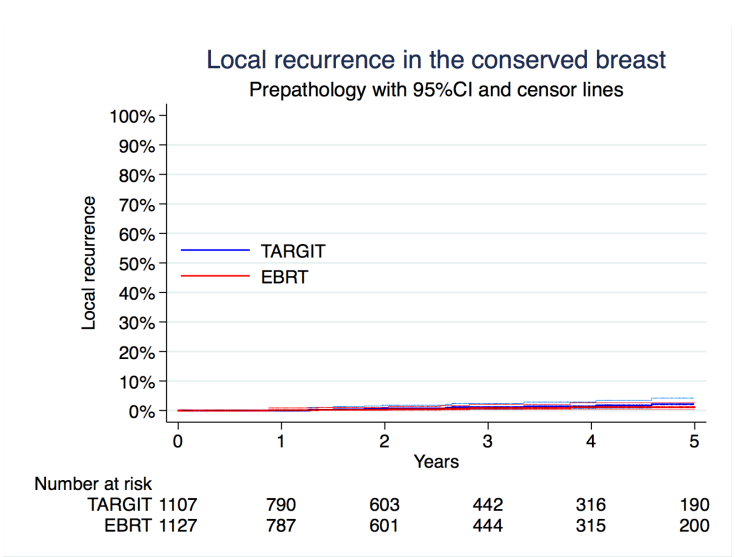
Pre-pathology group	Intrabeam	EBRT
Number of local recurrence events	10	6

A Kaplan-Meier analysis including all patients in the pre-pathology group using the most up-to-date follow-up data from TARGIT-A for each treatment group showing the cumulative risk of local recurrence over time using the latest available follow-up data. Please supply 4 figures for this survival analysis showing:[The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.]

1. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, with tick marks indicating censoring and 95% confidence intervals around the curve for each treatment group.

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines
Censoring – short vertical lines at the point of last follow up, withdrawal or death



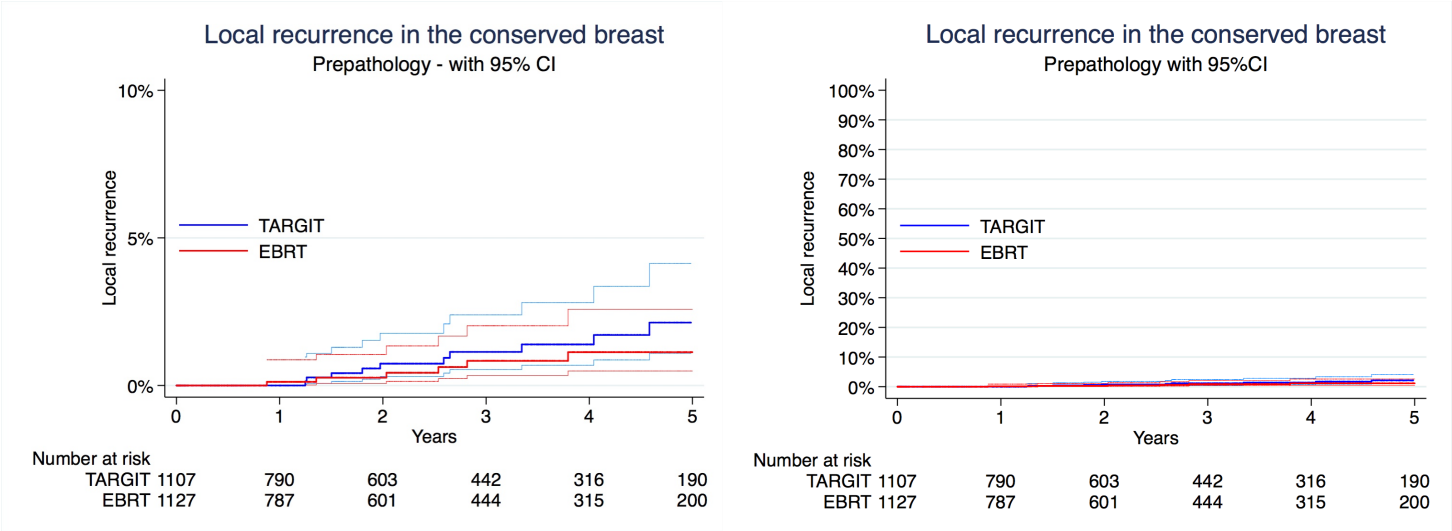


(Left: magnified y-axis, Right: full y-axis)

5. Prepathology stratum – Local recurrence … contd

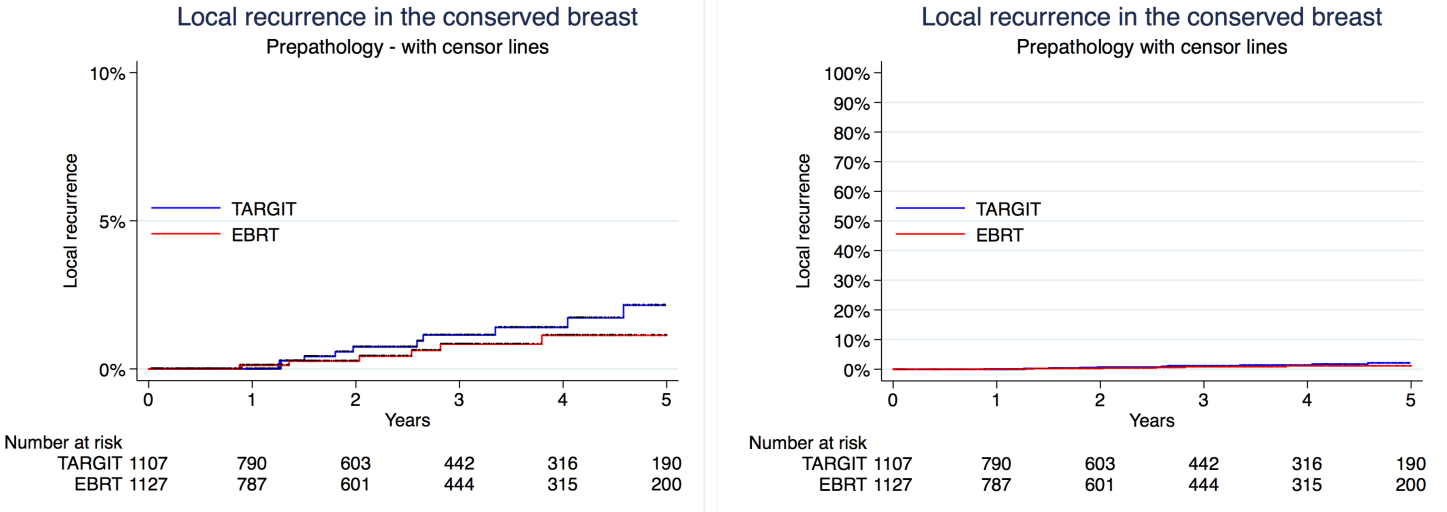
2. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, without tick marks indicating censoring but with 95% confidence intervals around the curve for each treatment group.

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(Left: magnified y-axis, Right: full y-axis)

3. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, with tick marks indicating censoring but without 95% confidence intervals around the curve for each treatment group. Censoring – short vertical lines at the point of last follow up, withdrawal or death.



