

REVIEW

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# Intraoperative radiotherapy (IORT) as boost in breast cancer

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## Abstract

The term IORT (intraoperative radiotherapy) is currently used for various techniques that show huge differences in dose delivery and coverage of the tissue at risk. The largest evidence for boost IORT preceding whole breast irradiation (WBI) originates from intraoperative electron treatments (IOERT) with single doses around 10 Gy. At median follow-up periods at 6 years, outstandingly low local recurrence rates of less than 1% are observed. Higher local relapse rates were described for G3 tumors and triple negative breast cancers as well as for IORT following primary systemic treatment for locally advanced tumors. Even there, long term (>5y) local tumor control rates mostly beyond 95% were maintained. Compared to other boost methods, an intraoperative treatment has evident advantages in terms of *precision (by avoiding a "spatial and/or temporal miss")*, *cosmetic outcome and patient comfort*. Direct visualisation of a tumor bed during surgery guarantees for an accurate dose delivery, which has additionally gained importance in times of primary reconstruction techniques after lumpectomy, since IORT is performed before breast tissue including parts of the tumor bed is mobilized for plastic purposes. As a consequence of direct tissue exposure without distension by hematoma/seroma, IORT allows for small treatment volumes and complete skin sparing, both having a positive effect on late tissue tolerance and, hence, cosmetic appearance. Boost IORT marginally prolongs the surgical procedure, while significantly shortening postoperative radiotherapy. Its combination with external beam radiotherapy to the whole breast (WBI) is currently tested in two multicentric prospective trials: as kV-IORT in the multicentric TARGIT-B (oost) study, and as IOERT in the HIOB trial (3 weeks hypofractionated WBI preceded by IORT electron boost).

**Keywords:** IORT, Intraoperative radiotherapy, IOERT, Boost, Electrons, Orthovoltage, Breast cancer, Tumor bed, Cosmesis, hypofractionation

## Introduction

In the Western World, breast cancer mortality rates have declined since 1975, attributed to the increased use of screening mammography and greater use of adjuvant treatments, including radiotherapy. For locoregional treatment, breast-conserving therapy is regarded as standard of care, comprising breast conserving surgery followed by ipsilateral whole-breast irradiation (WBI) as an integral component.

Postoperative radiotherapy significantly reduces local recurrence rates. The more pronounced the achieved reduction, the more substantially it translates into improved

survival. Four prevented local recurrences result in one avoided breast cancer death [1, 2].

## Rationale for IORT and Biology of Single High Doses

Pathological analyses revealed that the greatest tumour cell density (up to 90% of microscopic remainders) is observed in an area of 4 cm surrounding the macroscopic tumour edge [3, 4]. As a consequence, after a breast-conserving operation, the tumor bed represents the region with the highest probability of in-breast recurrence. Therefore, an additional booster dose to the tumor bed significantly reduces local recurrence rates [5]. Up to now, these boosts are traditionally still applied mostly by external beam electrons of 10–16 Gy (5–8 × 2 Gy) or, alternatively, by interstitial implants (HDR-brachytherapy).

The idea of intraoperative irradiation (IORT) during breast-conserving surgery is the delivery of a high single

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boost dose to the area at highest risk for subclinical tumour cell contamination with utmost precision, due to direct visualisation. The method was originally introduced by the Medical College of Ohio (MCO) in Toledo, Ohio, USA, and the Centre Regional de Lutte Contre Le Cancer (CRLC) in Montpellier, France, based on reports of 72 patients treated with an electron boost (intraoperative electron radiotherapy (IOERT)) [6–8].

