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Original article

# IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis

Gerd Fastner [a,*,1], Felix Sedlmayer [a,1], Florian Merz [a,1], Heinrich Deutschmann [a,1], Roland Reitsamer [b,c,1], Christian Menzel [b,1], Christoph Stierle [b,c,1], Armando Farmini [b,c,1], Torsten Fischer [b,c,1], Antonella Ciabattoni [d,1], Alessandra Mirri [d,1], Eva Hager [e,1], Gabriele Reinartz [f,1], Claire Lemanski [i,1], Roberto Orecchia [g,1], Vincenzo Valentini [h,1]

[a] Department of Radiotherapy and Radio-Oncology; [b] Department of Special Gynecology; [c] Department of Gynecology, Paracelsus Medical University, Salzburg, Austria; [d] Department of Radiotherapy, San Filippo Neri Hospital, Rome, Italy; [e] Department of Radiotherapy, Landeskrankenhaus Klagenfurt, Austria; [f] Department of Radiotherapy, University Clinic Münster, Germany; [g] Department of Radiotherapy, European Institute of Oncology, Milano, Italy; [h] Department of Radiotherapy, Università Cattolica S. Cuore, Rome, Italy; [i] Department of Radiotherapy, Montpellier, France

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ABSTRACT

*Purpose:* Linac-based intraoperative radiotherapy with electrons (IOERT) was implemented to prevent local recurrences after breast conserving therapy (BCT) and was delivered as an intraoperative boost to the tumor bed prior to whole breast radiotherapy (WBI). A collaborative analysis has been performed by European ISIORT member institutions for long term evaluation of this strategy.

*Material and methods:* Until 10/2005, 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).

*Results:* At a median follow up of 72.4 months (0.8–239), only 16 in-breast recurrences were observed, yielding a local tumor control rate of 99.2%. Relapses occurred 12.5–151 months after primary treatment. In multivariate analysis only grade 3 reached significance ($p = 0.031$) to be predictive for local recurrence development. Taking into account patient age, annual in-breast recurrence rates amounted 0.64%, 0.34%, 0.21% and 0.16% in patients <40 years; 40–49 years; 50–59 years and ⩾60 years, respectively.

*Conclusion:* In all risk subgroups, a 10 Gy IOERT boost prior to WBI provided outstanding local control rates, comparing favourably to all trials with similar length of follow up.

 Radiotherapy and Oncology xxx (2013) xxx–xxx

Throughout the last two decades, local recurrence rates (LR) after breast conserving treatment (BCT) have continuously decreased, which is attributable to a variety of factors: broad evolvement of preoperative diagnostic means, higher quality in pathological work-up, individualization and refinement of operative strategies as well as additive local effects of modern systemic treatment. However, the highest contribution in controlling remnant in-breast disease still comes from radiotherapy. Considering the tumor bed as the tissue at highest contamination with subclinical tumor cells, a local dose escalation has proven to lower in-breast recurrence rates most effectively. The high value of an additional 16 Gy booster dose to the tumor bed either by fractionated external electron beam treatment or by brachytherapy was corroborated in a follow-up analysis of the EORTC trial data, where local recurrence rates were shown to be halved in every patient age group. [1,2]. Accounting for age as strongest predictor for LR probability, annual in-breast recurrence rates following BCT nowadays are expected to be around 0.4–0.7% for patients >50 years, 0.72–1.2% at ages 41–50 years, and 0.72 and 2% for patients below 40 years of age, respectively [3–5]. The idea of a linac-based intraoperative treatment with electrons (IOERT) during breast conserving surgery is the delivery of a single booster dose to the tumor bed with utmost precision, helped by direct visualization. Moreover, apart from accuracy aspects, the skin as critical organ at risk for late cosmetic results is completely spared.

Following this treatment approach, to date only few reports on outcome are available, usually describing single center experiences on smaller cohorts, with local recurrence rates ranging between 0% and 4% at median follow-up periods from 8.9 to 109 months

* Corresponding author. Address: Department of Radiotherapy and Radio-Oncology, Paracelsus Medical University, Salzburg, Muellner Hauptstrasse 48, A-5020 Salzburg, Austria.
*E-mail address:* g.fastner@salk.at (G. Fastner).
[1] On behalf of the ISIORT Europe.

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[6–10]. A retrospective matched – pair analysis in 378 patients, comparing an IOERT-boost-group with a "conventional" external 12 Gy boost cohort showed a significant reduction of local-recurrence-rates at 5 years of 4.3% in the conventional group versus 0% in the investigational arm ($p < 0.01$) [8]. The IOERT boost-procedure was described as safe, without additional morbidity [9] and good cosmetic outcome compared to the standard treatment [6,9]. Despite this hypothesis – generating observation, reports on boost-IOERT for breast cancer are still scarce, rarely updated and restricted to rather few centers. In the absence of randomized prospective trials, we initiated a collaborative analysis within the European Group of the International Society of Intraoperative Radiotherapy (ISIORT). A first interim analysis was published in 2007 with data of 6 member-institutions [11]. This follow-up comprises the long-term data of seven European centers.