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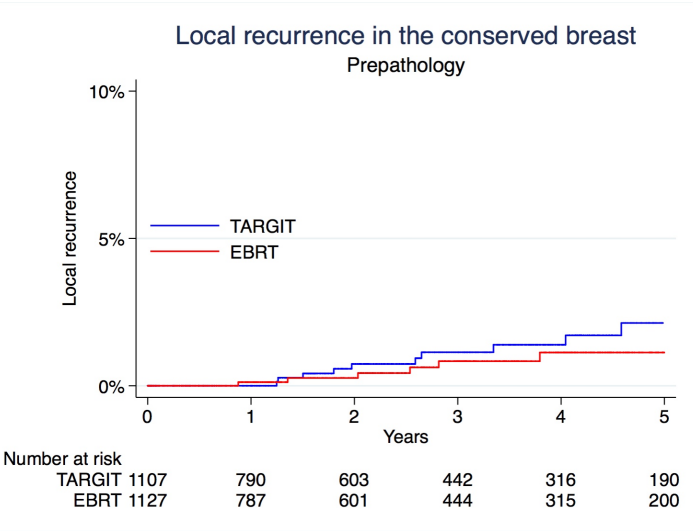
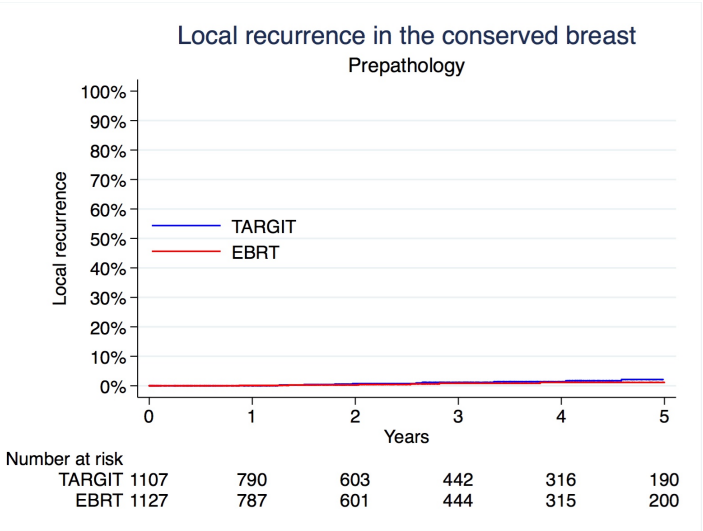
(Left: magnified y-axis, Right: full y-axis)

5. Prepathology stratum – Local recurrence … contd

4. Kaplan-Meier curves of cumulative risk of local recurrence over time for each treatment, without tick marks indicating censoring or 95% confidence intervals around the curve for each treatment group (Left: magnified y-axis, Right: full y-axis)

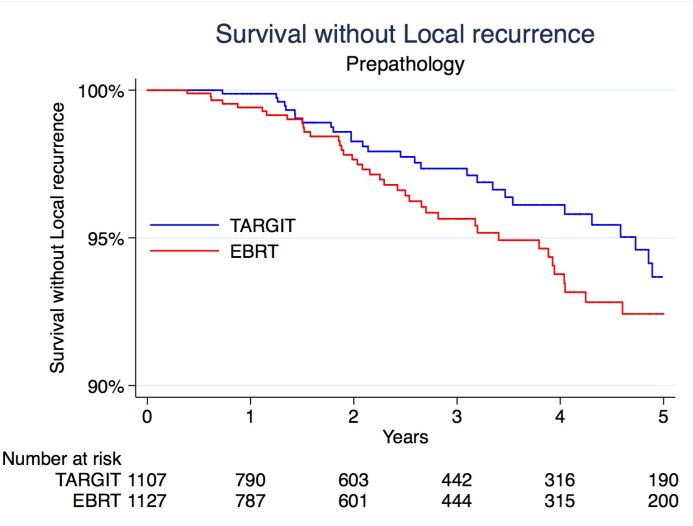


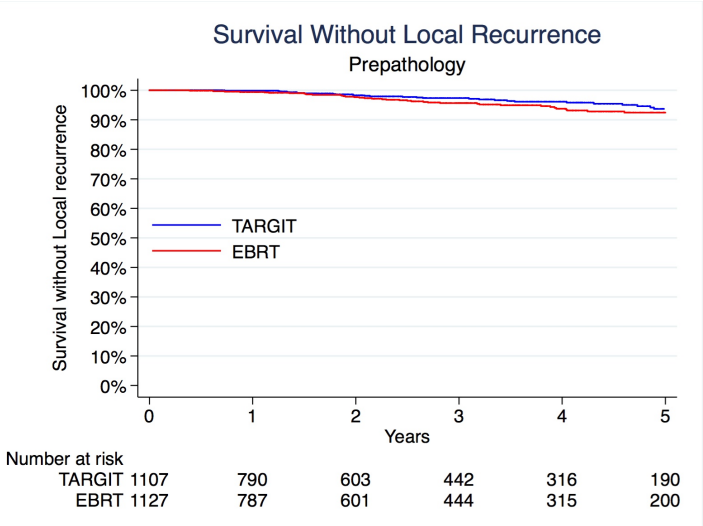


5. Kaplan-Meier curves of cumulative survival without local recurrence.

The following Kaplan-Meier plot is **the true representation** of how patients with breast cancer would fare in the first 5 years of their life following treatment with TARGIT during lumpectomy or EBRT, with respect to local control. Censoring is done at the point of last follow up or withdrawal[11 12]**. For any patient her chance of being alive without local recurrence can be read off this graph. 5-year survival without local recurrence**:

TARGIT: 93.9% (95%CI 90.9 – 95.9), EBRT: 92.5% (95%CI 89.7 – 94.6) p value = 0.35





(Left: magnified y-axis, Right: full y-axis)

5. Prepathology stratum – Local recurrence … contd

ii. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of local recurrence between treatment groups and the 95% confidence interval around that difference (Note: please present the 95% confidence interval, rather than the 90% confidence interval which has been reported previously).

- In the paper, we reported the 90% CI of the *difference in binomial proportions* – not of the difference in KM estimates*. The difference between binomial proportions of local recurrence for TARGIT and EBRT were:

  Difference = 0.37% (90% CI (*minus)* -0.23 – 0.97) (95%CI (*minus*) -0.33 – 1.07)

- In the presence of censoring, the K-M point estimate at a particular time point e.g., 5 years are not a simple binomial proportions. Therefore, it is inappropriate to apply the simple formula normally used to calculate the SE (and CI) of a difference between binomial proportions, viz., $\sqrt{SE1^2 + SE2^2}$, to calculate differences between such point estimates.

- Furthermore, when looking at KM curves, the right hand end of the curve is the one with the most uncertainty and with the widest confidence intervals. These values, i.e., 5-year point estimates, should not be used to calculate the confidence interval of the difference or for testing non-inferiority.

Professor Max Bulsara, Professor Jayant Vaidya, Ms Pilar Pinilla-Dominguez and Ms Janet Robertson met on 3 March 2015. It was agreed that the above points were absolutely valid and it was accepted that the difference in 5-year K-M estimate are not to be used for assessing non-inferiority, but are provided for completion:
For local recurrence the difference is
1% (95%CI -0.68 – 2.68) (90%CI -0.43 - 2.43)*
For survival without local recurrence the difference is
(*minus*) -1.32% (95%CI -4.74 – 2.10) (90%CI -4.24 – 1.60)*

It was agreed in this meeting that the appropriate method of calculating the difference between Kaplan-Meier curves is by using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17]:

The difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years is 0.3% (95% CI -0.4% to +1.03%).