Compared to squamous cell carcinoma, breast cancer seems to show a different sensitivity towards higher single doses. In 1989, Fowler postulated an alpha/beta ratio of 4 for breast cancer as its best approximation instead of 10 for most SCC [9]. This value was strongly supported by the clinical outcome of Canadian and British Hypofractionation Trials [10, 11]. A lower ratio results in higher sensitivity against higher doses per fraction, an argument clearly in favour of IORT. In the linear quadratic model, using an alpha/beta value of 4, an IORT dose of 10 Gy amounts to a BED of 35, hence, being isoeffective to a boost of about 24 Gy when applied in single fractional doses of 2 Gy. However, the model was only tested for single doses below 15 Gy [12]. The prediction of isoeffects of doses above this level leaves open questions and has to be further evaluated.

Beyond these dose-effect extrapolations, it was hypothesized that immediate irradiation during surgery has implications on the tumor microenvironment abrogating the proliferative cascade induced by surgical wound healing. In vitro, wound fluid has been described to stimulate tumor cell proliferation and invasion, which can be blocked by a high-dose IORT [13, 14]. Another aspect is the prevention of possible residual tumor cell repopulation between surgery and adjuvant radiotherapy. Furthermore, a good oxygenation status of the tumor bed during operation could also be a factor for enhanced biological effectiveness, which has not been investigated yet. All these cellular and trans-cellular reactions of irradiated tissues are neither clarified in detail nor understood in their particular impact on clonogenic cell inactivation—and hence, local control—and are subject of ongoing research [15–17].

### IORT Treatment Techniques

In the late 1990s, a broad clinical IOERT application started at the European Institute of Oncology (EIO) in Milan, Italy, and the Paracelsus Medical University (PMU) in Salzburg, Austria. Since then, IORT to the tumor bed during breast-conserving surgery has become a booming field of interest for partial breast irradiation, either as an anticipated boost or as the sole treatment strategy in limited-stage breast cancer.

This has given rise to the development of different technical approaches, with the term “IORT” now primarily used for the following techniques: low-kV orthovolt systems (e.g., Intrabeam) and intraoperative radiotherapy with electrons on mobile or standard linear accelerators (IOERT).

The orthovolt systems consist of a miniature, electron driven, low-kV energy X-ray source, emitting an isotropic X-ray spectrum. For breast irradiations, spheric applicators, chosen according to the excision cavity’s size, are put at the top of the source, resulting in a spherical dose delivery with very steep dose fall-off.

*Linac-Based IOERT* is possible with various electron energies (4–18 MeV). After tumour removal, the tissue surrounding the excision cavity is surgically mobilised and temporarily approximated by sutures in order to bring adjacent walls into reach of the electron beam. The tissue thickness is usually measured by intraoperative ultrasound for individual depth dose prescription, choice of proper electron energies, and electron tube diameters providing safe coverage of the tumour bed, respectively, building clear dosimetric and volumetric advantages in comparison to the kV system. The dosimetric properties of the two IORT methods in terms of dose homogeneity, flexibility towards asymmetric target volume shapes, and their consequent ability to deliver a specified minimum dose to a given volume differ tremendously [18]. Hence, outcome analyses of local control rates as well as cosmetic results after “IORT” must be performed according to the used technique.

### IORT Treatment Concepts: Boost versus Single Modality

For both technical IORT approaches (electrons and orthovolt), two different treatment concepts are proposed:

- (1) IORT as full dose partial breast irradiation (PBI) with either electrons (ELIOT) or orthovolt devices (TARGIT);
- (2) IORT as anticipated boost followed by whole-breast radiotherapy (WBI) (BIO-boost = breast intraoperative boost).

Pros and cons of PBI strategies including application by IORT are matter of ongoing debate [19–22]. Interpretation of the so-far results following sole IORT—by any means—to be isoeffective towards whole-breast treatment strategies is premature, the respective trials show partially conflicting results and, most important, median follow-up periods below 4 years [22, 23]. True local recurrences, however, are presumed to occur between 40 and 65 months after primary treatment [24, 25], out-quadrant relapses even later than that [26] when WBI was performed. Only adequate long term experience will reveal the potential of a sole IORT approach to replace WBI in selected patient groups. Therefore, this paper focuses on results after Boost IORT, where the duration in follow-up shows by far higher maturity, and is supplementing a previous publication [27].

