

**Targeted intraoperative radiotherapy tumour bed boost during breast conserving surgery after neoadjuvant chemotherapy.**

**Intraoperative Strahlentherapie als vorgezogener Boost im Rahmen der brusterhaltenden Operation nach neoadjuvanter Chemotherapie.**

Hans-Christian Kolberg, MD (1), Gyoergy Loevey, MD (2), Leyla Akpolat-Basci, MD (1), Miltiades Stephanou, MD (1), Peter A Fasching, MD, PhD (3), Michael Untch, MD, PhD (4), Cornelia Liedtke, MD, PhD (5), Max Bulsara, PhD (6)(7), Jayant S Vaidya, MD, PhD (7)

1. Marienhospital Bottrop, Bottrop, Germany
2. BORAD, Bottrop, Germany
3. University of Erlangen, Erlangen, Germany
4. Helios Klinikum Berlin-Buch, Berlin, Germany
5. University Hospital Schleswig-Holstein/ Campus Luebeck, Germany
6. University of Notre Dame, Fremantle Australia
7. University College, London, England

**Corresponding Author:**

Dr. med. Hans-Christian Kolberg  
Department of Gynecology and Obstetrics  
Marienhospital Bottrop gGmbH  
Josef-Albers-Str. 70  
46236 Bottrop  
Germany  
hans-christian.kolberg@mhb-bottrop.de

**Diclosures:**

Dr. Kolberg reports personal fees from Carl Zeiss meditec, personal fees from TEVA, personal fees from Theraclion, personal fees from Novartis, personal fees from Amgen, personal fees from Janssen, personal fees from GSK, personal fees from LIV Pharma, personal fees from Genomic Health, outside the submitted work. Dr. Loevey reports personal fees from Carl Zeiss meditec, outside the submitted work. Dr. Akpolat-Basci has nothing to disclose. Dr. Stephanou has nothing to disclose. Dr. Fasching reports personal fees from Roche, personal fees from TEVA, personal fees from Genomic Health, grants and personal fees from Novartis, grants and personal fees from Amgen, personal fees from Pfizer, outside the submitted work. Dr. Untch has nothing to disclose. Dr. Liedtke reports personal fees from Celgene, personal fees from TEVA, personal fees from Pierre Fabre, personal fees from Novartis, personal fees from Amgen, personal fees from Eisai, personal fees from GSK, personal fees from Roche, personal fees from Genomic Health,

outside the submitted work. Dr. Bulsara reports grants and personal fees from Carl Zeiss meditec, outside the submitted work. Dr. Vaidya reports grants from Photoelectron corporation 1996-1999, personal fees from Carl Zeiss, non-financial support and other from Carl Zeiss, during the conduct of the study; personal fees from Carl Zeiss meditec, non-financial support and other from Carl Zeiss meditec, outside the submitted work.

## **Abstract**

**Introduction:** The use of targeted intraoperative radiotherapy (TARGIT-IORT) as a tumour bed boost during breast conserving surgery (BCS) for breast cancer has been reported since 1998. We present its use in patients undergoing breast conservation following neoadjuvant therapy (NACT).

**Method:** In this retrospective study involving 116 patients after NACT we compared outcomes of 61 patients who received a tumour bed boost with IORT during lumpectomy versus 55 patients treated in the previous 13 months with external (EBRT) boost. All patients received whole breast radiotherapy. Local recurrence free survival (LRFS), disease free survival (DFS), distant disease free survival (DDFS), breast-cancer mortality (BCM), non-breast-cancer mortality (NBCM) and overall mortality (OS) were compared.

**Results:** Median follow up was 49 months. The differences in LRFS, DFS and BCM were not statistically significant. The 5-year Kaplan-Meier estimate of OS was significantly better by 15% with IORT: IORT 2 events 96.7% (95% CI 87.5 – 99.2), EBRT 9 events 81.7% (95% CI 67.6 – 90.1), HR 0.19 (0.04 – 0.87), log rank  $p = 0.016$ , mainly due to a reduction of 10.1% in NBCM: IORT 100%, EBRT 89.9% (77.3 – 95.7), HR (not calculable), log rank  $p = 0.015$ . The DDFS was: IORT 3 events, 95.1% (85.5-98.4), EBRT 12 events, 69.0% (49.1 – 82.4), HR 0.23 (0.06-0.80), log rank  $p = 0.012$ .

