

Targeted intraoperative radiotherapy tumor bed boost during breast conserving surgery after neoadjuvant chemotherapy – a subgroup analysis of hormone receptor positive HER2 negative breast cancer

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Keywords: Intraoperative radiotherapy, TARGIT-IORT, neoadjuvant therapy, breast cancer, breast conserving surgery, hormone receptor positive, HER2-negative

Abstract:

Introduction: Targeted intraoperative radiotherapy (TARGIT – IORT) as a tumor bed boost during breast conserving surgery is an increasingly used option for women with early breast cancer. In a previous study our group could show a beneficial effect of TARGIT-IORT on overall survival after neoadjuvant chemotherapy compared to an external boost in an unselected cohort, a result that could not be reproduced in the triple negative and HER2 positive subgroups. In this study we present the results of a detailed subgroup analysis of the hormone receptor positive HER2 negative patients.

Material and methods: In this non-randomized cohort study involving 46 patients with hormone receptor positive HER2 negative breast cancer after NACT we compared outcomes of 21 patients who received a tumour bed boost with IORT (TARGIT-IORT) during lumpectomy versus 25 patients treated in the previous 13 months with external (EBRT) boost. All patients received whole breast radiotherapy. Disease free survival (DFS), overall mortality (OM), breast-cancer-specific mortality (BCSM) and non-breast-cancer-specific mortality (NBCSM) were compared.

Results: There were no statistically significant differences between the two groups regarding tumor size, grading, nodal status and pCR rates. Median follow up was 49 months. Whereas DFS and BCSM were not significantly different between the groups, the 5-year Kaplan-Meier estimate of OM was significantly lower by 21% with IORT: TARGIT-IORT 0 events (0%), EBRT 5 events (21%), log rank $p = 0.028$. NBCSM was significantly lower by 16% with IORT: TARGIT-IORT 0 events (0%), EBRT 4 events (16%), log rank $p = 0,047$.

Conclusion: Although our results have to be interpreted with caution due to the non-randomized nature and the small size of the cohorts, we could show that the improved OS as previously demonstrated in our dataset for TARGIT-IORT during lumpectomy after neoadjuvant chemotherapy as a tumor bed boost compared to an external beam radiotherapy boost is driven by the hormone receptor positive HER2 negative subgroup. These data give further support to the inclusion of such patients in the TARGIT-B (Boost) randomised trial that is testing whether IORT boost is superior to EBRT boost.

Introduction:

Partial irradiation of the breast with TARGIT- IORT using an intraoperative dose of 20 Gray (Gy) with a 50kV X-Ray source is an increasingly used option for selected patients within a risk adapted approach to replace whole breast irradiation after breast conserving surgery for breast cancer (Sedlmayer F, Reitsamer R, Wenz F et al. (2017) Intraoperative radiotherapy (IORT) as boost in breast cancer. *Radiat Oncol* 2017; 12: 23). Although the results of the TARGIT-A trial demonstrated a non-inferiority of this approach after a careful risk stratification¹, the concept of reducing the extent of radiation is not unopposed and remains an issue of constant debate².

The use of TARGIT-IORT as an intraoperative boost has been an option for much longer. The first studies for the use of this technique as a replacement for the external boost demonstrated a reproducible local recurrence rate of 1.76 % after 5 years rather than the expected 4.3 % for the external boost^{3 4}. 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 outcome⁵. 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 surgery after neoadjuvant chemotherapy is not a standard yet.

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 its 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)⁶ 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 the same as in adjuvant therapy.

Use of chemotherapy and especially neoadjuvant chemotherapy in HER2 positive and TN breast cancer is common clinical practice, but high-risk hormone receptor positive HER2 negative patients with tumours showing a high proliferation rate 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 potential candidates for neoadjuvant chemotherapy⁷.

Achieving a pathological complete response (pCR) is considered to indicate a favourable prognosis⁸. These considerations have led to an increasing number of patients receiving neoadjuvant systemic therapy before breast surgery.

Patients receiving neoadjuvant systemic therapy have a higher risk of local and distant recurrence because they are representing a cohort with an unfavourable tumour biology. Based on the hypothesis that these high-risk patients might benefit from the better disease control achieved by intraoperative radiotherapy as a boost as mentioned above, several groups have investigated this approach. 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 boost⁹. 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 design¹⁰.