Boost IORT addresses the question of whether this approach is an effective and/or superior alternative to conventional boost techniques. The advocates of a BIO-boost emphasise the use of lower single doses compared with a full-dose concept, with dose ranges well understood in terms of tumour effects and late tissue reactions. Since IORT is followed by WBI, the concept still accounts for the (unknown) risk of occult tumour burden in distant quadrants. Therefore, it is less vulnerable to a possible underdosage in the periphery of a tumour bed and—unlike PBI concepts—remains applicable in every risk constellation.

## Clinical Results

### Boost IORT with Electrons (IOERT)

Despite its retrospective character, the International Society of Intraoperative Radiotherapy (ISIRT) Europe pooled analysis on IOERT provides the best available evidence so far [28, 29].

#### *The ISIRT Europe Pooled Analysis (BIO-Boost) [29]*

The joint investigation evaluated the long-term outcome of the IOERT strategy aimed at reducing local recurrence in breast cancer and was carried out in a joint effort by seven institutions from Austria, Germany, Italy, and France—all members of ISIRT's European Group (ISIRT Europe). Until October 2005, 1109 unselected patients of any risk group have been identified among seven centers using identical methods, sequencing, and dosage for intra- and postoperative radiotherapy. A median IOERT dose of 10 Gy was applied (90% reference isodose), preceding WBI with 50–54 Gy (single doses 1.7–2 Gy). 60% of all patients presented with at least one of the following adverse prognostic factors for local recurrence: tumour size > 2 cm, high grade, age < 45 years, and positive lymph nodes. In the most recent long-term analysis, at a median follow-up of 72.4 months (0.8–239), only 16 in-breast recurrences were observed, half of them accounting for true local recurrences; this yields an in-breast tumour control rate of 99.2% at 73.3 months. Relapses occurred 12.5–151 months after primary treatment. In a multivariate analysis, grade 3 tumour was found to be predictive of recurrence ( $p = 0.031$ ). A significant univariate trend was found for in-breast relapse in case of negative hormonal status and young age (below 40 years). Annual in-breast recurrence rates amounted to 0.64%, 0.34%, 0.21%, and 0.16% in patients <40 y; 40–49 y; 50–59 y, and  $\geq 60$  y, respectively. In all risk subgroups, a 10 Gy IOERT boost prior to WBI provided local control rates which compare favourably to the reported figures in all trials with similar length of follow-up, irrespective of the used boost methods [5, 30–32].

To ascertain the role of a WBI delay following IOERT, three time slots were considered: WBI onset <70 days, >70  $\leq$  140 days, and >140 days after IOERT, respectively. Along these slots, no influence on LR rates could be

identified. Patients recurring showed a mean time gap between their IOERT and WBI of 7.5 weeks (range: 3.2–31.6).

Furthermore, in a retrospective matched-pair analysis, 188 patients with external e-boost ( $6 \times 2$  Gy Dmax (1.8 Gy ref D)) were compared to the pooled analysis' first 190 patients from Salzburg IOERT (10 Gy Dmax (9 Gy ref D)) [33]. At 10-year follow-up, the in-breast recurrence rate in the external e-boost group was 7.2% and 1.6% in the IOERT group, respectively. This significant difference was almost entirely due to a reduction in true local recurrence.

### Boost IORT with Low-Kilovoltage X-Rays

Compared to IOERT, clinical long term experience following boost IORT with 50 kV X-rays is yet less solid, with published updates of two larger cohorts available [34, 35].

In a multicenter pilot study prior to the international Targit A-trial, the feasibility of 50 kV-IORT was tested among participating institutions [34]. Between 1998 and 2005, 299 patients were treated with a 20 Gy IORT boost (surface dose) during breast conserving surgery (BCS), followed by 45–50 Gy WBI (2 Gy single fraction) after wound healing or completion of adjuvant chemotherapy when indicated. After a median follow-up of 5 years, eight ipsilateral tumor recurrences were reported, resulting in a recurrence rate estimate of 1.73% (SE 0.77, Kaplan-Meier) and an observed rate of 2.67%, respectively. The authors concluded that, for patients with similar selection at risk for in-breast relapse, their findings compared favorably to the tumor control rates achieved in the EORTC boost trial [5] or the START-B trial [32].