**Conclusion:** IORT during lumpectomy after neoadjuvant chemotherapy as a tumour bed boost appears to give results that are not worse than external beam radiotherapy boost. 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.

**Einleitung:** Die intraoperative Radiotherapie (IORT) als vorgezogener Boost im Rahmen der brusterhaltenden Therapie (BET) ist seit 1998 Gegenstand der wissenschaftlichen Diskussion. Wir präsentieren Daten zum Einsatz der IORT bei der BET nach neoadjuvanter Therapie.

**Methoden:** In diese retrospektiven Analyse wurden 116 Patientinnen eingeschlossen, die nach neoadjuvanter Therapie brusterhaltend operiert wurden. 61 Patientinnen hatten den Boost als IORT erhalten, 55 Patientinnen hatten einen externen Boost (EBRT) erhalten. Bei allen 116 Patientinnen wurde postoperativ eine Granzbrustbestrahlung durchgeführt. Wir verglichen local recurrence free survival (LRFS), disease free survival (DFS), distant disease free survival (DDFS), breast-cancer mortality (BCM), non-breast-cancer mortality (NBCM) und overall mortality (OS).

**Ergebnisse:** Der mediane Follow –up war 49 Monate. Die Unterschiede bezüglich LRFS, DFS und BCM waren statistisch nicht signifikant. Beim 5-Jahres Kaplan-Meier-Schätzer für das OS zeigte sich ein signifikanter Vorteil von 15% für die IORT: IORT 2 Events 96.7% (95%CI 87.5 – 99.2), EBRT 9 Events 81.7% (95%CI 67.6 – 90.1), HR 0.19 (0.04 – 0.87), log rank p = 0.016, vor allem durch eine Reduktion von 10.1% bei der NBCM: IORT 100%, EBRT 89.9% (77.3 – 95.7), HR (nicht errechenbar), log rank p=0.015. Des Weiteren zeigte sich eine signifikante Verbesserung beim DDFS: IORT 3 Events, 95.1% (85.5-98.4), EBRT 12 Events, 69.0% (49.1 – 82.4), HR 0.23 (0.06-0.80), log rank p=0.012.

**Schlussfolgerung:** Die IORT als intraoperativer Boost ist dem externen Boost nach neoadjuvanter Therapie nicht unterlegen. Diese Daten unterstreichen die Wichtigkeit der Rekrutierung in die TARGIT-B (Boost)-Studie.

**Keywords:**

Targeted Intraoperative radiotherapy, IORT, neoadjuvant therapy, tumour bed boost, breast cancer

**Schlüsselwörter:**

Intraoperative Strahlentherapie, IORT, neoadjuvante Therapie, Boostbestrahlung, Brustkrebs

## **Introduction**

After publication of the TARGIT-A trial results (1), the concept of partial irradiation of the breast with IORT with the TARGIT technique using an intraoperative dose of 20 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 for use and government funding in Australian national health system. There remains a vocal opposition to reducing the extent of radiation, that is not too dissimilar to the opposition to breast conservation when it was proposed as an alternative to mastectomy. On the other hand other techniques of partial breast irradiation are also becoming part of the spectrum (2).

However, the use of IORT as an intraoperative boost has been an option for much longer. The data for the use of this technique as a replacement for the external boost show a rate of local recurrence of 1.76 % after 5 years rather than the expected 4.3 % for the external application of the boost (3). These results were reproducible in other cohorts (4). This has led to an integration of the intraoperative boost into breast conserving therapy, yielding favourable outcomes also in high risk groups such as patients with triple negative breast cancer in a trial using electrons as an intraoperative radiation (IOERT)(5). In some countries such as Germany these treatments carry full reimbursement. However, results of patients who have received an intraoperative boost with a 50kV X-Ray source after neoadjuvant chemotherapy have hitherto not been published.

