Targeted intraoperative radiotherapy tumour bed boost during breast conserving surgery after neoadjuvant chemotherapy in HER2 positive and triple negative breast cancer

Running title: IORT after NAT for TN and HER2 positive breast cancer

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Abstract

Introduction: Targeted intraoperative radiotherapy (TARGIT – IORT) as a tumour bed boost after breast conserving surgery is well established for women with early breast cancer. A previous study from our group shows a beneficial effect of TARGIT-IORT on overall survival (OS) but not disease-free survival (DFS) after neoadjuvant chemotherapy compared to an external boost suggesting a potential non-inferiority of TARGIT-IORT. In this study we present results regarding the high-risk subset of patients (i.e. with triple negative (TN) and HER2 positive tumours) from this cohort.
Method: In this non-randomized cohort study involving patients with HER2 positive (n= 28) and triple negative (n=42) tumours after NACT we compared outcomes of 40 patients with tumour bed boost applied with TARGIT IORT during lumpectomy versus 30 patients treated in the previous 13 months with external (EBRT) boost. All patients received whole breast radiotherapy. Rates of DFS and OS were compared.
Results: Median follow up was 49 months. In comparison of TARGIT-IORT vs. EBRT 5-year Kaplan-Meier estimates of OS showed no significant difference among patients with HER2 positive tumours (100% vs. 91.7%, log rank p = 0.22). The same was seen for DFS (83.3% vs. 77.0%, log rank p=0.38). The results for TN cases were similar (OS : 87.5% vs. 74.1%, log rank p=0.488; DFS 87.5% vs. 60%, log rank p=0.22).
Conclusion: Although survival estimates trended towards favouring TARGIT-IORT, no significant differences could be observed and the significantly positive result for OS favoring TARGIT-IORT in the whole cohort of 116 patients could not be reproduced in this subset analysis of patients with TN and HER2 positive tumours. This may be contributable to the limited number of patients but may also indicate that effects seen in the whole cohort were mainly driven by ER and/or PR positive and HER2 negative tumours. Most importantly, non-inferiority of TARGIT-IORT as an intraoperative boost could be reproduced in these high-risk patients.

Introduction

Since the results of the TARGIT-A trial were published (1), partial irradiation of the breast with TARGIT-IORT using an intraoperative dose of 20 Gray (Gy) with a 50kV X-Ray source is being increasingly used within a risk adapted approach to replace whole breast irradiation in selected patients (http://goo.gl/kGFSJx). It is included in several national guidelines and has been approved and reimbursed in the Australian national health system. The concept of reducing the extent of radiation is not unopposed, although the emotionality of this discussion may well be compared to oppositions against breast conservation when it was first proposed as an alternative to mastectomy.

However, use of TARGIT-IORT as an intraoperative boost has been an option for much longer. The first study for the use of this technique as a replacement for the external boost demonstrated a local recurrence rate of 1.76 % after 5 years rather than the expected 4.3 % for the external boost, a local recurrence rate that could subsequently be reproduced in other cohorts (2)(3). Even when used in high-risk patient cohorts such as patients with triple negative (TN) breast cancer in a trial using electrons as an intraoperative radiation (IOERT) the intraoperative boost resulted in a favourable outcome (4). However, although the use of intraoperative radiotherapy as an intraoperative boost is widely used in primary surgery, its use in patients who undergo breast conserving operations is still a not a standard.

In the last decade neoadjuvant therapy has become a standard of care not only for inoperable or locally advanced cases but also for smaller operable tumours. Although neoadjuvant chemotherapy has been proven to increase the rate of breast conserving surgeries this is commonly not regarded as main rationale for use. Instead, it is commonly regarded as an option for all patients where systemic therapy is definitely indicated at the time of diagnosis with the goal of improving disease free survival (DFS) and overall survival (OS) (5) by carrying the potential for response-guided treatment since allowing an in-vivo observation of chemotherapy sensitivity in an individual tumour. Regimens used in the neoadjuvant setting in clinical practice are usually extrapolated from the adjuvant therapy.