A second series provides a single-center experience following kV-boosts with 18–20 Gy plus WBI (46–50 Gy/2 Gy per fraction) [35]. A total of 197 patients were treated, with the cohorts partially overlapping with the multicenter study. The last update was published at a median follow-up period of 37 months. At this point of time, six in-breast events were recorded (5 invasive, one in situ relapse), accounting for a 3% in-breast recurrence rate (both at 3 and at 5 years).

Compared to the results following IOERT, local recurrence rates look somewhat higher, despite similar patient selection. In addition, sample sizes were significantly lower, and follow-up was also less mature. However, a definitive answer on the superiority of a respective IORT method would necessitate a randomized trial. Indirect evidence on the basis of observational head-to-head comparisons indicates a trend in favor of IOERT. A possible explanation might be the superior coverage of breast tissue by electrons, where larger volumes of a putative tumor bed are treated with uniformly high doses. Moreover, clinical target volumes often appear asymmetric, which is better compensated by IOERT in terms of spatial direction of dose deposition (margin-directed applicator guidance) [18].

### Boost IOERT for the new “high risks”

#### *Boost IOERT after Primary Systemic (Neoadjuvant)*

##### *Treatment*

In patients with locally advanced breast cancer (LABC), in-breast tumor recurrence rates (IBTR) are reported to be increased after breast BCS following primary systemic treatment (PST). To date, there are no publications on the effect of an IOERT boost in these high-risk constellations. In a retrospective analysis, a subgroup from the Salzburg cohort was evaluated for subsequent IBTR following PST, BCS, and IOERT preceding whole breast irradiation [36].

Eighty-three patients with clinical stage II or III breast cancer treated between 2002 and 2007 were identified and analysed in 2012. Patients received 3 to 6 cycles of anthracycline/taxane containing preoperative chemotherapy. All patients had breast conserving surgery with sentinel node biopsy and axillary lymph node dissection and received IOERT with 9 Gy to the 90% reference isodose as anticipated tumor bed boost. WBI was performed after surgery for all patients with single fractional doses of 1.7–1.8 Gy (5x/week) to total doses of 51–57 Gy.

Two patients refused WBI, leaving 81 patients for further analysis. Pathologic complete response was achieved in 14/81 (17%) patients. After a median follow-up of 59 months (range 3–115), two IBTR, both in the former index quadrant, were observed, corresponding to a local control rate (LC) of 98.5%. In this retrospective analysis, boost IOERT turned out to be a highly effective tool for the prevention of IBTR in LABC following neoadjuvant chemotherapy, likewise to its demonstrated potential in multimodal adjuvant regimen.

#### **IOERT in triple-negative Breast Cancer**

In a retrospective evaluation, survival and local control rates of triple-negative breast cancer subtypes, treated with breast-conserving surgery and boost IOERT followed by WBI, were analysed [37]. Triple-negativity was subclassified as five marker negative (5NP) and core basal (CB) types, respectively. A total of 71 patients were enrolled, chemotherapy was applied in a neoadjuvant (12%), adjuvant (75%), or combinational setting (7%).

After a median follow-up of 97 months (range 4–170 months), 5 in-breast recurrences were detected (7.0%). For all patients, 8-year actuarial rates for local control, metastases-free survival, disease-specific survival, and overall survival amounted to 89, 75, 80, and 69%, respectively. All local recurrences occurred in grade 3 (G3) tumors irrespective of their specific immunohistochemical phenotype; thus, the local control rate for grades 1/2 (G1/2) was 100% for both 5NP and CB, while for G3 it was 88% for 5NP and 90% for CB ( $p = 0.65$  and  $0.82$ , respectively, n.s.). For disease-specific survival, only the difference of the best-prognosis group 5-NP/G3 vs. the worst-prognosis cohort CB/G1/2 was statistically significant: 90% vs. 54% ( $p = 0.03$ ).

