

The Intrabeam Radiotherapy System for the adjuvant treatment of early breast cancer

1. Following comments received on its [appraisal consultation document](#) and discussion of those comments at the second appraisal Committee meeting (27 August 2014), the NICE Technology Appraisal Committee wishes to request further information from the TARGIT-A trial to be discussed in a future meeting. Its particular interest is in local recurrence and mortality rates at 5 years from randomisation and beyond. The Committee considered it needed the latest available follow-up data from the trial in order to be reassured that its recommendations are based on the best available evidence. It acknowledged that these further data and analyses would also help clinicians to offer informed choice to patients as stated in the preliminary recommendations in the appraisal consultation document.
2. The Committee noted comments from professional organisations that at least 5-year follow-up would be needed for clinicians to feel confident about data on local recurrence and to establish the clinical effectiveness of Intrabeam compared with EBRT in people with early breast cancer with low risk of local recurrence. The Committee noted that in the analysis presented in the publication of TARGIT-A (Vaidya, et al., 2014), the median follow-up duration was 2 years and 5 months in the whole trial population and 5 years in the so-called ‘earliest cohort’ (excluding participants enrolled in the last 4 years of the study; 35% of the total population). It also noted that in the analysis of local recurrence in the pre-pathology group from the recent TARGIT-A publication only 190 patients who had Intrabeam and 200 patients who had EBRT were at risk of local recurrence at 5 years, which represents 17.5% of the patients included in this subgroup (390 of 2234 patients as per Figure 3A in TARGIT-A publication), and that a 95% confidence interval around the absolute difference in the Kaplan-Meier estimates of 5-year risk of local recurrence comparing the 2 treatment groups had not been provided. The Committee heard that there are more recent data available from TARGIT-A to allow for a more up-to-date analysis.
3. The Committee also restated its previous concerns about the non-inferiority criterion in TARGIT-A given that the non-inferiority margin for the absolute difference at 5 years in the rate of local recurrence between treatment groups of 2.5% was pre-specified based on an estimated rate of 5-year local recurrence of 6% in the EBRT group.
4. The Committee noted comments from professional organisations highlighting that because of the uncertainty and immaturity of the evidence presented for Intrabeam, it is difficult for clinicians to fully explain the treatment options

available to patients, including their associated risks and benefits, so that patients can make an informed choice about their treatment.

5. Therefore, the Committee requested the following results and analyses **using the most up-to-date data:**

- a. **Please provide the full patient-level dataset so that these analyses can be critically appraised independently**

Whole study population

- a. Local recurrence:

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

Whole study population	Intrabeam	EBRT
Number of local recurrence events		

- 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:

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.
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.
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.
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

The numbers of patients at risk of local recurrence in each treatment group at yearly intervals should be reported below the plot.

(Please see Figure at end of document for an example).

- iii. 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).

b. Survival

- iv. The absolute number of deaths (n)

Whole study population	Intrabeam	EBRT
Number of deaths		

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

Whole study population, causes of death	Intrabeam	EBRT
Cause A		
Cause B		
Cause C		
...		

- vi. 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 (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.
- vii. 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.

c. Breast cancer mortality

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

Whole study population	Intrabeam	EBRT
Number of breast cancer deaths		

- ix. 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 (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.
- x. 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.
- d. Non-breast cancer mortality:

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

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

- xii. 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 (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.
- xiii. 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.
- 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		

Pre-pathology group

a. Local recurrence:

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

Pre-pathology group	Intrabeam	EBRT
Number of local recurrence events		

ii. 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:

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.
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.
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.
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

The numbers of patients at risk in each treatment group at yearly intervals should be reported below the plot.

(Please see Figure at end of document for an example).

- iii. 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).

b. Survival:

- i. The absolute number of deaths (n)

Pre-pathology group	Intrabeam	EBRT
Number of deaths		

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

Pre-pathology group, causes of death	Intrabeam	EBRT
Cause A		
Cause B		
Cause C		
...		