Use of chemotherapy in HER2 positive and TN breast cancer is common clinical practice, but high-risk HR positive, HER2 negative patients with tumours showing a high proliferation rate, high tumour burden in breast and/or axilla or further risk factors such as grade 3 or high risk classification based on a multigene assay may benefit from cytotoxic therapy and are therefore

also candidates for neoadjuvant chemotherapy. A lack of expression of oestrogen and progesterone receptor with or without overexpression of HER2 in combination with high proliferative activity indicated by grade 3 according to Elston and Ellis, high expression of Ki67 or genomic grade index are the main predictors for response to neoadjuvant therapy (6)(7). Achieving a pathological complete response (pCR) is considered to indicate a better prognosis especially for ER negative tumours (8). These considerations have led to an increasing number of patients receiving neoadjuvant systemic therapy before breast conserving therapy.

Patients receiving neoadjuvant systemic therapy have a higher risk for local and distant recurrence because of their tumour biology. One might expect that these high-risk patients might benefit from the better disease control achieved by intraoperative radiotherapy as a boost as mentioned above. Electrons as an intraoperative boost (IOERT) after primary systemic therapy were found to achieve excellent local control rates and a trend for superiority compared to a cohort receiving an external boost (9). First data for the use of IORT with the 50kV X-ray source in this indication have been presented by our study group in 2015 showing a favourable outcome in a one arm observational design (10).

A previous study from our group including 116 patients showed a beneficial effect of TARGIT-IORT on OS but not DFS after neoadjuvant chemotherapy compared to an external boost (11). Although these data have to be interpreted with caution because of the retrospective design of the study and the comparatively small number of patients this can be seen as a sign for non-inferiority of TARGIT-IORT as an intraoperative boost. In this study we present an analysis of the subset of patients with TN and HER2 positive tumours from this cohort in order to test the hypothesis of non-inferiority of TARGIT-IORT among in the subset of patients with high-risk breast cancer.

Method

Patients

TARGeted Intraoperative radioTherapy (TARGIT-IORT) was introduced at the Marienhospital, Bottrop, Germany, in 2010 and from April 2010 all patients undergoing breast-conserving therapy after neoadjuvant chemotherapy were treated with TARGIT-IORT boost (20Gy to the surface of the applicator) during their surgery. Use of IORT as an intraoperative boost was indicated according to the national guidelines in Germany. Patients were counselled considering use of IORT by a radiooncologist and a breast surgeon in an interdisciplinary setting. All patients gave their informed consent. The local ethics committee approved retrospective analysis of the data.

We performed a longitudinal non-randomised retrospective cohort study based upon data from the centre database including 40 consecutive patients treated between April 2010 and November 2011 as the experimental TARGIT group, 24 of whom were HER2 positive and 16 were triple negative. The control group consists of 30 consecutive patients treated with breast conserving therapy after neo-adjuvant chemotherapy in the previous 13 months (396 days). 18 patients in this group were HER2 positive, 12 were triple negative. HER2 positive tumours were defined as either 3+ in immunohistochemistry or 2+ and positive by fluorescence in-situ hybridization. Triple negative tumours were defined as 0% stained cells in immunohistochemistry for oestrogen and progesterone receptor and HER2 negative either by 0 or 1+ in immunohistochemistry or 2+ and negative by fluorescence in-situ hybridization. Postoperative external beam radiotherapy (EBRT) boost was given to all patients in the control EBRT group with 16 Gy in 8 fractions. All patients in both groups received whole breast radiotherapy with 50 Gy in 25 fractions. Radiotherapy to the supraclavicular lymph nodes was given to all patients with 4 or more histologically proven positive lymph nodes (positive either before or after neoadjuvant chemotherapy). Positive lymph nodes were confirmed with either a sentinel lymph node biopsy or core cut biopsy performed before the start of neo-adjuvant chemotherapy. Patients with positive nodes received an axillary dissection when the patient had surgery after neoadjuvant chemotherapy.