***NB: For non-inferiority testing the convention is to use 90% CI rather than 95%[13-16]**

6. Prepathology stratum – Survival

b. Survival (Prepathology stratum)

i. The absolute number of deaths (n)

Pre-pathology group	Intrabeam	EBRT
Number of deaths	29	42

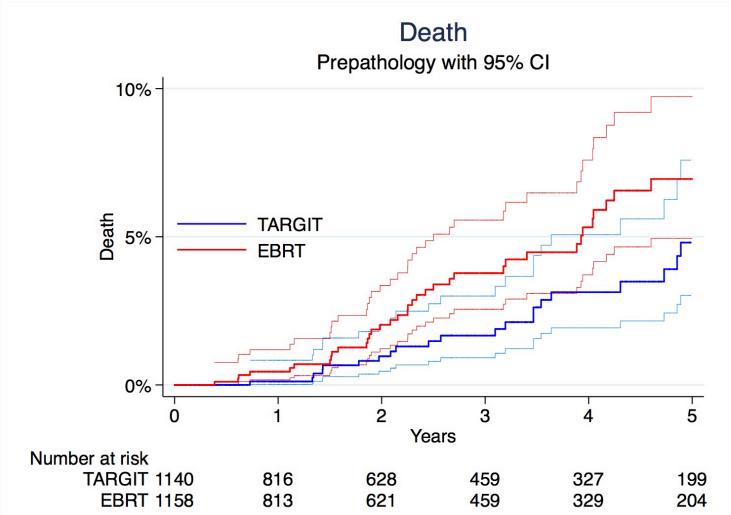
ii. The number of patients with different causes of death (n)

Pre-pathology group, causes of death	Intrabeam	EBRT
Breast Cancer	17	15
Other Cancer	5	12
Cardiac	2	6
Other Vascular	0	2
Other	5	7

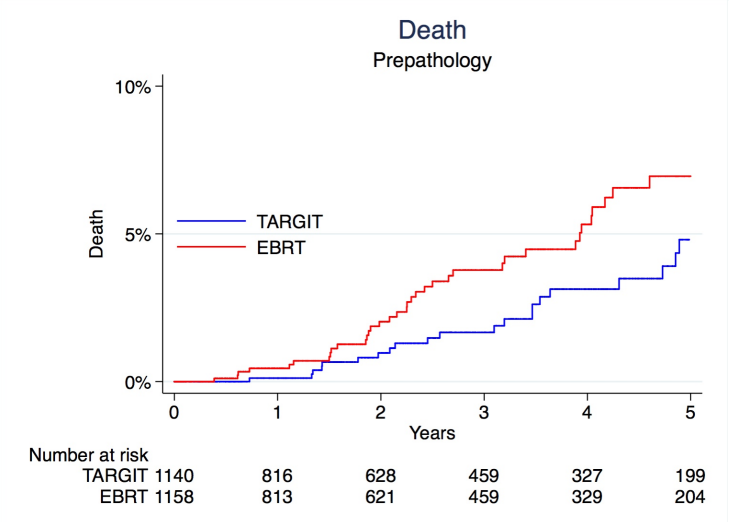
iii. Kaplan-Meier curves (including all patients in the pre-pathology group) for each treatment group showing the cumulative risk of overall mortality. Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



6. Prepathology stratum – Survival … contd

iv. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of overall mortality between treatment groups (Intrabeam and EBRT) in the whole study population and the 95% confidence interval around that difference.

NB. The caveats mentioned on page 21 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is
(*minus)* -2.33% (95%CI -5.48 – 0.82) (90%CI -5.02 - 0.36)
Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], we found that the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years, is -1.43 % (95% CI -2.66 to -0.2).

6. Prepathology stratum – Survival … contd

c. Breast cancer mortality (Prepathology stratum):

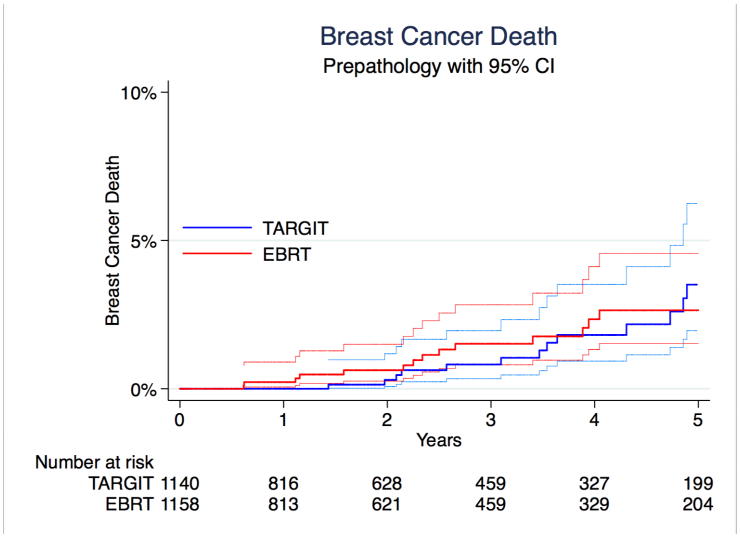
i. The absolute number of breast cancer deaths (n)

Pre-pathology group	Intrabeam	EBRT
Number of breast cancer deaths	17	15

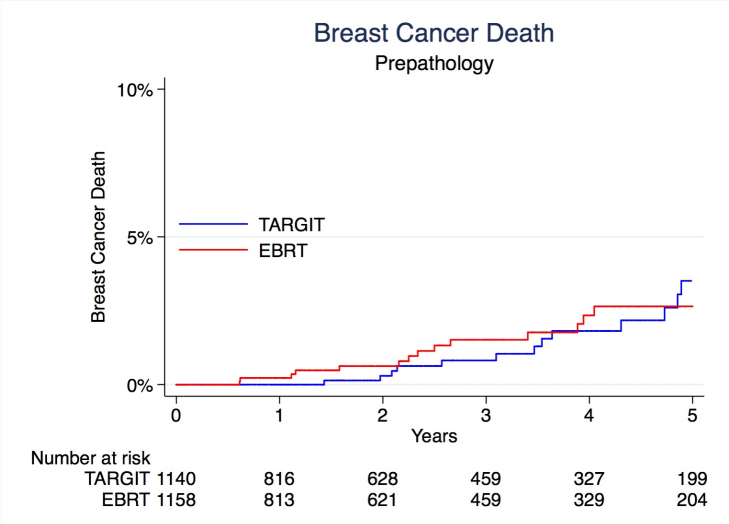
ii. Kaplan-Meier curves (including all patients in the pre-pathology group) for each treatment group showing the cumulative risk of breast cancer death. Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



iii. The absolute difference in the Kaplan-Meier estimate of the 5-year risk of breast cancer mortality between treatment groups (Intrabeam and EBRT) in the whole study population and the 95% confidence interval around that difference.

NB. The caveats mentioned on page 21 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is
0.66% (95%CI -1.72 – 3.04) (90%CI -1.36 – 2.68)
Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], we found that the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years, is -0.34 % (95% CI -1.17 to +0.49).

6. Prepathology stratum – Survival … contd

d. Non-breast cancer mortality (Prepathology stratum):

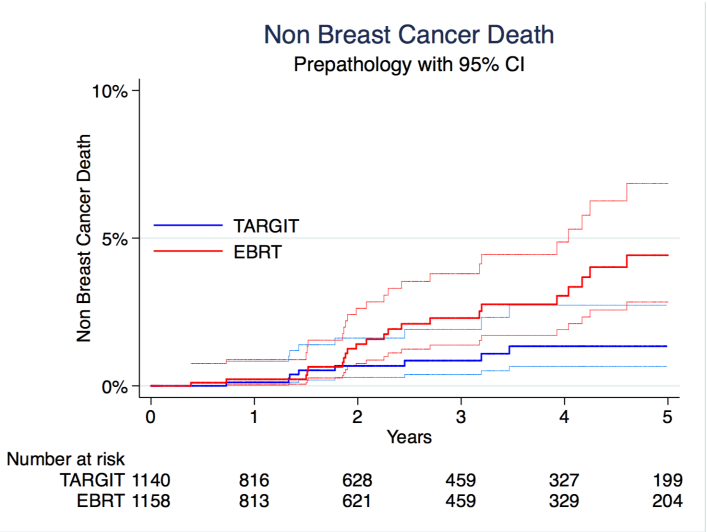
i. The absolute number of non-breast cancer deaths (n)

Pre-pathology group	Intrabeam	EBRT
Number of non-breast cancer deaths	**12**	**27**