In sum, in this prognostically impaired subgroup of breast cancer patients, boost-IOERT also provided high long-term in-breast control, comparing favourably with results from non-IORT cohorts.

#### **Toxicity and Cosmesis following Boost IORT**

In all studies, IORT manoeuvres turned out to be safe and feasible, showing no treatment related mortality or excess acute local morbidity in terms of delayed wound healing or infection rates compared to conventional treatment [6, 38–40]. As to late reactions, cumulative incidences of fibrosis/sclerosis within the IORT volumes were slightly different according to the treatment concept: for boost patients, tolerance was excellent with incidences of 20–25% G1-2 and less than 2% G3-reactions [6, 8, 41, 42]. Following full-dose IORT, reported rates amounted up to 80% G1, 30% G2, and up to 6% G3-sequelae [43–45].

Cosmetic outcome after IORT boosts was analysed in four reports altogether comprising roughly 500 patients. In two smaller trials, no difference was described for the boost patients in comparison to conventional groups: results were rated as 86/91% to be good or excellent for IORT-Boosts and 81/96% for the control groups, respectively [39, 41]. Longest-term experience is provided by Lemanski et al. [8] who reported about late reactions in 42 recurrence-free patients after a median follow-up of 9 years following IOERT. Six patients (14%) experienced Grade 2 late subcutaneous fibrosis within the boost area. Overall cosmesis was scored to be good to excellent. Based on their experience in 48 patients, Wenz et al. described inferior cosmetic results when time intervals between orthovoltage IORT and onset of WBI fall below 30 days [46].

In all these studies, the authors used different standardized cosmetic scoring systems based on qualitative estimations. However, in comparison to conventional techniques, no negative impacts on cosmesis following IORT have been reported so far in any concept.

In the Salzburg Series, cosmetic long term results following boost IOERT with 10 Gy, were evaluated in 403 patients by photo-documentation in four standardized positions in order to provide reproducible examination conditions [47]. Cosmetic outcome was assessed separately by patients and treating physicians (surgeon and radiation oncologist), respectively, within a 5-point-score as described by Harris and van Limbergen. Patient-, tumor- and treatment-related factors were analysed with regard to possible impact on the cosmetic result. For the whole cohort, median time between end of radiotherapy and cosmetic evaluation was 45 months; a separate subgroup analysis was carried out for 261 patients with a minimum follow-up of three years (median 56 months). For the whole cohort, the patients' self-assessments yielded around 93% “Satisfactory” (Excellent/Good) and 98% “Acceptable” (Excellent/Good/Moderate). These figures were almost identical to

the scorings in the subgroup with longer follow up: 91% satisfactory and 97% acceptable scorings, respectively. Physicians' evaluation revealed 64% satisfactory and 95% acceptable results for both groups. Telangiectasia were not described at all. A significant positive correlation was found between physicians' and patients' evaluation. Age and applicator diameter (possibly as surrogate for length of surgical scar) had a significant negative impact on the cosmetic outcome, whereas, for example, tumor-stage, grading, electron-energy, and boost-volume had no significant influence. IORT as a 10 Gy electron-boost within breast conserving treatment shows in the longer follow-up excellent cosmetic results. A negative impact of factors attributable to IORT on the cosmetic outcome was not identified.

### Ongoing Trials

#### *TARGIT-B (oost)*

In order to test the superiority of a TARGIT IORT boost compared to an external- beam boost, the multicentric, prospective, randomized TARGIT-B study was initiated. More than 20 centers have already started recruiting, and 1,800 young or high-risk patients will be included [<https://clinicaltrials.gov/ct2/show/NCT01792726>].