The rationale for neoadjuvant chemotherapy has traditionally been for conversion from a need for mastectomy to the feasibility of breast conserving surgery. A biologically attractive reason for treating a patient with systemic therapy before surgery can be to test in vivo sensitivity to chemotherapy: for example, achieving a pathological complete response (pCR) is considered to indicate a better prognosis especially for ER negative tumours (6). There are thus 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 (7). Data for the use of IORT with the 50kV X-ray source in this indication have been first presented by our study group in 2015 showing a favourable outcome (8).

In this study we present longer term follow up outcomes after IORT as a boost after neoadjuvant therapy compared to a matching cohort that received an external boost.

## Method

Targeted intraoperative radiotherapy (IORT) was introduced in the Marienhospital, Bottrop, Germany, in 2010 and from April 2010 all patients undergoing breast-conserving therapy after neoadjuvant chemotherapy were treated with IORT boost (20Gy to the surface of the applicator) during their surgery. The use of IORT as an intraoperative boost was indicated according to the national guidelines in Germany. Patients were counselled considering the use of IORT by a radiation oncologist and a breast surgeon in an interdisciplinary setting. All patients gave their informed consent. Retrospective analysis of the data was approved by the local ethics committee on January 30<sup>th</sup> 2015.

This longitudinal non-randomised cohort study retrospectively analysing data from the database of the centre includes 61 consecutive patients treated between April 2010 and November 2011 as the experimental TARGIT- IORT group. The control group consists of 55 consecutive patients treated with breast conserving therapy after neo-adjuvant chemotherapy in the previous 13 months (396 days). Postoperative external beam radiotherapy (EBRT) boost was given to all patients in the control EBRT group as a photon boost. Patients older than 60, tumor size smaller than 2cm, no HER2 overexpression and positive hormone receptor status received 10Gy in 5 fractions, all other patients received 16 Gy in 8 fractions. All patients in both groups received whole breast radiotherapy with 50Gy in 25 fractions. Radiotherapy for 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 neo-adjuvant 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. Boost volume was defined by the location of these 5 clips.

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 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: Patients with hormone receptor positive/ HER2 negative disease (IORT: 21; EBRT: 25) received 4 cycles of epirubicin and cyclophosphamide q3w followed by 12 weeks of weekly paclitaxel (EC-Pw), triple negative patients (IORT: 16; EBRT: 12) received 6 cycles of docetaxel, adriamycin and cyclophosphamide (TAC), HER2 positive patients (IORT: 24; EBRT: 18) received docetaxel, carboplatin and trastuzumab (TCH).

The cause of death was ascertained by an independent clinician who was blind to the type of radiation used.

*Statistical analysis:*

We censored the follow up of each patient in the control group by 396 days in order to ensure that the follow up of the IORT and EBRT groups remained similar. This exclusion of additional 13 months of follow up led to just 1 event (a non-breast-cancer death) 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, HER2 status 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 IORT-Boost and EBRT-Boost groups: a) Overall survival (OS), event = any death, b) breast cancer specific mortality (BCM), event = breast cancer death, and c) non-breast-cancer mortality (NBCM), event=death from causes other than breast cancer, d) disease-free survival (DFS), event = any relapse or death e) local-recurrence-free survival (LRFS), event= local recurrence or death, f) distant disease free survival (DDFS), event = distant disease or death, g) local recurrence, h) distant recurrence and i) any recurrence. For outcomes of a to f, patients were censored at the time of last follow up. For outcomes of g, h and i, patients were censored at the time of last follow up or death. For Kaplan-Meier curves were plotted and we estimated outcomes at the 5-year time point.

Cox proportional hazard model was used to analyse the effects of age, pathological tumour size in mm, nodal status, grade, hormone receptor status, HER2 status and pathological complete response. This model was used to calculate the adjusted hazard ratio (HR) for IORT status.

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. The characteristics of the study population are shown in Table 1. Apart from tumour size before the start of neoadjuvant chemotherapy there were no significant differences between the two cohorts. The toxicity data for the cohort from which the experimental group receiving IORT as a boost after neoadjuvant chemotherapy have been reported before and were comparable with the average postoperative morbidity after breast conserving surgery in our institution (8).