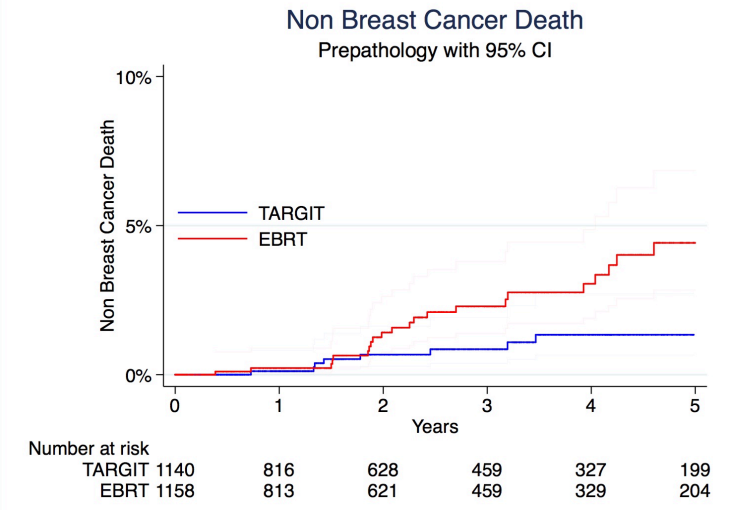
ii. Kaplan-Meier curves (including all patients in the pre-pathology group) for each treatment group showing the cumulative risk of non-breast cancer death. Please supply 2 figures for this survival analysis:

(i) one figure including the 95% confidence intervals around each curve for each treatment group

95% CI of TARGIT– two light blue lines
95% CI of EBRT – two light red lines



(ii) one figure not including 95% confidence intervals. The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.



(iii) The absolute difference in the Kaplan-Meier estimate of the 5-year risk of non-breast cancer mortality between treatment groups (Intrabeam and EBRT) in the whole study population and the 95% confidence interval around that difference.

NB. The caveats mentioned on page 21 about using 5-year estimates to calculate the difference between treatments and its confidence intervals should be read before using these figures. The difference between 5-year K-M estimates is
(*minus*) -3.07% (95%CI -5.25 – 0.89) (90%CI -4.93 - 1.21)
Using the integrated difference of the two survival functions to quantify the difference between the Kaplan-Meier curves[17], we found that the difference between the Kaplan-Meier curves for TARGIT and EBRT from 0 to 5 years, is -1.11 % (95% CI -2.05 to -0.17).

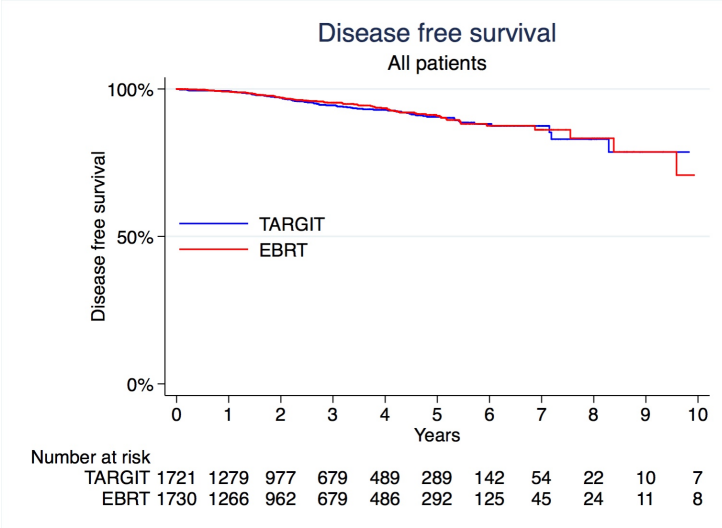
6. Prepathology stratum – Survival … contd

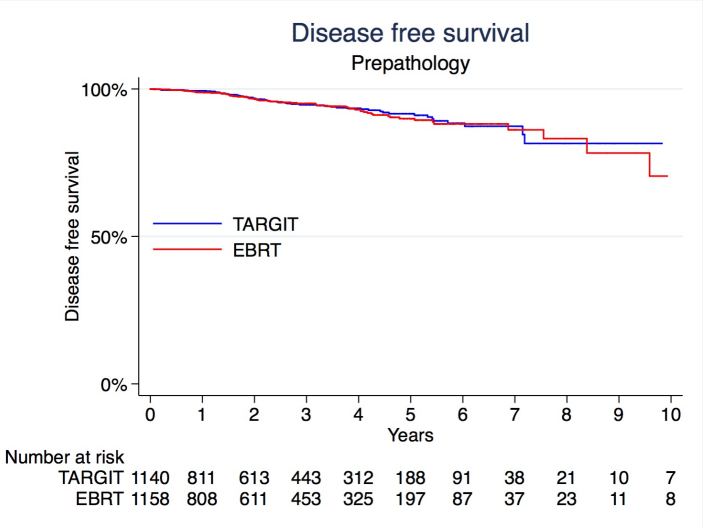
e. Tabulation of the number of patients with at least 5 years of follow-up data

Pre-pathology group	Intrabeam	EBRT
Number of patients with at least 5 years of follow-up data (as of 25 Jun 2012)	199	204
Number of patients with at least 5 years of follow-up data (as of 1 Oct 2014)-	776 Detailed New Analysis below (p27)	

7. New Analyses

1. During the meeting of 8 December 2014, we presented an additional analysis of the data published in The Lancet recently, viz. that the disease free survival of the patients in the TARGIT and EBRT arms is identical for the whole trial (p=0.78) and for the Prepathology stratum (p = 0.68), with the Kaplan Meier curves overlapping each other.
   The K-M estimates for disease free survival for the prepathology stratum are:
   TARGIT 91.6% (88.7-93.8) vs. EBRT 90.1% (86.8- 92.6) at 5 years and
   TARGIT 81.3% (71-88) vs. EBRT 71.2% (49-85) at 10 years





2. As was made clear to us that the NICE committee did not expect us to unblind the trial at this moment, we presented new updated data resulting from increased follow up as of 1 October 2014, using the total number of events without unblinding the trial.
3. **FURTHER FOLLOW UP:** Currently, the median follow up is 4 years, which means that a very large number of patients (n=1725) have at least 4 years of follow up or longer. This number is large when compared with majority of breast cancer trials.
4. **NEW EVENTS** With additional follow up since the last data lock in June 2012, there were 15 total new local recurrences in the Prepathology stratum. This was in addition to the 16 already reported in the Lancet out of 2298 total patients.
5. *Remaining blind to the randomisation arm, we presented two hypothetical scenarios* – one worst-case and one less extreme but still weighted against TARGIT.
6. For the 15 total new events of local recurrence, rather than an even split of 7 vs. 8 or 8 vs. 7, remaining blind to the randomisation arm, we modeled
   a. **A worst-case hypothetical scenario** might be that the new local recurrences are distributed as TARGIT 12 : EBRT 3. Even in this case, the difference between the binomial proportions of the two arms is only 1.19% ((90%CI 0.4 -2.0) (95% CI 0.2-2.2), $P_{noninferiority}$= 0.0041. So even in this worst-case scenario, TARGIT remains non-inferior to EBRT.
   b. **A less extreme hypothetical scenario, still weighted against TARGIT** might be that the new local recurrences are distributed as TARGIT 10: EBRT 5. In this case, the difference between the binomial proportions of the two arms is 0.83 (90%CI 0.0 -1.6) (95% CI -0.1-1.8), $P_{noninferiority}$= 0.00038 and TARGIT remains non-inferior to EBRT

7. New Analyses… contd

7. For death, the secondary end point, there were 28 new events – and these would need to have occurred in a ratio of 20 in TARGIT vs. 8 in EBRT in order to equalise the total number of deaths between the two treatments. As the initial observation was 29 deaths in TARGIT vs. 42 in EBRT, probability of such drastic reversal is low (p=0.008), so the difference in deaths is likely to remain in favour of TARGIT.