A previous study from our group including 116 patients showed a statistically beneficial effect of TARGIT-IORT on OS but not DFS after neoadjuvant chemotherapy compared to an external boost¹¹. Although these data have to be interpreted with caution because of the retrospective design of the study and the small size of the cohorts they may be interpreted as a signal of non-inferiority of TARGIT-IORT as an intraoperative boost. An analysis of the subset of patients at highest risk with triple negative and HER2 positive tumours from this cohort showed a similar result for DFS but only a trend for a better OS without reaching statistical significance¹². Based on these results we hypothesized that the effect especially on OS in the unselected cohort was driven by the hormone receptor positive HER2 negative subgroup since the local recurrence rate after neoadjuvant chemotherapy shows significant differences according to tumor biology and in our rather short follow up of 49 months a difference in local control for a subgroup representing luminal tumors was rather improbable (Jwa E, Shin KH, Kim JY et al. (2016) Locoregional Recurrence by Tumor Biology in Breast Cancer Patients after Preoperative Chemotherapy and Breast Conservation Treatment. *Cancer Res Treat.* 2016 Oct;48(4):1363-1372.). Here we are presenting the results for this subgroup.

Material and methods

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 (20 Gy to the surface of the applicator) during their surgery. The use of IORT as an intraoperative boost was performed 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 21 consecutive patients with hormone receptor positive

and HER2 negative tumors treated between April 2010 and November 2011 as the experimental TARGIT group. The control group consists of 25 consecutive patients treated with breast conserving therapy after neo-adjuvant chemotherapy in the previous 13 months (396 days). Hormone receptor positive tumours were defined as more than 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 received adjuvant endocrine therapy, postmenopausal patients received an aromatase inhibitor, premenopausal patients younger than 40 received a GnRH analogue and tamoxifen and premenopausal patients older than 40 received tamoxifen. All patients received the same neoadjuvant chemotherapy regimen consisting of 4 cycles epirubicin and cyclophosphamide (EC) followed by 12 weeks of weekly paclitaxel.

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 one event being excluded from the EBRT group. Therefore, we believe that this methodology would not change the results of the analysis and at the same time 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 and pathological complete response rate were compared using the Chi-square and Fisher's Exact test.

The following survival outcomes were analysed and compared between the TARGIT-Boost and EBRT-Boost groups: a) Overall mortality (OM), event = any death, b) breast cancer specific mortality (BCSM), event = breast cancer death, and c) non-breast-cancer mortality (NBCSM), event=death from causes other than breast cancer, d) disease-free survival (DFS), event = any relapse or death For all outcomes patients were censored at the time of last follow up. Kaplan-Meier curves were plotted and we estimated outcomes at the 5-year time point.

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

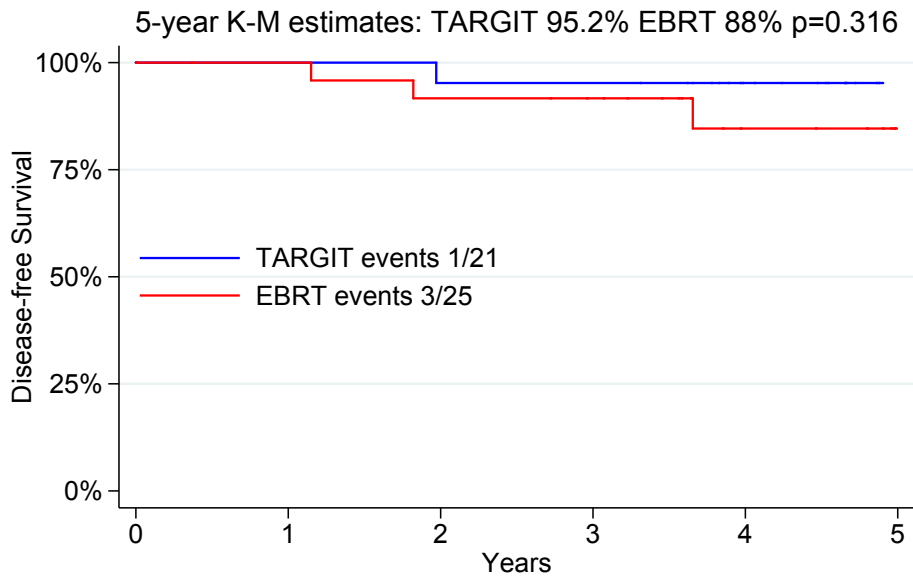
Median follow-up was 49 months for both cohorts. No subject was lost to follow-up. Characteristics of the study population are shown in table 1. Age at the time of first diagnosis was the only significant difference between the two cohorts with the TARGIT cohort being significantly younger than the EBRT cohort. 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 (10). There was no statistically significant difference between TARGIT and EBRT in terms of disease free survival and breast-cancer-specific mortality although TARGIT fared numerically better than EBRT regarding these variables. Overall mortality was lower by 21% with TARGIT.