During the median follow-up of 49 months 10 local recurrences, 10 distant metastases, 15 total relapses, 6 breast cancer deaths and 5 deaths from non-breast-cancer causes occurred. The results are given in Table 2.

There was no significant difference between IORT and EBRT in terms of local recurrence, distant relapse or any relapse. IORT fared numerically but not statistically better than EBRT for local recurrence free survival and disease free survival (DFS). IORT was statistically significantly better by 18.2% for distant disease free survival (DDFS).

The overall survival was higher by 15% with IORT. The 5.8% difference in breast cancer mortality was not statistically significant, but the difference in non-breast-cancer mortality was statistically significant.

*Cox proportional hazard model.* Overall survival, breast cancer survival, non-breast-cancer survival and distant disease free survival were assessed in this model. The following parameters were entered in the model, age and tumour size in mm as continuous variables: type of radiotherapy boost (IORT or EBRT), nodal status (node negative or node positive), grade (grade 1, 2 or 3), ER status (positive or negative), HER2 status (positive and negative) and pathological complete response (yes or no) status were categorical variables.

For overall survival, IORT vs. EBRT remained the only statistically significant factor with a hazard ratio of 0.19 (95% CI 0.039 – 0.903). For breast cancer survival, tumour size (HR 1.07; 95% CI 1.002 – 1.147,  $p=0.042$ ) and ER status (HR 0.067; 95% CI 0.006 – 0.723) remained significant. For non-breast-cancer-survival the difference remained statistically significant,  $p=0.011$  but hazard ratio of IORT vs. EBRT could not be calculated due to no events in the IORT group; no other patient and tumour characteristics were significant. For distant disease free survival, type of radiotherapy (IORT or EBRT) (HR 0.18; 95% CI 0.05 – 0.67,  $p=0.011$ ), and lymph node status (HR 3.98; 95% CI 1.07 – 14.7,  $p=0.039$ ) remained statistically significant.

**Table 1:** Patient and tumour characteristics of IORT and EBRT groups.

**Table 2:** Causes of death

**Table 3:** Results of survival analyses

**Figure 1.** Local-recurrence-free survival, Disease-free-survival and Distant-disease-free survival (TARGIT: targeted intraoperative radiotherapy boost / EBRT: external beam radiotherapy boost)

**Figure 2** Overall survival, Breast-cancer deaths and Non-breast-cancer deaths (TARGIT: targeted intraoperative radiotherapy boost / EBRT: external beam radiotherapy boost)

## Discussion

In this longitudinal non-randomised cohort study we compared tumour bed boost with targeted intraoperative radiotherapy vs. external beam radiotherapy, for patients undergoing breast conserving surgery after neo-adjuvant chemotherapy; all patients received whole breast radiotherapy. We found that the two treatments achieve similar local control. In this series with all the limitations of a small retrospective analysis IORT appears to be advantageous in terms of overall survival, distant disease free survival and non-breast-cancer survival.

The initial series of patients treated with IORT as an intraoperative boost suggested that it might provide superior local control rates in breast conserving surgery of breast cancer (3) and has become a standard in some centers, particularly in Germany and USA. TARGIT-Alone 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 (1). The data from Sperk and colleagues (9) has been previously misinterpreted as showing a higher level of breast fibrosis after IORT as a boost. Firstly the rate they found is within the range seen with EBRT alone, and secondly, we could not see any increase in fibrosis in our patients. In previous studies we found that adapting this approach in patients who were undergoing breast conserving therapy after neoadjuvant systemic therapy does not compromise cosmetic outcome (10); it also does not interfere with pathological evaluation of the margins and does not alter re-excision rates (11).

Patients who need to be treated with neoadjuvant therapy are generally at a high risk of local and distant relapse and of dying from breast cancer (12, 13). 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 (7).

This cohort study is the first to assess the efficacy of IORT with the 50 kV X-ray-source in patients undergoing breast conserving therapy after neoadjuvant chemotherapy.