A titanium clip was placed in all tumours previous to neoadjuvant chemotherapy and the localisation of the original tumour bed prior to surgery was performed using a needle placed under control either by mammography (in the patients with a clinical complete remission) or sonography (in the patients with sonographically detectable residual disease). All specimens underwent intraoperative radiography with identification of the titanium clip. In the patients of the control group with a planned external boost 5 clips representing all levels of the tumour bed were placed intraoperatively.

Pathological complete response (pCR) in this study was defined as no residual invasive or non-invasive tumour in breast or lymph nodes. All patients in this study had negative margins after definitive surgery defined as "no tumour touching ink" and all patients with hormone receptor positive tumours – defined as ER and/or PR positive - received adjuvant endocrine therapy, postmenopausal patients received an aromatase inhibitor, premenopausal patients younger than 40 received a GnRH analogue and tamoxifen and

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premenopausal patients older than 40 received tamoxifen. All patients with HER2 positive tumours received trastuzumab starting together with the neoadjuvant chemotherapy and after surgery completed to 52 weeks. Chemotherapy regimens used were as follows: TN patients received 6 cycles of docetaxel, adriamycin and cyclophosphamide (TAC), HER2 positive patients received docetaxel, carboplatin and trastuzumab (TCH).

Statistical analysis:

Follow-up for each patient was censored in the control group by 396 days in order to ensure that the follow up of the TARGIT and EBRT groups remained similar. This exclusion of additional 13 months of follow up led to just no event being excluded from the EBRT group. Therefore, we believe that this methodology would firstly not change the results of the analysis and secondly also counter the criticism of potentially unequal follow-up between the groups.

Age and tumour size in mm were compared using the t-test. Categorical variables of grade, lymph node positivity, hormone receptor status and pathological complete response rate were compared using the Chi-square and Fisher's Exact test.

OS was calculated as time from diagnosis to time of death from any cause. DFS was defined as time from diagnosis to time of any relapse or death. Both intervals were determined and compared between the TARGIT-Boost and EBRT-Boost groups. Patients were censored at the time of last follow-up. Kaplan-Meier curves were plotted and outcomes at the 5-year time point were estimated

All of the tests were two-sided, and a p-value of < 0.05 was regarded as statistically significant. The software used was: the R system for statistical computing (version 3.0.1; R Development Core Team, Vienna, Austria, 2013), and STATA (version 14.0).

Results

Median follow-up was 49 months for both cohorts. No subject was lost to follow-up. Characteristics of the study population are shown in tables 1 and 2. Apart from tumour size before start of neoadjuvant chemotherapy in the TN group there were no significant differences between the two cohorts. The toxicity data for the cohort from which the experimental group receiving TARGIT-IORT as a boost after neoadjuvant chemotherapy was extracted have been reported before and were comparable with the average postoperative morbidity after breast conserving surgery in our institution (8).

5-year Kaplan-Meier estimates of OS showed no significant difference among HER2 positive tumors: on the cohort of TARGIT and EBRT 0 vs. 1 event occurred (100% vs. 91.7%, log rank p = 0.22). The same was seen for DFS with 2 vs. 4 events (83.3% vs. 77.0%, log rank p=0.38). The results for TN cases were similar: OS rates were 87.5 vs. 74.1% (2 vs. 3 events, log rank p=0.488) and DFS rates were 87.5 vs. 60.0% (2 vs. 4 events, log rank p=0.22). Kaplan-Meier curves can be found in figures 1 to 4.

Table 1: Patient and tumour characteristics of IORT and EBRT groups in the HER2 positive cohort.

		IORT N=24		EBRT N=18		
		N	%	N	%	
Age	Mean (SE)	55.1 (10.31)		56.4 (9.00)		0.681
Tumour size in cm at baseline (sonography)	Mean (SE)	1.88 (0.53)		2.54 (1.18)		0.019
Nodal status at baseline (SLNB or core cut biopsy)						1
	Node negative	12	50.0	9	50.0	
	Node positive	12	50.0	9	50.0	
Grade						1
	Grade 1	0	0	0	0	
	Grade 2	15	62.5	11	61.1	
	Grade 3	9	37.5	7	38.1	
ER positivity						1
	ER positive	18	75.0	13	72.2	
	ER negative	6	25.0	5	27.8	
Pathological complete response rate (PCR)						0.321
	No PCR	14	58.3	14	77.8	
	PCR	10	41.7	4	22.2	

Table 2: Patient and tumour characteristics of IORT and EBRT groups in the triple negative cohort.