   Although you clarified that mortality was not the remit of this committee, we are compelled to bring a point of fact to your attention because it arose during the discussion. It is important to recognise that when a study actually finds a difference, the question of power is not relevant any more. Then the probability that the difference favouring TARGIT was seen by pure chance, is given by the p-value which in case of TARGIT-A trial was 0.099 for all deaths and 0.0086 for deaths from causes other than breast cancer. We believe we cannot ignore these randomized data particularly when deaths were more than recurrences (88 vs 34) and non-breast-cancer deaths (52) were more than breast cancer deaths (36) or local recurrences (34)

8. We were asked whether we would offer Intrabeam to patients in the control arm of the TARGIT-A trial who have already received EBRT, if NICE gives a positive response. In fact, the surgery and radiation treatment (whether Intrabeam or whole breast radiotherapy) of patients in the TARGIT-A trial has already been long completed (the trial closed in June 2012). Therefore, all those who received EBRT in the TARGIT-A trial *will not* be offered an operation to re-open their wounds and give Intrabeam.

9. Please note that as published in the Lancet, that there is no significant difference between TARGIT and EBRT by conventional logrank test (p=0.31) and TARGIT was non-inferior to EBRT using the standard test for non-inferiority ($P_{noninferiority}<0.00001$).

Professor Max Bulsara, Professor Jayant Vaidya, Ms Pilar Pinilla-Dominguez and Ms Janet Robertson met on 3 March 2015. The TARGIT-A trial investigators were very willing to supply the raw data as long as all the governance, consent, custody, data access and security issues are looked after appropriately. However, it was agreed that that is not necessary to supply the raw data because all the analysis requested by the committee was satisfactorily supplied.

In conclusion:

Using three quite separate statistical methodologies, the TARGIT-A trial has demonstrated that the risk-adapted approach using single dose TARGIT IORT given during lumpectomy provides breast cancer control that is not inferior to several weeks of conventional radiotherapy.

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***Acknowledgment**: We thank Dr. Hajime Uno PhD, Department of Biostatistics, Harvard University, Boston, for providing the software code and for independently verifying our results and our interpretation.

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	NHS Professional		**Results of TARGIT-A** Slightly less than half as effective as standard EBRT (Lancet, 2014; 383: 603–13) **No dosimetric RT QA** Considered equivalent because of the inappropriate selection of likely within-breast recurrence rate. The authors express concerns about excess cardiac toxicity but these are based on comparisons which are statistically insecure and biological implausible (N Engl J Med 2013; 368:987-998) **(statistical methodological concerns)** Double counting – nested cohorts Very short follow up (median 2 years 5 months) Non-pre-specified toxicity endpoints Concerns raised by the ex-chair of the data monitoring committee (Lancet, 2014; 383: 603–13) **History of partial breast radiotherapy trials** Previous negative (reduced efficacy/higher toxicity) studies of PBR (Breast J., 2010, May-Jun;16 (3):245-51) Higher toxicity and recurrence rates in US insurance/claim-based studies (JCO,30(25), 4302–7, JAMA, 2012, 307(17)1827–36) ELIOT trial negative (Lancet Oncology, 14 (13), 1269–1277)	Consultant in Clinical Oncology	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			NICE process Why issue a [very positive] press statement (engendering the predictable unqualified endorsement in the media) during consultation? This does seem to undermine the credibility of the consultation process and provides little confidence that responses are likely to exert much influence. The recommendation suggests discussing the potential ineffectiveness of the intervention with patients. This will represent a significant communication challenge! The recommendation suggests a clinical trial but no information on how this is to be resourced (organisation, finance, follow up) or the likely usefulness of any outcomes. A registry based 'trial/audit' of intrabeam conducted in low risk patients is not going to provide useful audit information given the likely low recurrence rates. Further follow up of TARGIT is preferable. Why make a positive recommendation in the presence of unreliable data and reduced clinical effectiveness (the Committee's words). **NHS practicalities** Oncological-surgical co-operation in theatres, time consuming, often impractical and resource Current machines in the UK are underutilized Increased use of axillary radiotherapy as an alternative to axillary node clearance based on the results of AMAROS (J Clin Oncol 31, 2013 (suppl; abstr LBA1001) which suggests equivalent disease control but reduced toxicity, so avoidance of EBRT may be of no value Evidence from RCTs that reduced fractionation of EBRT is the direction of travel with likely associated cost savings			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	NHS Professional		The 'expectation' was of a likelihood of 5-year within-breast recurrence of 6% at study design. Although reasonable at that time contemporary series and studies presented and published over the last 5-10 years suggest a figure of around 2%. A margin for non-inferiority of 2.5% as was defined for TARGIT-A is therefore much less appropriate in the context of current practice as this allows a doubling of recurrence risk to be classified as non-inferior. TARGIT-A does reveal a doubling of within-breast recurrence risk overall (worse [and accepted as inferior] for the post pathology patient stratum) for IORT. There are however fewer non-breast cancer deaths in the IORT arm of TARGIT-A and the TARGIT-A authors have suggested this may relate to radiation-induced cardiac deaths and new cancers caused by standard external beam radiotherapy (EBRT). This is very unlikely because of the short time frames involved. Despite specific requests no information on the excess non-breast cancer deaths in the context of tumour laterality is provided which is critical to the issue of possible radiotherapy induced cardiac deaths. Although a supportive editorial suggests a possible role for IORT in 'low risk' disease (2) the Lancet correspondence is otherwise very critical. The statistical methodology of TARGIT-A has been substantially criticized both within the HTA and within the correspondence section of the Lancet following the recent publication of TARGIT-A (1). Of particular concern is the serious criticism of statistical methodology and process raised by the (ex) chair of the data monitoring committee of TARGIT-A, who has stated that he has resigned from this role (3). The reasons for his resignation are not stated but this does raise concerns concerning study oversight. The HTA concludes that IORT is not cost effective in a UK environment, that the manufacturers economic analysis (suggesting an advantage) is flawed, that there are no proven QL advantages to IORT and that further	Consultant in Clinical Oncology	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			research and follow up of patients within TARGIT-A are needed. The short follow up time is also raised as a concern. Other studies of other forms of partial breast radiotherapy including the ELIOT trial (4) and an overview of older studies of external beam radiotherapy (5) report higher local recurrence rates and the US insurance claims based studies (6,7) which suggest higher mastectomy rates and toxicity following IORT provide further concern. Further follow up of patients within TARGIT-A is needed. Uncontrolled 'registration' studies attempting to evaluate the role of IORT in 'low risk' patient groups are problematic as the very low recurrence rates likely to be seen will obscure any potential inferior efficacy of IORT. Such studies would need to be very carefully designed with realistic & achievable endpoints and with informed and independent biostatistical input. Such studies should be developed and agreed purely to advance knowledge and with this objective alone. PBR/brachytherapy should not, given the current state of knowledge, be used outside clinical research. David Dodwell 21-5-2014 1 Lancet 2014; 383: 603–13 2 http://dx.doi.org/10.1016/S0140-6736(13)62304-1 3 Lancet, 383, 9930, 1716, (2014) 4 Lancet Oncology, 14 (13) 1269 – 1277 5 Breast J. 2010 May-Jun;16(3):245-51. 6 JCO 30(25), 4302-7 7 JAMA 2012 307(17) 1827-36			
[redacted]	Academic Health Researcher		I was informed by Dr Charlotte Coles that the it had been stated at the hearing that DMC had approved the publication of the most recent Lancet paper. This is not the case and as I have stated in my published letter to	Director , Wolfson Institute of	England	Resigned as Chair of the Independent Data