This result and the difference in non-breast-cancer-specific mortality of 16% were statistically significant.

Kaplan-Meier curves and p-values can be found in figures 1 to 4.

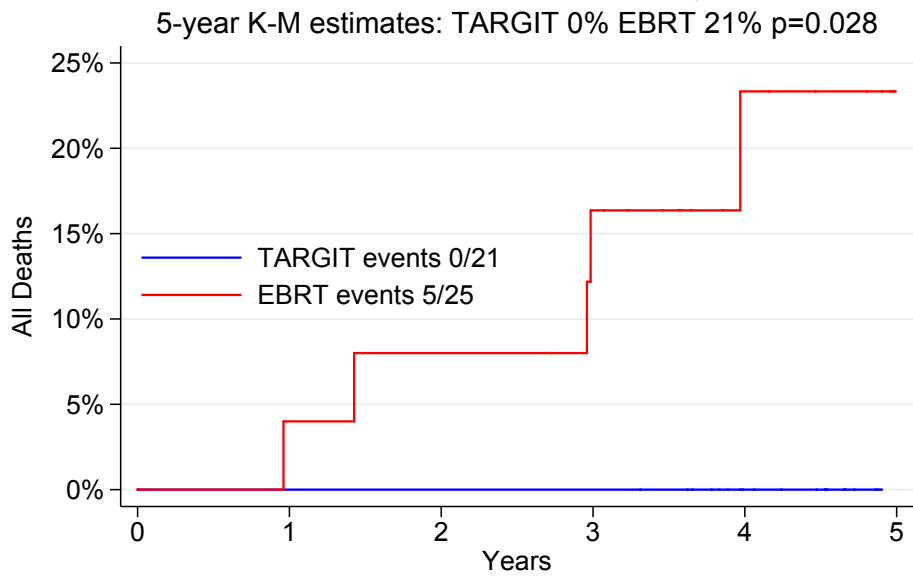
Age (years)	IORT+	IORT-		p-value	
N	21	25			
Mean	51.381	60.2			
Sd	10.84	11.453		0.011	
Tumour Size (mm)	IORT+	IORT-			
N	21	25			
Mean	26	27.84			
Sd	11.6276	9.5029		0.558	
Grading	G1	G2	G3		
IORT+	0	13	8		
IORT-	1	14	10	1	Fishers Exact
Node	Pos	Neg			
IORT+	14	7			
IORT-	16	9		1	Fishers Exact
pCR	Pos	Neg			
IORT+	4	17			
IORT-	3	18		1	Fishers Exact