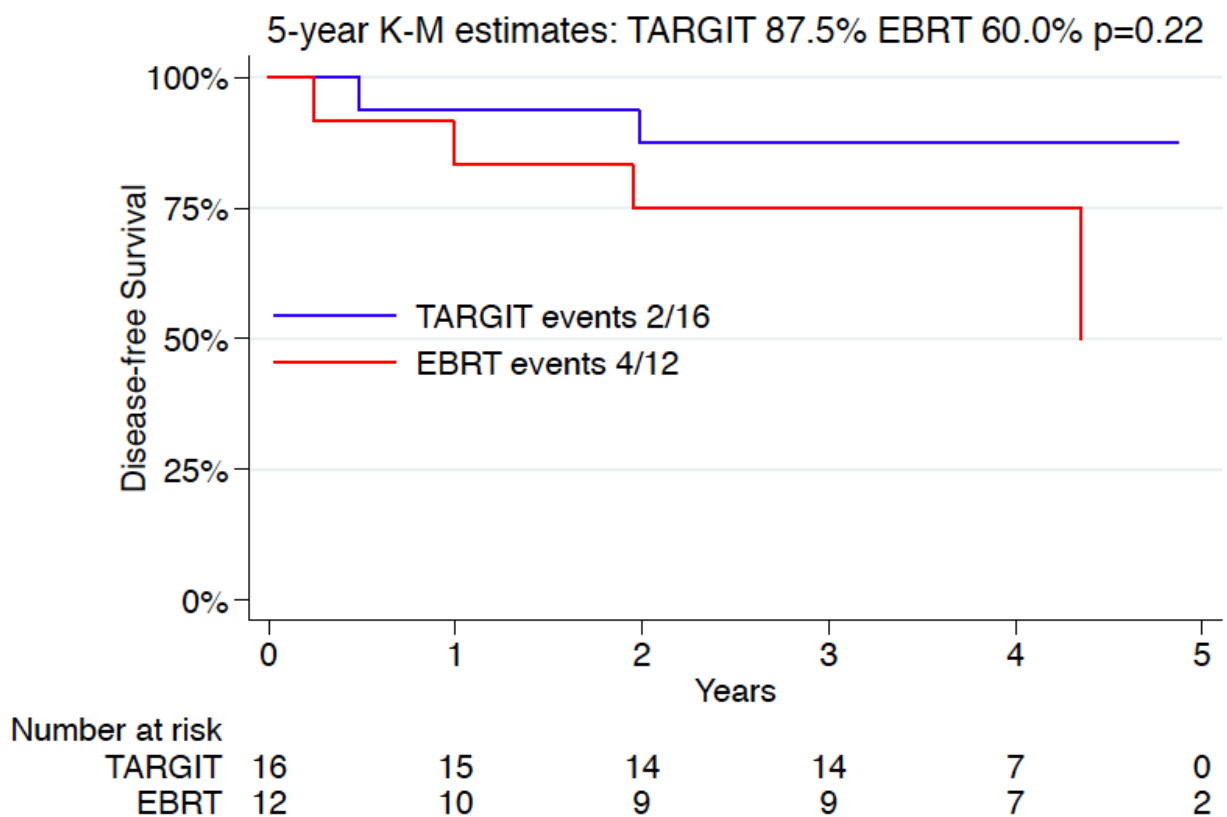|		IORT N=16		EBRT N=12		
		N	%	N	%	p-value
Age	Mean (SE)	59.3 (12.54)		54.8 (11.70)		0.336
Tumour size in cm at baseline (sonography)	Mean (SE)	1.99 (0.65)		2.29 (0.76)		0.274
Nodal status at baseline (SLNB or core cut biopsy)						1
	Node negative	9	56.3	7	58.3	
	Node positive	7	43.7	5	41.7	
Grade						1
	Grade 1	0	0	0	0	
	Grade 2	3	18.8	2	16.7	
	Grade 3	13	81.2	10	83.3	
Pathological complete response rate (PCR)						0.441
	No PCR	11	68.8	6	50.0	
	PCR	5	31.2	6	50.0	