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			the Lancet there are serious flaws in the analysis. For the avoidance of any doubt about my view on this, I append the email related to this: Dear Mike, David and Norman, Thank you for your letter. Your termination of the DMC has just preceded my letter of resignation. I remain very dissatisfied with the last draft of the paper I have seen, and feel it serious distorts the findings of this study. My desire remains that these results should be published in an honest and straightforward manner I hope these issues will be addressed. Please be clear that the DMC has not approved this draft in any way and I trust you will transmit my concerns to the SC who have final say in this matter. I must say that while I took on this role willingly it has become a very unpleasant task and I have never felt so manipulated in all of my career. Sincerely [redacted] [redacted] Head of Centre, Centre for Cancer Prevention Director, Wolfson Institute of Preventive Medicine Queen Mary University of London Charterhouse Square London EC1M 6BQ United Kingdom Tel. +44 (0)20 7882 3504 | Fax +44 (0)20 7882 3890 | j.cuzick@qmul.ac.uk	Preventive Medicine		Monitoring Committee for this trial
[redacted]	NHS Professional		I am against this because:	Consultant Clinical Oncologist	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			• In the ELIOT trial the recurrence rate was 9 times higher after only 5 years. Local recurrences were seen both in the index quadrant as well as elsewhere within the breast. • In the TARGIT A trial the median follow up was outrageously short and the results seem to be comparable to other trials looking at external beam radiotherapy vs no treatment at all. 15% of patients had high risk features and ended up having external beam treatment anyway. It is too soon to implement this.			
[redacted]	President of The Association of Surgery (the association has 1200 members 500 of whom are consultant breast surgeons or equivalent position across the UK)	Association of Breast Surgery	The Association of Breast Surgery The Royal College of Surgeons 35-43 Lincoln's Inn Fields London WC2A 3PA [redacted] 6th August 2014 Your ref: NICE in development (GID-TAG353) Dear Sir BREAST CANCER (early-intrabeam radiotherapy system: appraisal consultation) The Association of Breast Surgery Executive Trustees have considered this topic in detail. It is a matter of great importance to us as adjuvant external beam radiotherapy is currently delivered as an integral part of the surgical breast conservation approach to the management of early breast cancer. We are also aware of the potential benefits to the patient of intra-operative radiotherapy.	President of Association of Breast Surgery	Other	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			Across the United Kingdom patients present to breast clinics and their diagnosis of breast cancer is made under the supervision of breast surgeons. The breast surgeon then counsels the patients as to the available therapeutic options. Current advice is if a patient opts for breast conservation then post-operative adjuvant radiotherapy is recommended. It is the breast surgeon who explains this to the patients and can refer the patient to authoritative guidelines and publications which support this advice. It is an area of consensus across the management of breast cancer. It is accepted practice that the patient will not usually be seen by a breast radiotherapist until their surgery is complete and that breast conservation was offered to and accepted by the patient in the absolute understanding that such a surgical approach of delivering less than a mastectomy will be accompanied by adjuvant external beam radiotherapy. It is the opinion of the Association of Breast Surgery that at this time there is insufficient evidence to support a change in current recommendations. You will be very aware of the relevant literature which is included in many of the submissions and in your evaluation report. The data on outcomes from intra operative partial breast irradiation is, in our opinion, immature. There is insufficient knowledge of breast cancer recurrence rates within the breast at a standard five year time point and at longer time intervals. There is insufficient information on the implications for the patient of such a recurrence including the potential impact on the necessity for mastectomy if such a local recurrence occurs and also the impact on future survival rates. There is insufficient information on the outcomes from intra-operative partial breast irradiation when compared to no irradiation. There is insufficient information on the textural and cosmetic outcomes of partial breast irradiation particularly when supported by subsequent external beam radiotherapy. There is insufficient information on the criteria for selection as to the most suitable group of breast cancer patients that should be offered partial breast irradiation as an option.			

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			Due to these limitations in the current evidence base it is the opinion of the Association of Breast Surgery that breast surgeons across the UK are not in a position to satisfactorily counsel patients that intra-operative radiotherapy is currently a proven, safe alternative to external beam radiotherapy. Offering informed choice to patients with early breast cancer is, pleasingly, an established practice in the UK but it is not possible to offer as a therapeutic option a procedure that has insufficient reliable background information. We do not support the initiative to offer intra-operative partial breast radiotherapy as an option outside of a controlled trial at this time. The Association of Breast Surgery Executive Trustees have no conflict of interest to declare in this matter. Yours sincerely [redacted] [redacted] Association of Breast Surgery on behalf of the ABS Trustees			
[redacted]	NHS Professional	National Institute for Health Research Clinical Research Network: Cancer	Dear Members of the Appraisal Committee We have read and fully endorse the detailed response of the NCRI Breast Clinical studies, CT Rad, RCP and JCCO to the NICE Appraisal Committee preliminary recommendations on the Intrabeam Radiotherapy System. The assessment group concluded that non-inferiority of local recurrence, the main endpoint of the TARGIT trial was not proven. However they were prepared to ignore this in their recommendation. Strategies to reduce local recurrence have been viewed as an essential aim in successful breast conservation and have been derived in part from the conclusions of many past clinical trials and changes in the management of clinical pathways.	National Clinical Lead for Radiotherapy	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			The length of follow up in the TARGIT trial is considered to be too short by the vast majority of breast cancer experts and professional opinion to make a meaningful assessment of risk to patients. The current results would allow for a doubling of risk of local recurrence and consequent mastectomy rates. What motive is there not to wait until the degree of risk is better objectively quantified? There are methodological flaws in the production of this recommendation and we would strongly suggest that Intrabeam should not be offered as a routine option to patients until there is secure evidence of, at best, equivalent long term results of local recurrence. Even then it requires more realistic cost effective modeling and setting within the true context of NHS management pathways. There is a strong argument that if the conclusion of this draft NICE recommendation is confirmed it will fundamentally undermine the whole rationale behind undertaking high quality clinical trials in order to inform clinical practice and future policy based on a clear evidence base. Yours sincerely [redacted] National Clinical Lead for Radiotherapy, NIHR CRN: Cancer and [redacted] Director, NIHR CRN: Cancer			
[redacted]	NHS Professional	NHS England - Cancer & Blood Programme of Care	**Summary of Response** • The Radiotherapy CRG's view is that the clinical effectiveness of IORT is, as yet, unproven and that the NICE recommendation has been based on a single, immature, methodologically flawed study	National Programme Director Cancer & Blood	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			• The cost effectiveness analysis does not reflect likely developments in UK breast radiotherapy practice over the next 5-10 years. • The training costs and capital required to implement the guidance as it stands have been underestimated and would be a costly financial risk for the NHS and divert funding for existing services. • This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices. • The Radiotherapy CRG does not consider the NICE recommendations to be a suitable basis for guidance to the NHS • The Radiotherapy CRG does not support the use of the INTRABEAM for the delivery of IORT in the adjuvant treatment of early breast cancer outside of well designed and conducted clinical trials.	Specialised Services		
[redacted]	NHS Professional	NHS England - Cancer & Blood Programme of Care	**Clinical Effectiveness** • The appraisal has been based on a single RCT (TARGIT A) with inadequate follow up. In this good prognosis group of patients with breast cancer, it is the clear dominant clinical and professional opinion that a minimum of 5 years of follow up should be expected before any changes to policy are implemented. The TARGIT trial has reported with a median follow up of the whole cohort of only 2 years and 5 months. • Local recurrence is higher with IORT At the initiation of the TARGIT study local recurrence rates were commonly reported of approximately 6% and it was on this basis a non-inferiority threshold of 2.5% was determined. With advances in treatment an expected local recurrence rate would be about 2%. The results of the TARGIT A trial allow for an absolute increased risk of local recurrence of	National Programme Director Cancer & Blood Specialised Services	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			2.5% to be classified as non-inferior. In practical terms, with inadequate follow duration available now, this would allow a doubling of the risk of local recurrence for patients. Given the most likely salvage treatment would be mastectomy this would be of huge consequence for patients. It effectively allows a doubling of the failure rate for breast conservation strategy for patients. There is wider evidence of higher mastectomy rates for partial breast irradiation with the ELIOT trial and other older and US insurance based registration studies. The appraisal consultation document states that 'the committee therefore concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven' (4.4.6). The Radiotherapy CRG's view is that a recommendation for IORT as a treatment option should not be made until the mature results of the TARGIT trial are published and non-inferiority is proven. • The TARGIT A trial methodology The appraisal consultation document does not fully reflect the concerns regarding the methodological flaws of the TARGIT A trial raised by the expert members of the appraisal committee. The statistical method of the trial was questioned substantially with the resignation of the chair of the Data Monitoring Committee and subsequent critical correspondence within the Lancet • Positive margins There is uncertainty about what are safe options of treatment if the pathology, post immediate IORT, demonstrates positive circumferential margins. • Current EBRT is safe and effective Breast radiotherapy using forward planned Intensity Modulated Radiotherapy (IMRT) is very safe and effective treatment offering both a low local recurrence rate and successful breast conserving option with minimal risks. Modern techniques of external beam radiotherapy have a			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			substantially lower risk relating to cardiac events and other side effects. It should be noted that there was no quality control of the EBRT delivered within the TARGIT A trial. Partial breast irradiation (PBI) reduces irradiation of normal tissue, potentially lowering late normal tissue effects and improving quality of life. IORT is only one of a number of techniques for delivering PBI. PBI can be delivered simply by all radiotherapy centres in the UK using EBRT and the results of the UK IMPORT LOW study testing whole breast radiotherapy vs PBI are awaited.			
[redacted]	NHS Professional	NHS England - Cancer & Blood Programme of Care	**Cost Effectiveness** • The EBRT comparator is not future proofed for UK breast radiotherapy practice. A large UK randomised trial (FAST FORWARD), has completed accrual, testing 15 fractions over 3 weeks versus 5 fractions over just 1 week. If this were to show non-inferiority, it would be likely that 5 fractions would become the UK standard of care within the next 5-10 years and would significantly impact the cost effectiveness modelling in favour of EBRT. One week of radiotherapy would also counterbalance important arguments made about patient experience, convenience, travel times and QOL put forward in favour of IORT. The potential future combination of hypofractionation with PBI using EBRT offers an alternative to IORT that all UK radiotherapy centres could deliver without additional investment in infrastructure. • Omission of radiotherapy has not been considered in the economic model In any informed discussion with patients in this low risk group could equally include the omission of radiotherapy. This has been tested in a number of RCTs including the UK PRIME II study. This study shows a local	National Programme Director Cancer & Blood Specialised Services	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			recurrence risk of 4.1% at 5 years with no radiotherapy. This is not fully considered in the appraisal. • Pathway assumptions based on the TARGIT trial underestimate the use of axillary radiotherapy For significant numbers of patients where greater prognostic information will not inform decision making about systemic treatment options, it is clear from the AMAROS trial that axillary radiotherapy is an equivalent option in terms of local control compared to axillary clearance but with less oedema side effects following on from axillary nodal sampling. The trend is towards the use of more radiotherapy in conjunction with breast conserving therapy. Significant numbers of patients will have axillary nodal irradiation as a subsequent treatment and so arguments about saving 15 visits of social and psychological impact for breast radiotherapy do not apply in this group. • Impact on surgical pathways Expert physics advice to the Radiotherapy CRG is that necessary routine quality assurance for the Intrabeam device requires 30-45 mins prior to each theatre session. Typically standard operation times are prolonged by 45-60 mins for the required treatment (beam on) time (30 minutes) and applicator placement, preparation and clear up (30 minutes). This will significantly impact on theatre throughput and capacity. • The workforce requirements for the safe delivery of IORT have been underestimated The radiotherapy CRG is clear that delivery of IORT should be by an appropriately trained multi-professional team including clinical oncologists, radiographers, surgeons and physicists. Two operators under IRMER would be required for checking/setting up purposes. Radiotherapy should be prescribed by a clinical oncologist. The costing of extra surgical lists, reduced theatre throughput as well as extra medical physics,			

