The issue of follow up duration in the TARGIT-A trial

In this short paper, we provide a detailed explanation about the follow-up of the TARGIT-A trial[1, 2] and clarify how it is long enough to be relied upon to guide the application of TARGIT using Intrabeam in routine clinical practice in appropriate patients. We have explained this in the correspondence columns of the Lancet (17 May 2014)

It may appear tempting to speculate that years in the future a difference in local recurrence will become apparent and the difference in mortality that we have already seen will go away, but neither our data nor previous trial results support this speculation, which ignores our understanding about the complex natural history of breast cancer and robust literature about the toxic effects of EBRT on other organs such as the heart. Continuing to ignore the TARGIT-A trial data can potentially put a large proportion of breast cancer patients at a significant disadvantage.

The temporal distribution of local recurrence shows that the first 2 to 3 year period covers the peak hazard of local recurrence after surgery[3, 4] (see figure 1 from SEER (Surveillance, Epidemiology and End Results) data base, Cheng et al[4]). More importantly, various local therapy trials (surgery and radiotherapy) have repeatedly shown that the effect of local therapy such as surgery or radiation is mainly seen in the first 5 years, with the peak of the hazard being bracketed by the first 2-3 years. As seen in Figure 2, the lines representing local recurrence between radiotherapy and no-radiotherapy in Kaplan-Meier plots remain virtually parallel after 5 years in the US National Surgical Adjuvant Breast and Bowel Project NSABP B06[5] (figure 2 left), NSABP B04[6], and the Oxford Overview[7] (latter two not shown). The conclusion of the 25 year follow up of the Swedish trial of radiotherapy vs. no radiotherapy[8] was explicit: "*Radiotherapy protects against recurrences during the first 5 years of follow-up..*"- whatever difference was going to be seen at 25 years was already seen at 5 years[8] (figure 2 right). The biological rationale that adequately explains these observations are covered by Retsky et al [1] and further explored in greater detail with their relevance to the interpretation of the results of randomized controlled trials by Baum in 2013[9].

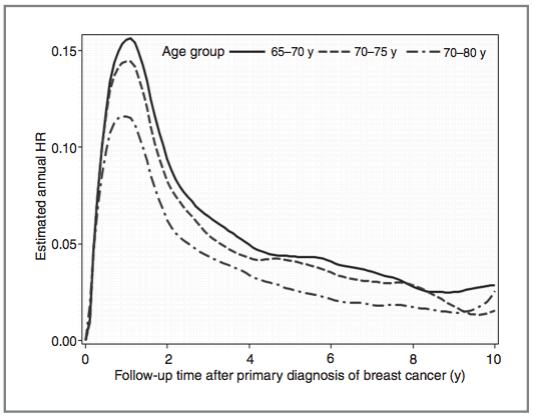

Figure 2. Smoothed hazard functions by age group for first recurrence among women after primary breast cancer treatment. The HRs describe showed hazard of recurrence for each 1-year interval.

Figure 1 is taken from 10 year follow up using data from SEER-Medicare showing that the peak hazard of recurrence is in the first 2-3 years. [4]

Statistically, it is inappropriate to use median follow up on its own without taking into account the absolute number of patients. The TARGIT-A trial has a substantial number of patients (n=1222) with a median follow up of 5 years and 2232 patient had a median follow up of nearly 4 years. As regards the number of patients (with a risk of recurrence similar to those in the TARGIT-A trial) that would have enough statistical power to prove non-inferiority in the TARGIT-A trial is much smaller because of the vanishingly low risk of recurrence. We had calculated that this number is 585 (table 6 of reference[2]). The TARGIT-A trial has many more patients than that with a 5-year follow up.

We believe that clinicians and policy makers can rely on our published results[1] and the results can be extrapolated to 10 years (figure 3).