- 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 (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.
- 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.

c. Breast cancer mortality:

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

Pre-pathology group	Intrabeam	EBRT
Number of breast cancer deaths		

- 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 (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.

d. Non-breast cancer mortality:

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

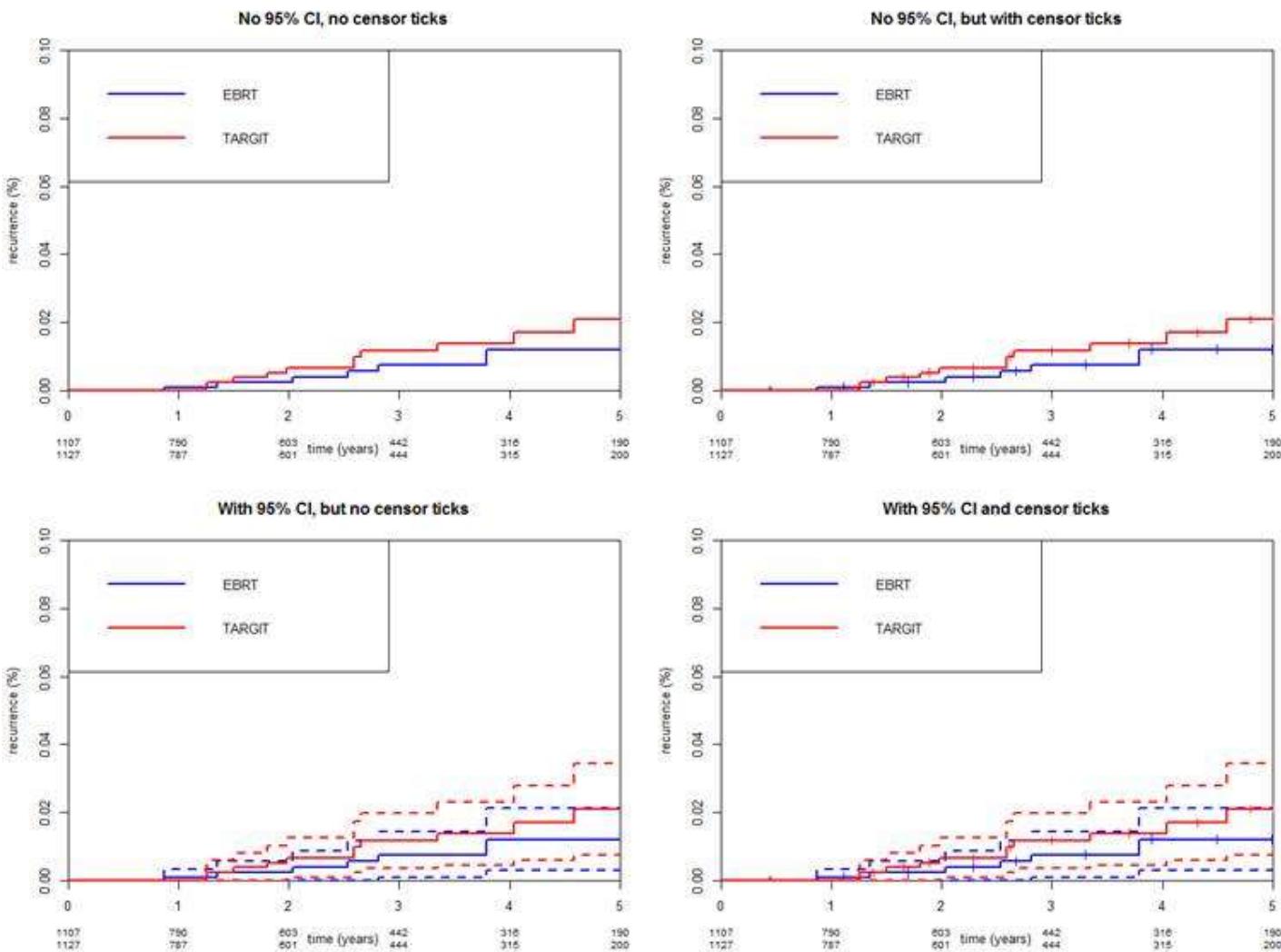
Pre-pathology group	Intrabeam	EBRT
Number of non-breast cancer deaths		

- 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 (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.

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		

Example:



Reference List

Vaidya JS, Wenz F, Bulsara M, et al. (2014) Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial *The Lancet* 383 (9917) : 603-613.