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			radiographer and clinical oncology time are simplistic and do not place them in the context of NHS practice. The radiotherapy CRG supports the routine national collection of high quality data on clinical outcomes and this will require additional resource that has not been considered in the model. • The cost analysis underestimates equipment requirement If multiple patients are treated with IORT in a single theatre session there is a likelihood that the same applicator size may be required. The applicator cannot be used without re-sterilizing and therefore it is likely that additional applicators would be required. • Clinical input into the economic model The Radiotherapy CRG note that NICE have developed a de-novo economic model. What was the level of expert clinical advice taken about the assumptions in economic and clinical pathways? Given the complexity of the subject and uncertainties was this robust? For example the need for axillary radiotherapy was not modelled.			
[redacted]	NHS Professional	NHS England - Cancer & Blood Programme of Care	**Implications for Implementation into NHS Practice** • Inequity of Care Rightly patient choice has been a priority in this appraisal. However, there is a risk of an undue weight being applied in many areas in the evaluation on hope and expectation rather than on evidence. Of course patients would rather avoid extra visits for radiotherapy but if the alternative is a potential doubling their risk of mastectomy is this a successful strategy? Many years of clinical trials and improvements in surgery and radiotherapy have made breast conserving options a very safe and predictable one. In a balanced discussion of treatment options a significant proportion of patients will decline a treatment which potentially doubles their risk for	National Programme Director Cancer & Blood Specialised Services	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			local recurrence. Whilst there are patients for whom IORT will be an attractive option, most patients will opt for the treatment offering highest probability of disease control which is EBRT. This NICE recommendation, if left unaltered, would create inequity of care and variable practice based on differing clinical opinion and patient choices. • Wider use of IORT will have detrimental effects on surgical pathways The consequence of wider use of IORT has not been taken into account in the surgical pathway with longer operating times, reduced throughput and potential impact on Cancer Waiting Time Targets. Current pressures on CWT compliance suggest that increased demand and pressure early in the treatment pathway may be undeliverable. Radiotherapy 31 day waiting times are no longer a critical problem. Surgical referral pathways would also require reconfiguration as the radiotherapy is delivered at the time and place of surgery. It is unlikely that IORT would be available at every radiotherapy centre and the impact for patient choice about surgeon and place of surgery needs to be taken into consideration. There is a risk of fragmentation of services with IORT being delivered outside an integrated care pathway.			
[redacted]	NHS Professional	On behalf of the Specialist Breast Cancer Clinical Oncologists from the North of England Cancer Network	**Intrabeam** **Background** Current practice in the UK for the treatment of early stage breast cancer is breast conserving surgery followed by adjuvant external beam radiotherapy (EBRT) to the whole breast. EBRT requires 15 treatments, delivered consecutively during the working week. Patients therefore need to attend daily for a period of ~ 3 weeks. There is considerable interest in both shortening the duration of this treatment and reducing the amount	Consultant Clincal Oncologist	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
		(South Tees NHS Foundation Trust and Newcaslt University Teaching Hospitals)	of breast tissue that is irradiated and trials are ongoing (FAST-FORWARD[1], IMPORT-HIGH[2]). The Intrabeam device achieves both of these desires by delivering the radiotherapy dose at the end of the surgical procedure as a single dose to the tumour bed/surgical cavity. The patients deemed suitable for intraoperative radiotherapy represent a particularly low risk group of patients, in whom a discussion about the omission of radiotherapy may represent a valid treatment option, as has been tested in the PRIME II trial. **Clinical efficacy & cost-benefit analysis** Only one randomised trial has reported on the efficacy of Intrabeam compared to EBRT. TARGIT-A compared EBRT to Intrabeam in a pan-European study that recruited 3451 patients. Updated results were reported in November 2013[3], outcomes were broadly equivalent to EBRT – local control rates were essentially the same with fewer side effects. The NICE analysis[4] of the TARGIT-A data includes several key points: – The data is essentially immature with a median follow up of 2 years and 5 months). At least 5 (and preferably 10) year median follow up is required. – A significant investment would be required to provide equipment and training. – Ongoing EBRT trials may well demonstrate that further reductions in fractionation are possible with EBRT (a 5# regime)[1]. – The treatment is not suitable for all early breast cancer patients: NICE estimated 16% of patients who currently receive EBRT for breast would be eligible. The professional organisation statement on behalf of the NCRI Breast Clinical Studies Group, Royal College of Physicians and Association of Cancer Physicians (requested by NICE as part of their assessment) states[4]			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			– Breast radiotherapy of any form may not be required for certain sub-groups of the patient population in the future. **Conclusion** Trial data for Intrabeam is immature which causes uncertainty about the TARGIT-A findings of equivalent outcomes. It is likely that by the time mature data regarding Intrabeam emerges, further improvements in the use of EBRT will have occurred (reduction in number of treatments, reduction in area of breast irradiated, reduction in numbers of patients requiring any form of radiotherapy post surgery). When mature data is available, and if the subsequent cost benefit analysis were to demonstrate a clear advantage, it's not suitable for all patients requiring adjuvant radiotherapy after breast conserving surgery. The impact on our EBRT activity levels would most probably be small (assuming England average of 28% of all EBRT being breast treatments), some 4% of overall activity. The practical implementation of intraoperative radiotherapy is not straight forward. It would require considerable reorganisation of surgical as well as radiotheraputic services. We feel that the widespread adoption of intraoperative radiotherapy for breast cancer is grossly premature. **References** 1) http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=10896 2) http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=2254 3) http://dx.doi.org/10.1016/S0140-6736(13)61950-9 4) http://www.nice.org.uk/guidance/gid-tag353/resources/breast-cancer-early-intrabeam-radiotherapy-system-evaluation-report2			