The comparator groups were well balanced. Although the tumour size was different with IORT patients having smaller tumours, other risk factors such as triple negative or HER2 positive biology were numerically though not statistically significant higher in the IORT cohort. Both cohorts received the same chemotherapy schedules including trastuzumab in HER2-positive cases, and achieved similar proportions of pathological complete response. However, even though these were consecutive patients, a selection bias cannot be excluded because this was not a randomised trial. In the Cox model, the survival outcomes remained significant. Thus it is unlikely that the small difference in tumour size (difference in means was 0.44cm) was responsible for all the difference that we have seen in the outcomes of the two cohorts. Also, tumour size on its own has a small effect on survival when lymph node status and other tumour characteristics indicative of tumour biology are similar (14).

The improvement in overall survival was statistically significant. This result has to be interpreted with caution not only because of the retrospective design of our study, when we could not factor in any differences in comorbidities between the two non-randomised groups. In the TARGIT-A study (1), there

was a trend for superior overall survival with 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 vs. 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  $p = 0.012$ . (15). 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 wound fluid after lumpectomy stimulates breast cancer cell proliferation, motility and invasiveness, an effect that is abrogated if the patient receives IORT during the lumpectomy(16). It has also been discussed previously 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 (17).

Another possible explanation is the idea of a possible influence of IORT 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). There are strong signals that local therapies may play a role in the presentation of tumour cells as antigens to the immune system. For example, use of focused ultrasound can result in increased accumulation of natural killer cells within the tumour (18).

The clinical data in this paper seem to support the hypothesis that the benefit of IORT may not be limited to avoiding a geographic and temporal miss. However, our results need to be interpreted with caution. Although the observed survival benefit appears to be in line with the hypothesis discussed above, we cannot exclude a selection bias due to the missing information on comorbidities, location of the cancer on the left or right side and mean heart doses. A relatively small sample size, short follow-up and retrospective design are further limitations.

Nevertheless as the data in this study appear to favour IORT, we believe that using IORT as a tumour bed boost after neo-adjuvant chemotherapy is unlikely to be detrimental.

It is planned that the hypothesis about possibility of systemic beneficial effect of IORT will be tested in the TARGIT-B international randomised trial comparing IORT 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:**

In conclusion, in the first study of its kind, we found that use of IORT tumour bed boost with a 50kV X-Ray source during breast conserving therapy after neoadjuvant chemotherapy is at least not worse than external beam radiotherapy boost. The statistically significant overall survival benefit mainly triggered by non-breast-cancer deaths in our study needs to be interpreted with extreme caution due to limitations of our study design. However, these data give further support to the inclusion of such patients in the TARGIT-Boost randomised trial. When trial participation is not possible, we are reassured by these data that it is safe to use IORT as a tumour bed boost after neoadjuvant therapy.

**Conflicts of interest:**

Dr. Kolberg reports personal fees from Carl Zeiss meditec, personal fees from TEVA, personal fees from Theraclion, personal fees from Novartis, personal fees from Amgen, personal fees from Janssen, personal fees from GSK, personal fees from LIV Pharma, personal fees from Genomic Health, outside the submitted work. Dr. Loevey reports personal fees from Carl Zeiss meditec, outside the submitted work. Dr. Akpolat-Basci has nothing to disclose. Dr. Stephanou has nothing to disclose. Dr. Fasching reports personal fees from Roche, personal fees from TEVA, personal fees from Genomic Health, grants and personal fees from Novartis, grants and personal fees from Amgen, personal fees from Pfizer, outside the submitted work. Dr. Untch has nothing to disclose. Dr. Liedtke reports personal fees from Celgene, personal fees from TEVA, personal fees from Pierre Fabre, personal fees from Novartis, personal fees from Amgen, personal fees from Eisai, personal fees from GSK, personal fees from Roche, personal fees from Genomic Health, outside the submitted work. Dr. Bulsara reports grants and personal fees from Carl Zeiss meditec, outside the submitted work. Dr. Vaidya reports grants from Photoelectron corporation 1996-1999, personal fees from Carl Zeiss, non-financial support and other from Carl Zeiss, during the conduct of the study; personal fees from Carl Zeiss meditec, non-financial support and other from Carl Zeiss meditec, outside the submitted work.