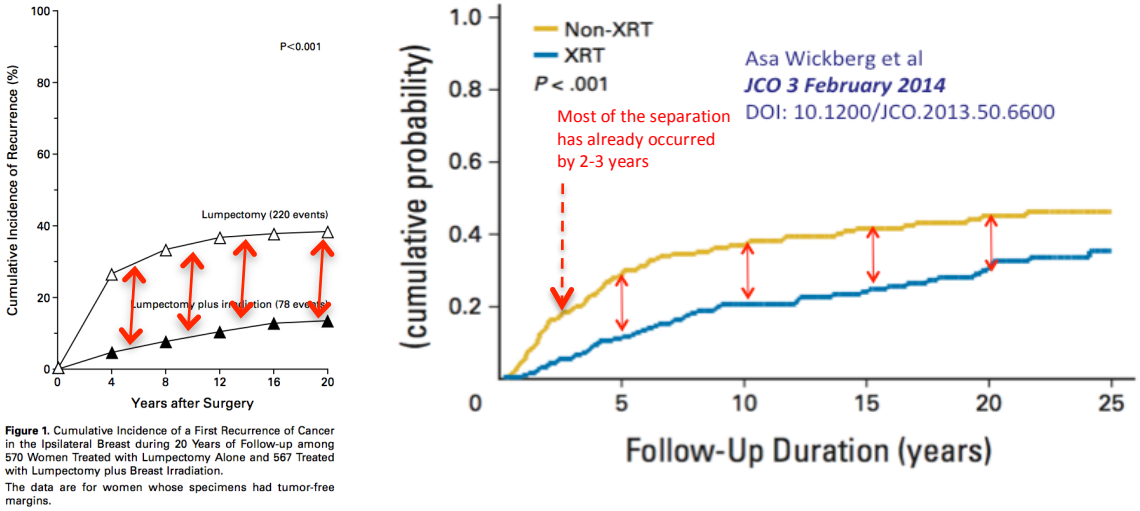

Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.
The data are for women whose specimens had tumor-free margins.

Figure 2: The effect of radiotherapy on local recurrence is only in the first 5 years and most of its benefit is already finished in the first 2-3 years. The difference between radiotherapy and no radiotherapy remains the same after the first 5 years.

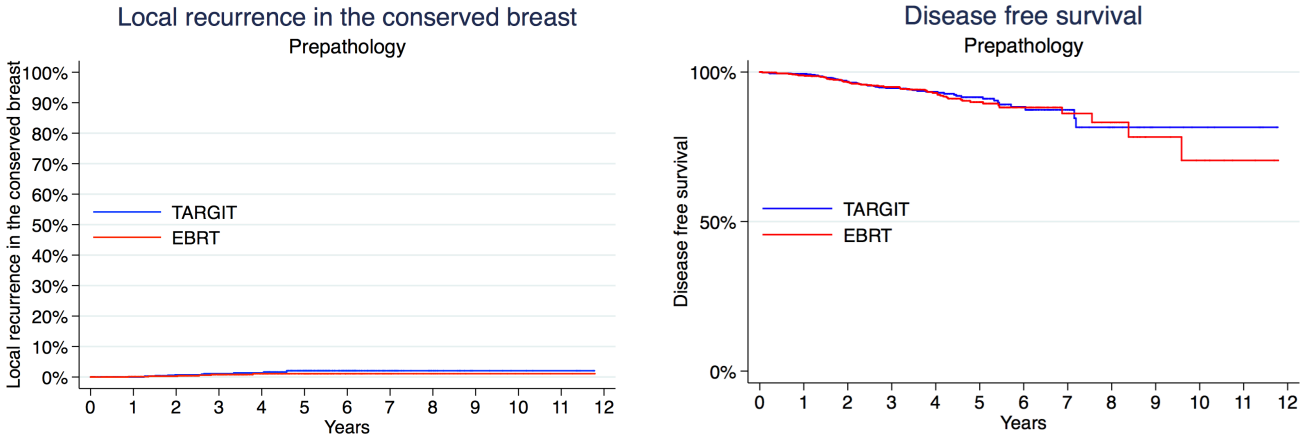

Figure 3 shows comparative results of TARGIT vs. EBRT in the Prepathology stratum in which TARGIT was given during the initial lumpectomy. Over a 12-year period it shows no significant difference between the two randomised arms in terms of local recurrence or disease free survival

The primary outcome of the TARGIT-A trial was local control and the secondary outcome was survival. Therefore, the best composite parameter to assess the comparative benefit/harm and quality of life is diseases free survival. In the latest publication[1] we concluded that the preferred method of delivery of TARGIT was during initial lumpectomy. There was no difference in the K-M estimates for disease-free survival with EBRT compared with TARGIT given during initial lumpectomy (p= 0.68). The diseases free survival at 5 years was TARGIT 91.6% (88.7-93.8) vs. EBRT 90.1% (86.8- 92.6); and at 10 years TARGIT 81.3% (71-88) and EBRT 71.2% (49-85)

The study of natural history of breast cancer and in particular its treatment with radiation therapy has repeatedly shown that the effect of radiation on local recurrence is only in the first few years -maximum in the first 2-3 years and none after the first 5 years. Therefore, in conclusion, there is already sufficient follow up data in the TARGIT-A trial for a large number of patients to allow us to derive reliable conclusions.

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