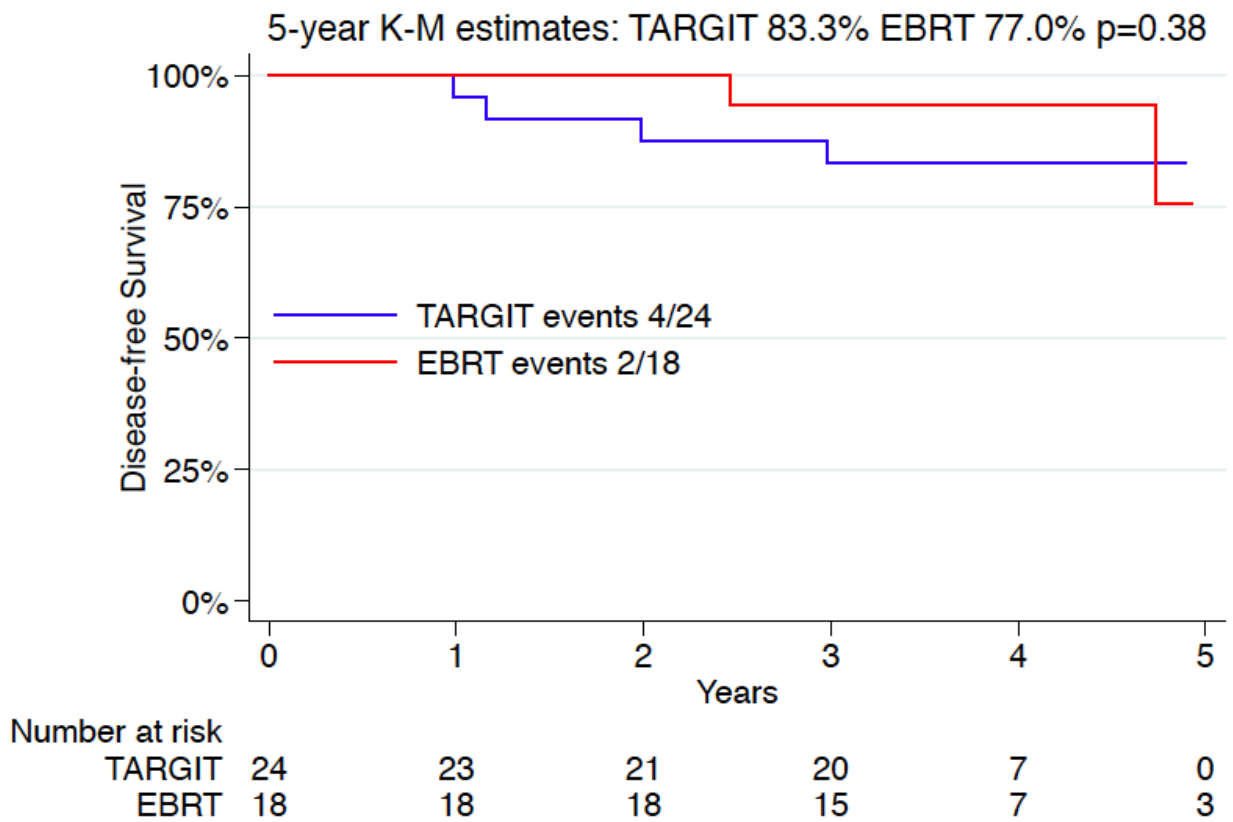**Figure 1: Disease free survival in triple negative cases**