Table 1: Patient and tumour characteristics



Number at risk		0	1	2	3	4	5
TARGIT	21	21	20	20	12	0	
EBRT	25	24	22	20	10	3	

Figure 1: Disease free survival



Number at risk		0	1	2	3	4	5
TARGIT	21	21	21	21	13	0	
EBRT	25	24	23	20	11	3	

Figure 2: Overall mortality

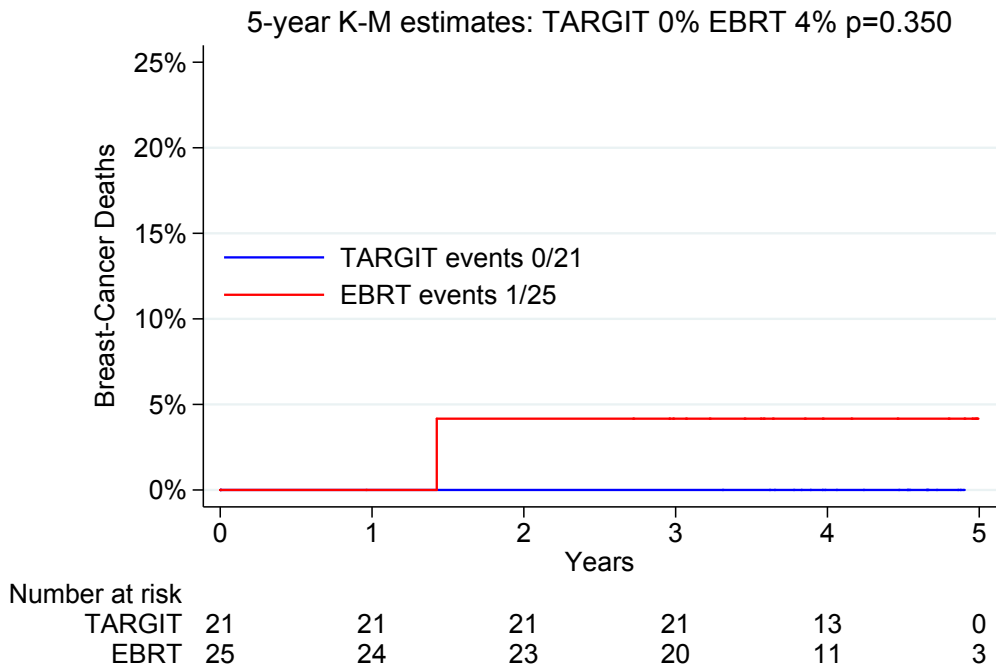


Figure 3: Breast-cancer-specific mortality

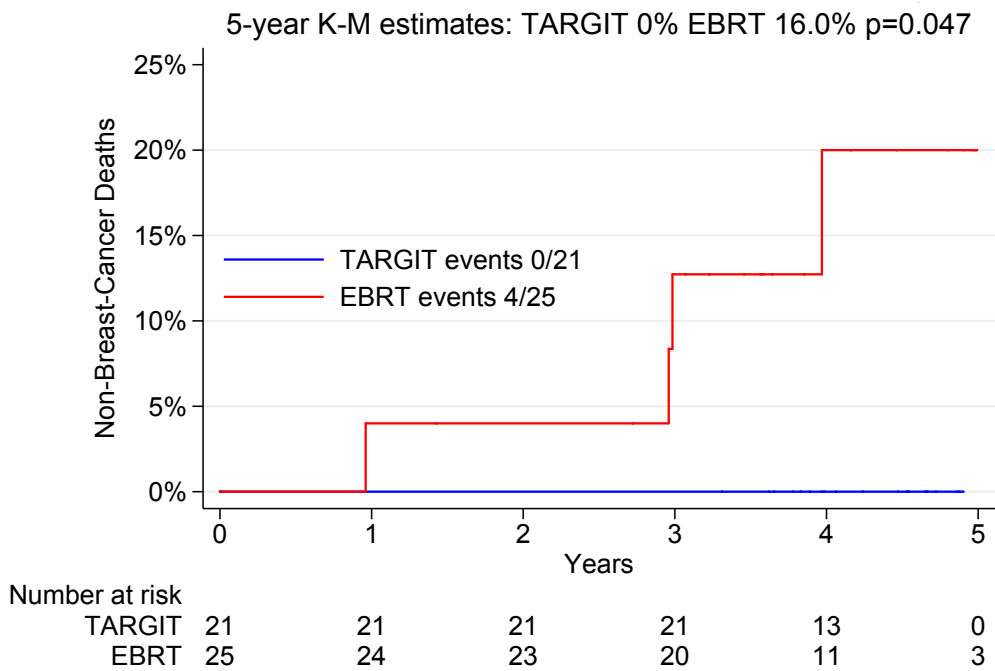


Figure 4: Non-breast-cancer-specific mortality

Discussion

Initial reports about patients treated with TARGIT- IORT as an intraoperative boost during breast conserving operations suggested that it might achieve superior local control³⁴. This approach has become a standard in several breast cancer centres particularly in Germany and the United States. In an attempt of de-escalation TARGIT-IORT was tested as the only

radiotherapy in the course of breast conserving therapy and has been found non-inferior to external whole breast irradiation in selected patients in a risk adapted approach in the TARGIT A trial¹. There has been concern regarding a possible higher rate of breast fibrosis found with TARGIT-IORT. An analysis of the TARGIT A population demonstrated a rate of breast fibrosis within the range seen with EBRT alone¹³. In previous studies of our group we found that adapting this approach among patients who were undergoing breast conserving therapy after neoadjuvant systemic therapy does not compromise cosmetic outcome¹⁴, does not interfere with pathological evaluation of the margins and does not alter re-excision rates¹⁵.

Patients who are candidates for neoadjuvant therapy are generally at high risk of local and distant relapse and of death from breast cancer^{16 17}. A retrospective analysis using a different technique of intraoperative radiotherapy – Intraoperative Electron radiotherapy (IOERT) - compared 83 patients receiving IOERT after neoadjuvant therapy with a group of 26 patients receiving conventional EBRT boost and found a trend for superiority for IOERT⁹.

In the non-randomized retrospective cohort analysis presented here 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 patients with hormone receptor positive HER2 negative tumours. All patients received external beam whole breast irradiation. The rationale for our investigation was based on our findings regarding the whole cohort. In this previous analysis patients receiving their boost as TARGIT-IORT had a statistically significant better overall survival¹¹. Based on the hypothesis that this difference might be attributed to the subset of patients with the worst prognosis at baseline we had then decided to look at patients with triple negative and HER2 positive tumours specifically. In this analysis neither DFS nor OS differed significantly between patients receiving an external boost and patients receiving TARGIT-IORT although trends favoured TARGIT-IORT¹². These findings triggered the analysis presented here assuming the effect in the unselected cohort must have been driven by the hormone receptor positive HER2 negative subgroup.