#### *HIOB Trial*

Hypofractionated Whole-Breast Irradiation following Intra-Operative Electron Boost. (<http://www.clinicaltrials.gov/ct2/show/NCT01343459?term=hiob&rank=1>).

In an attempt to further reduce overall treatment duration without compromising local control rates, the multicentre HIOB trial was started in January 2011 as an ISIOR investigator initiated study. In this trial, Boost IOERT of 10 Gy is combined with hypofractionated WBI (15 × 2.7 Gy) for stage I/II breast cancer. A similar concept of IOERT plus short-term WBRT was tested in a phase II design by the Milano Group [38]. In the HIOB trial, annual in-breast recurrence rates are defined as benchmarks for successful treatment. Superiority of the intervention is given by falling below the best published evidence in non-IORT cohorts. Beside tumor-related endpoints, major emphasis is made on cosmetic outcome. This study is still recruiting, a last interim analysis on early results is available by August 2014 [48].

At this point of time, 645 patients have been recruited within ten active institutions, 481 of them already in follow-up. For IOERT, the median energy chosen was 7 MeV (range 4–12) with median tube diameters of 6 cm (4–8) and mean prescription depths of 19 mm (6.2 SD), resulting in mean D90 volumes of 19 ml. Perioperatively, no major complications were observed. Four weeks after the end of WBI and 479 evaluated patients, 177 (37%) showed no reactions (CTC 0), 277 (58%) presented with faint (CTC 1) and 24 (5%) with moderate to brisk erythema (CTC 2), respectively. G0-I late reactions (LENT-

SOMA) occurred in a mean frequency of 97%, 96%, 98% and 96% after 4–5 months, 1, 2 and 3 years follow-up, respectively. Cosmesis was assessed postoperatively by patients themselves (subjective) and doctors (objective). Baseline appearance was first assessed after wound healing prior to WBI and scored as sufficient (excellent and good) in 69%/74% of 614 subjective/447 objective evaluations. Respective results at 4–5 months, one, two and three years post RT were 87%/75% of 418/378, 89%/77% of 306/164, 83%/75% of 132/107 and 84%/87.5% of 31/24 ratings. At a median follow-up period of 12.6 months (range 0.5–37), three patients were metastasized, two have died, and no in-breast recurrence was noted yet.

In sum, tolerance of a combined IOERT/hypofractionated WBI regimen was excellent, acute reactions moderate, and late reactions insignificant in short-term assessment. With regard to postoperative appearance, early cosmetic results are not impaired by this regimen. Both tumor control and cosmetic outcome have to be evaluated on long-term follow-up.

### Conclusion

The term IORT is currently used for various techniques, which show decisive differences in dose delivery. To date, all publications on boost IORT for conservatively operated breast cancer report about outstandingly low local recurrence rates in almost all risk settings, with the maturest evidence for electron based treatments (IOERT). These facts are interpreted as a consequence of utmost precision in dose delivery, and hypothesized to be biologically superior to conventional boosts due to avoidance of geometric and temporal miss, and possibly also due to abrogating the proliferative cytokine cascade induced by surgical wound healing. In addition, IORT allows for small treatment volumes and complete skin sparing, both having positive impact on late tissue tolerance and hence, cosmesis. Last, in terms of patient comfort, IORT prolongs the surgical procedure only in a small degree, while drastically shortening - or in selected cases maybe even replacing - postoperative radiotherapy.

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### Authors' contributions

FS and GF performed data acquisition and statistical analysis of IOERT patients and drafted the manuscript. CF, JK and FZ participated in IOERT of patients, clinical data acquisition, statistical analysis and drafting the manuscript. IZ, HD and PK participated in IOERT data acquisition (radiation physics), statistical analysis and drafting of the manuscript. RR was involved in OP and IOERT, data acquisition and analysis of IOERT patients. FW and ES performed data acquisition and statistical analysis of kV-IORT patients and revised the manuscript critically. All authors read and approved the final manuscript.

### Competing interests

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