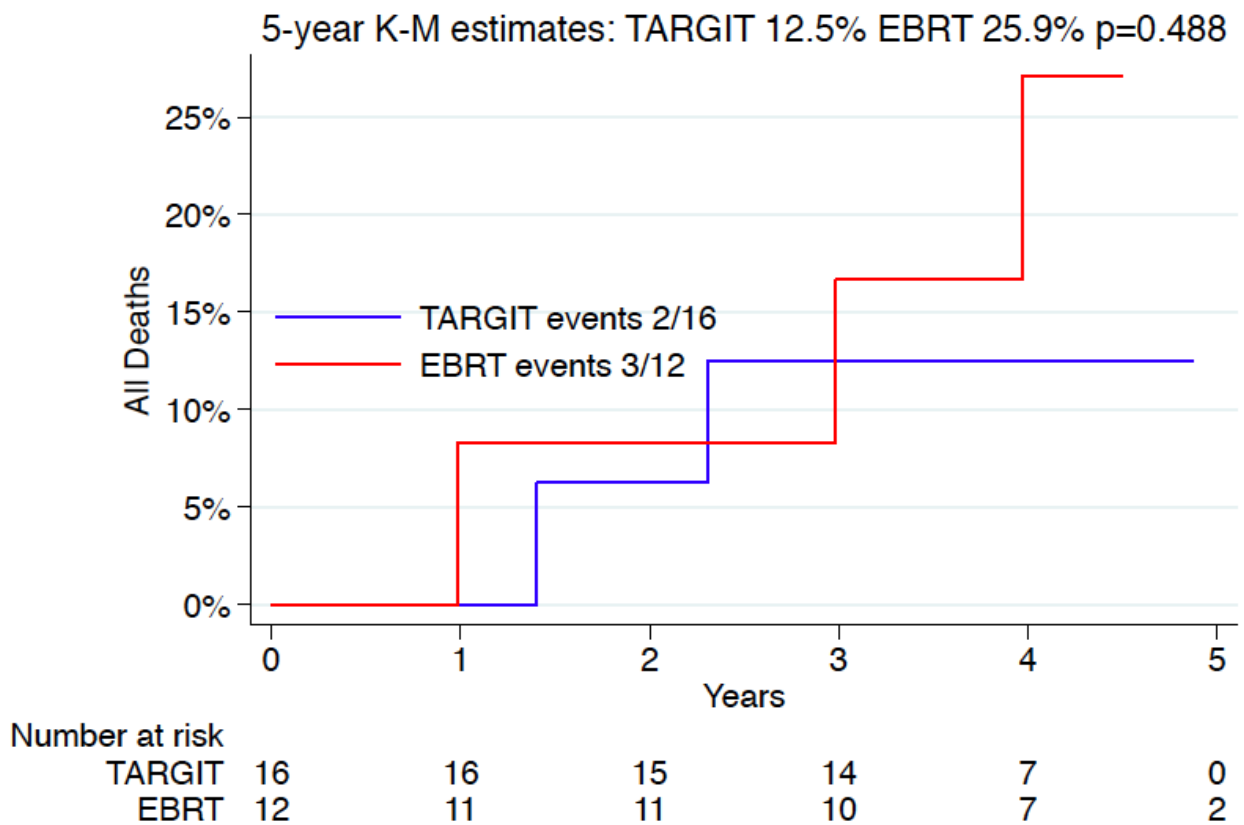**Figure 2: Disease free survival in HER2 positive cases**