The comparator groups were well balanced with age being the only significant difference. Of course this difference has to be addressed regarding the significant difference in overall survival driven by non-breast-cancer mortality. Considering the median follow up of 49

months the mean age of 51 years in the TARGIT group and 60 years in the EBRT group will probably not have influenced the non-breast-cancer mortality difference significantly since the short time survival probability is 0.99769726 for a female aged 51 in Germany and of 0.99471509 for the age of 60 respectively (www-genesis.destatis.de).

Both cohorts received the same chemotherapy schedules and achieved similar proportions of pathological complete response. Endocrine therapies according to menopausal status were the same for both groups. However, even though we found no significant difference in patient characteristics between the two cohorts, a selection bias cannot be excluded because this was not a randomised trial.

In the TARGIT-A study¹ a trend for superior overall survival with TARGIT-IORT compared with EBRT was observed. This was mainly attributable to reduced mortality from causes other than breast cancer. It has 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 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. Tumour cell line experiments have shown that the stimulating effect of wound fluid after lumpectomy on breast cancer cell proliferation, motility and invasiveness is abrogated if the patient receives IORT during the lumpectomy¹⁹. An analysis of the same study group demonstrated an induction of miR-223 in the peritumoral breast tissue resulting in a downregulation of the local expression of epidermal growth factor (EGF) and a decreased activation of epidermal growth factor receptor (EGFR) after IORT as a possible explanation for this effect²⁰. 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 ischemic heart disease for the better²¹. Another explanation of the general effects of intraoperative radiotherapy could be a possible influence on factors of tumour immunology such as “programmed death 1” (PD-1, ligands PD-L1 and PD-L2) and “cytotoxic T-lymphocyte

antigen 4" (CTLA-4, ligands CD80 und CD 86) due to the localized character of the therapy. There are signals that local therapies may play a role in the presentation of tumour cells as antigens to the immune system thus triggering generalized immunological responses. Investigations on the use of high focused ultrasound applied to tumours for example showed an increased accumulation of natural killer cells within the tumour ²². The outcome data reported from our group before ¹¹ and reproduced in the subgroup analysis presented here seem to support the hypothesis that the benefit of IORT may not be limited to a local effect by simply avoiding a geographic miss. The significantly better overall survival in the unselected cohort as well as in the hormone receptor positive HER2 negative subgroup was driven by the significantly better non-breast-cancer specific mortality. As mentioned above a similar effect was demonstrated in the TARGIT-A study in the whole study population ¹ as well as in the subgroup of patients receiving whole breast irradiation after IORT, i.e. receiving the same therapy as our study population ¹⁸.

Due to the retrospective character of our trial we are recommending a cautious interpretation of these data, but still our findings confirm that the use of TARGIT-IORT as a boost is yielding results not worse than external boost irradiation. Regarding the supposed beneficial effect of TARGIT-IORT on non-breast-cancer-specific mortality more research is needed. We are planning a matched-pairs analysis of our dataset of the more than 700 cases treated at our institution with TARGIT-IORT as an intraoperative boost yet compared with cases treated with an external boost with a focus on comorbidities at baseline and non-breast-cancer-specific morbidity and mortality and the influence of tumour biology. Furthermore the hypothesis of possible systemic beneficial effects of IORT will be prospectively tested in the randomised TARGIT-B trial comparing TARGIT-IORT boost to an external boost in women who are either younger than 45 or have a higher risk of local recurrence. This trial is including a stratification for the use of neoadjuvant chemotherapy and planned subgroup analyses regarding tumour biology. We encourage active participation in the TARGIT-B trial.

Conclusion

In a previous analysis we demonstrated non-inferior and numerically superior overall survival attributable to a lower non-breast-cancer mortality for TARGIT-IORT during

lumpectomy after neoadjuvant chemotherapy as a tumour bed boost compared to an external beam radiotherapy boost in an unselected population. In our current analysis we could show that this difference is driven by the hormone receptor positive HER2 negative subgroup, although we acknowledge that our results have to be interpreted with caution due to a possible selection bias, the comparatively small sample size and a rather short follow-up for a hormone receptor positive cohort. These data give further support to the inclusion of such patients in the randomised TARGIT-B trial testing whether IORT boost is superior to EBRT boost and the analysis of subgroups based on tumour biology in this trial. Furthermore our results are warranting further investigation on effects of TARGIT-IORT on non-breast-cancer-specific endpoints.

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