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[redacted]	Healthcare Other	Ariane Medical Systems	We are delighted to see that NICE have invited comments related to the proposal to approve accelerated partial breast irradiation with low energy x-rays as per the "TARGIT-A" trial protocol. The "TARGIT-A" trial evaluated the effects of a particular radiation beam; such a beam can be generated by various technologies other than that used for the trial (just as the x-ray beams used in conventional radiotherapy can be produced by the linear accelerators of numerous manufacturers). A simple analogy would be to consider the biological effects of radiation in the same way as producing a current across a resistor, this would be identical whether the source of energy was a "Duracell" or an "Ever-Ready" battery of the same voltage. The 50kV generated by "Intrabeam" will be no different to the equivalent beam produced by another machine with appropriate filtration. A number of papers support this contention. The first is a paper on the biological effects of the "TARGIT" x-rays by Herskind et al. The characteristics of the beam from a physical and biological point of view are illustrated within the article. The second document was presented at UKRO 2013; in this Kris Armoogum shows how a comparable beam can be produced by other equipment and goes on to make further biological calculations which are beyond the scope of this correspondence. The point we are making is that the Herskind and Armoogum papers show a beam of comparable physical characteristics and biological effects of the physically defined "Intrabeam" x-rays can be reproduced using other 50kVp systems. (note: papers will be sent via email) In the UK and other countries IORT partial breast irradiation is already being delivered using alternative equipment based on the evidence of the TARGIT and other trials. Furthermore it is normal within radiotherapy practice to “fine tune” techniques on an ongoing basis using professional experience and published literature. As such it would be unusual to issue	Sales Manager	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			approval for a technique that would preclude the potential for further improvement whether due to the technology used or its application. Whilst 'TARGIT-A' has proven the efficacy of the technique, the involvement of multiple centres worldwide (in both arms of the trial) is likely to have resulted in variations in aspects of radiation delivery. Whilst these variations will clearly have been taken into account they do not appear to be considered of sufficient significance to be reported within the trial recommendations. This supports the argument that if the trial and its conclusions are robust enough to allow for 'individual' variations any minor variations from the use of alternative machines would be comparable. We are fully supportive of a draft recommendation being made by NICE with reference to the "TARGIT-A" trial protocols for IORT partial breast irradiation. However, we feel issues relating to patient selection, choice of equipment and delivery technique as described are unduly restrictive to the extent that maximum patient benefit may be compromised. In this context, as a manufacturer of x-ray brachytherapy equipment we would not wish to be excluded as a potential vendor of equipment suited for this application.			
[redacted]	Healthcare Other	Xoft, Inc.	August 14th, 2014 NICE Committee on breast cancer (early) – intrabeam radiotherapy system (GID-TAG353) To Whom It May Concern: Recently we became aware that the United Kingdom's NHS is considering approval of reimbursement for breast IORT treatments from a single vendor. We are quite pleased to learn of the growing acceptance of breast IORT in the United Kingdom, but we were disappointed and surprised to learn that only a single vendor of IORT technology had been specified. We	Chief Technology Officer	United States	I work for a manufacturer that makes a product that competes with the Intrabeam technology.

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			suggest that the reimbursement be offered for similar IORT technologies such as our Xoft Axxent System, in order to stimulate competition and offer medical providers a range of treatment options. The Xoft Axxent System is used to treat breast IORT, breast APBI, and skin and gynecological cancers in over 125 facilities in the United States, and 9 facilities outside of the U.S. The product received US FDA clearance in 2005, and received a CE Mark in 2009. Other details: – Like the Zeiss Intrabeam, the Xoft Axxent System is a 50 kV X-ray system that delivers 20 Gy of radiation to the applicator surface for Breast IORT treatments. – The Axxent product, in our opinion, offers certain advantages (mobility, multiple additional treatment indications) that may improve access to critical cancer treatments for a broader range of the population. – Over 8000 patients have been treated with the Axxent System as of May 2014, including over 1300 breast IORT patients. – Over 40 U.S. hospitals have used the Axxent System for breast IORT treatments. – Axxent is in use in over 125 facilities in the United States, including UCLA, UCSD, City of Hope Hospital, Vanderbilt, Barnes Jewish Hospital, Rush University Medical Center and Virginia Mason Medical Center. – Over 40 U.S. hospitals and 9 hospitals outside of the U.S. have used the Axxent System for breast IORT treatments. – Axxent is currently being used for breast IORT treatments in four hospitals in the United Kingdom. – Over 50 scientific and clinical publications on the Xoft Axxent System have been published over the last several years. – In 2012 the Center for Medicaid and Medicare services in the United States approved a CPT1-level reimbursement code for IORT. Code			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			77424 is specific to 50 kV X-ray treatments and applies to both Xoft and Zeiss. Again, we were stunned to learn that NICE is recommending a single company's product for breast IORT as opposed to endorsing the treatment modality. Excluding similar products unfairly limits competition and treatment choices for both physicians and patients. We urge you to reconsider this decision. Sincerely, Thomas Rusch, Ph. D Chief Technology Officer Xoft, Inc. – a subsidiary of iCAD, Inc.			
[redacted]	Research organisation - representative	Cancer Research UK	We are encouraged that NICE is looking into innovative radiotherapy techniques. Cancer Research UK and NHS England recently published a joint 10 year Vision for Radiotherapy and we recognise the important role that NICE plays in promoting uptake of innovative radiotherapy treatments on the NHS as they arise from research. But it is crucial that decisions on which treatments should be routinely used in the NHS are based on the appropriate level of evidence. In the case of Intrabeam, we believe that NICE should wait until longer term follow up data on its effectiveness is available before deciding whether to roll this treatment out on the NHS. We support the responses from the clinical and research community – namely the NHS England Radiotherapy Clinical Reference Group and the NCRI Breast Clinical Studies Group – that NICE should not approve the routine use of Intrabeam at this time.	Policy Adviser	England	
[redacted]	Research organisation -	Cancer Research UK	Women with early stage breast cancer have a high chance of surviving 10 years or more due to current standards of care, so extreme caution must be taken when appraising new therapies that could impact on cure rates, or risk of recurrence. In addition, although the draft recommendation is	Policy Adviser	England	

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
	representative		for Intrabeam to be implemented in a controlled manner, it is hard to see how a truly informed discussion with patients about the risks of this treatment can take place when evidence of the long term impacts are not clear. We hope NICE will continue to monitor the evidence base for Intrabeam and revisit the decision once the evidence of its effectiveness is more clear.			