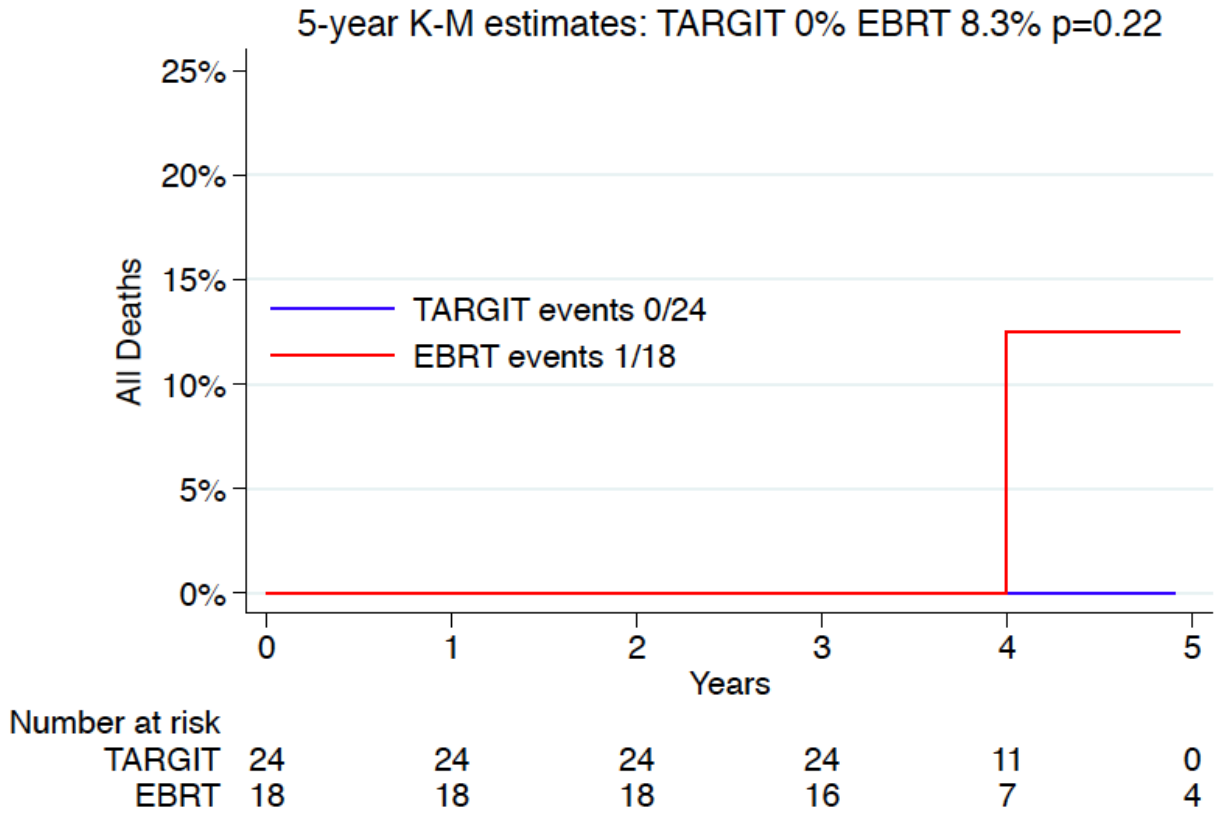**Figure 3: Overall survival in triple negative cases**

Figure 4: Overall survival in HER2 positive cases

Discussion

In this non-randomized retrospective cohort analysis we compared intraoperative tumour bed boost with a 50kV X-ray device with an external boost among patients undergoing breast conserving surgery after neoadjuvant chemotherapy including only the two high-risk groups of patients with TN and HER2 positive tumours. All patients received external beam whole breast irradiation. Disease control rates found in our series were similar. Whereas in the whole cohort reported before OS was significantly better in the TARGIT-IORT cohort (11), in this analysis of patients representing an even higher risk in the high-risk group of patients after neoadjuvant chemotherapy neither DFS nor OS differed significantly between patients receiving an external boost and patients receiving TARGIT-IORT although trends favoured TARGIT-IORT.

Initial reports about patients treated with TARGIT- IORT as an intraoperative boost during breast conserving operations suggested that it might achieve superior local control (3). This approach has become a standard in some centers, particularly in Germany and the USA. TARGIT-IORT as the only radiotherapy in the course of breast conserving surgery has been found to have local recurrence rates that are not significantly different from external whole breast irradiation in selected patients in a risk adapted approach in the TARGIT A trial (1). Regarding the question of local side effects the rate of breast fibrosis found with TARGIT-IORT is within the range seen with EBRT alone (12). In previous studies we found that adapting this approach among patients who were undergoing breast conserving therapy after neoadjuvant systemic therapy does not compromise cosmetic outcome (13); it also does not interfere with pathological evaluation of the margins and does not alter re-excision rates (14).