## References

1. 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. *Lancet* 383(9917): 603-613
2. Krug D (2016) Accelerated partial breast irradiation using interstitial multicatheter brachytherapy : A valid treatment option for breast cancer patients with a low-risk profile? *Strahlenther Onkol* 192(2):127-129
3. Vaidya JS, Baum M, Tobias JS et al. (2011) Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys*: 81(4):1091-1097
4. Wenz F, Welzel G, Blank E et al. (2010) Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: the first 5 years of experience with a novel approach. *Int J Radiat Oncol Biol Phys*: 77(5):1309-1314
5. Fastner G, Hauser-Kronberger C, Moder A et al. (2016) Survival and local control rates of triple-negative breast cancer patients treated with boost-IOERT during breast-conserving surgery. *Strahlenther Onkol* 192(1):1-7
6. Huober J, von Minckwitz G, Denkert C et al. (2010) Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: Overall results from the gepartrio study. *Breast Cancer Res Treat* 124:133-140.
7. Fastner G, Reitsamer R, Ziegler I et al. (2015) IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer – Results of a case series after 5-year follow-up. *Int J Cancer*: 136: 1193-1201
8. Kolberg HC, Loevey G, Akpolat-Basci L et al. (2015) Intraoperative radiotherapy as a boost after neoadjuvant chemotherapy: DFS after a median follow-up of 4 years. *J Clin Oncol* 33 (suppl: abstr e12050)

9. Sperk E, Welzel G, Keller A et al. (2012) Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. *Breast Cancer Res Treat* 135(1):253-260
10. Kolberg HC, Stephanou M, Akpolat-Basci L et al. (2013) Intraoperative Radiotherapie mit dem Intrabeam® als vorgezogener Boost bei der brusterhaltenden Therapie des Mammakarzinoms - Erfahrungen nach den ersten 200 Fällen. *Senologie* 2013; 10 - A73
11. Kolberg HC, Stephanou M, Akpolat-Basci L et al. (2014) Intraoperative Radiotherapie mit dem Intrabeam® als vorgezogener Boost nach neoadjuvanter Chemotherapie des Mammakarzinoms – Erfahrungen nach den ersten 130 Fällen. *Senologie* 11: A67
12. Loibl S, Volz C, Mau C et al. (2014) Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. *Breast Cancer Res Treat* 144:153-162
13. Krug D, Lederer B, Debus J (2015) Relationship of omission of adjuvant radiotherapy to outcomes of locoregional control and disease-free survival in patients with or without pCR after neoadjuvant chemotherapy for breast cancer: A meta-analysis on 3481 patients from the Gepar-trials. *J Clin Oncol* 33 (suppl: abstr 1008)
14. Dent R, Hanna WM, Trudeau M et al. (2009) Time to disease recurrence in basal-type breast cancers: effects of tumor size and lymph node status. *Cancer* 115(21), 4917–4923
15. Vaidya JS, Bulsara M, Wenz F, et al. (2013) The Lower Non-Breast Cancer Mortality With TARGIT in the TARGIT-A Trial Could Be a Systemic Effect of TARGIT on Tumor Microenvironment. *Int J Radiat Oncol Biol Phys* 87(2): S240
16. Belletti B, Vaidya JS, D`Andrea S et al. (2008) Targeted Intraoperative Radiotherapy Impairs the Stimulation of Breast Cancer Cell Proliferation and Invasion caused by Surgical Wounding. *Clin Cancer Res* 14(5): 1325-1332
17. Vaidya JS, Bulsara M, Wenz F (2013) Ischemic heart disease after breast cancer radiotherapy. *New Engl J Med* 368(26):2526-2526.
18. Sta Maria NS, Barnes SR, Weist MR et al. (2015) Low Dose Focused Ultrasound Induces Enhanced Tumor Accumulation of Natural Killer Cells. *PLoS One* 10(11):e0142767