Patients who need to be treated with neoadjuvant therapy are generally at high risk of local and distant relapse and of death from breast cancer (15, 16). A retrospective analysis using a different technique of intraoperative radiotherapy – Intraoperative Electron radiotherapy (IOERT) compared 83 patients receiving IOERT after neoadjuvant therapy with a rather small group of 26 patients receiving conventional EBRT boost found a trend for superiority for IOERT (9).

The rationale for our investigation was based on our findings regarding the whole cohort. In this analysis patients receiving their boost as TARGIT-IORT had a statistically significant better overall survival (11). Our hypothesis was that this difference might be attributed to the fraction subset of patients that had the worst prognosis at baseline. Therefore, we decided to look at patients with TN and the HER2 positive tumours specifically.

The comparator groups were well balanced with tumour size at baseline in the TN cohort being the only significant difference. This difference seems to be irrelevant because tumour size on its own has no effect on survival when lymph node status is similar especially in patients with TN tumours (17).

Both cohorts received the same chemotherapy schedules and in the HER2-positive cohort the same amount of trastuzumab. They achieved similar proportions of pathological complete response. Endocrine therapies according to menopausal status were the same for both groups. However, even though these were consecutive patients, a selection bias cannot be excluded because this was not a randomised trial.

In the TARGIT-A study (1) there was a trend for superior overall survival with TARGIT-IORT compared with EBRT and this was mainly attributable to reduced mortality from causes other than breast cancer. It has also been suggested that the favourable effects of IORT on surgical wound fluid may result in wider systemic beneficial effects that may have contributed to the reduced mortality seen in the TARGIT-A trial. A non-randomised comparison of those patients in the TARGIT-A trial who received IORT + EBRT versus those who received EBRT found a statistically significant reduction in non-breast-cancer mortality. There were no deaths from non-breast cancer causes in the IORT+EBRT group compared with 24 in the EBRT group 0/218 vs 24/892, log-rank p = 0.012. (18). An explanation that the authors suggested for this phenomenon was a potential influence of immediate IORT on local tumour microenvironment and wound fluid that could get absorbed and cause systemic beneficial effects. Laboratory experiments using tumour cells lines have shown that would fluid after lumpectomy stimulates breast cancer cell proliferation, motility and invasiveness, an effect that is abrogated if the patient receives IORT during the lumpectomy (19). It has also previously been discussed that IORT during lumpectomy may be changing the systemic course of not just breast cancer but also that of other fatal diseases, for the better (20).

The clinical data reported from our group before (11) seem to support the hypothesis that the benefit of IORT may not be limited to avoiding a geographic and temporal miss. But due to the retrospective character of our trial we are recommending a cautious interpretation of these data. In the analysis presented in this paper including only the triple negative and HER2 positive cases we could not reproduce the significant overall survival benefit shown for the use of TARGIT-IORT as a boost after neoadjuvant chemotherapy in the whole cohort. The reason for this may be the small number of events, but it may also indicate that the results for the whole cohort were mainly attributable to the subset of patients with hormone receptor positive and HER2 negative tumours. However, trends for DFS and OS were favourable for TARGIT-IORT in the present analysis. Therefore we believe that using TARGIT-IORT as a tumour bed boost after neo-adjuvant chemotherapy is unlikely to be detrimental.

The hypothesis of a possibility of systemic beneficial effects of IORT will be prospectively tested in the TARGIT-B international randomised trial comparing TARGIT Boost vs. EBRT Boost in women who are either younger than 45 or have a higher risk of local recurrence, including those who have received neo-adjuvant chemotherapy. We encourage active participation in this trial.

Conclusion: Although trends were favourable for TARGIT-IORT, no significant differences could be shown and the significantly positive result for overall survival in the whole cohort of 116 patients could not be reproduced in this subset analysis of patients with TN and HER2 positive tumours. The reason for this may be the small number of events, but it may also indicate that the results for the whole cohort were mainly attributable to the subset of patients with hormone receptor positive and HER2 negative tumours. The non-inferiority of TARGIT-IORT as an intraoperative boost could be reproduced in these high-risk patients.

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