## Patients and methods

A pooled analysis has been performed among 7 member institutions of the ISIORT-Europe (Table 1). Each institution conducted its own prospective program on breast boost IOERT preceding WBI in agreement with the requirements of their local ethic's committees' or internal review boards. All patients gave informed consent.

Data of 1235 consecutive patients were collected, with the vast majority treated between 10/98 and 10/05, and a smaller cohort of 50 patients from Montpellier dating back to the early nineties [6]. In 2006, all anonymized data sets were allocated to the study center for further collaborative analysis. Institutional updates were reported continuously. 126 patients had to be excluded for one of the following reasons: immediate secondary mastectomy due to massive margin involvement in the final histologic workup (65), IOERT as re-irradiation for local recurrence (1), patient's refusal of WBI (10), WBI by hypofractionated schedules (42), inadequate IORT – booster dose (5) and missing follow-up data since finishing WBI treatment (3), leaving 1109 patients for the present analysis. Patients' characteristics, histologic workup and tumor staging are summarized in Table 2.

### *Operative and IOERT procedure*

Breast tumor resections were primarily performed by circular incision. Surgical margins were assessed by frozen section after tumorectomy. A resection margin of at least 2 mm to invasive and 5 mm to in-situ tumor components was warranted. *R*0 excision was achieved in 95% (1056) of all patients, only 1.5% (17) was classified as *R*1 and/or RX. Prior to IOERT, the tissue surrounding the excision hole was temporarily approximated by sutures to bring it into reach of the electron beam. In most cases, intraoperative sonography was performed for depth dose measurement prescription, alternatively mobile CT or direct ruler measurement was used. As IOERT, median single fractional doses of 10 Gy (SD = 0.87, range 6–15) were applied to the 90% reference isodose, using round perspex tubes with diameters of 5–8 cm and electron energies of mainly 4, 6 and 8 MeV (range 4–18 MeV). Whole-breast irradiation (WBI) was prescribed with 50–54 Gy of single fractional doses of 1.7–2 Gy in supine position on linear accelerators following 3D-CT-planning. The median time delay between IOERT to WBRT was 6.8 weeks (range 2.3–51). Over 93% of the patients received additional systemic therapy, dependent on TN-stage, menopausal and hormonal receptor status: 78.6% antihormonal treatment, 35.3% chemotherapy and 20.2% both, respectively. Additionally, Her2-status was evaluated, showing 638 patients with negative and 73 with positive status, out of them 18 received Trastuzumab in addition to their respective systemic therapy. For 398 patients, no information was available.

**Table 1**
Studypopulation.

| Institution | Country | Patients |
|---|---|---|
| European Inst. of oncology Milano | Italy | 65 |
| General hospital of Klagenfurt | Austria | 74 |
| University clinic of Münster | Germany | 51 |
| San Filippo Neri hospital Rome | Italy | 154 |
| Universita Cattolica S. Cuore Rome | Italy | 11 |
| University Clinic of Montpellier | France | 50 |
| Paracelsus University Clinic of Salzburg | Austria | 830 |

**Table 2**
Patient-characteristics: *T*/*N*/*G* and histology.

| T | Pts | *N* | Pts | *G* | Pts |
|---|---|---|---|---|---|
| No. statement (ns)-Tx | 20 | ns/Nx | 38 | ns/Gx | 67 |
| In situ | 9 | N0 | 697 | G1 | 154 |
| T0 | 4 | N1 | 335 | G2 | 595 |
| T1 | 771 | N2 | 32 | G3 | 292 |
| T2 | 298 | N3 | 7 | G4 | 1 |
| T3 | 6 | | | | |
| T4 | 1 | | | | |
| *Histology* | | *HR-Status* | | *Multifocality* | |
| No. statement (ns) | 226 | ns | 33 | ns | 214 |
| IDC | 605 | Pos | 905 | Yes | 126 |
| ILC | 90 | Neg | 171 | No | 769 |
| Mixed | 90 | | | | |
| Other [a] | 71 | | | | |
| Undifferentiated | 3 | | | | |
| Invasive and EIC | 24 | | | | |

[a] Tubular, mucinous, medullary.

## Statistics

Univariate and multivariate Cox proportional hazards regression models were used to estimate the influence of patients' or tumor characteristics on the risk of local recurrence for a 95% confidence level. SPSS (IBM PSWA Statistics 18, version 18.0.3) was used to perform the analyses [12].

## Results

As of March 2009, a median follow up period of 72.4 months (range 0.8–239) was reached. The quality of follow-up was high, with lacking information for more than one year of only 107 patients (9.6%), the latter group still providing a median FU-time of 67.5 months (3.8–208.6). At the time of analysis, 951 patients were alive without evidence of breast disease.

110 patients had developed metastases, 106 patients have died, thereof 47 from breast cancer and 13 from other malignancies. The actuarial disease free survival rates amount 88.6%, disease specific survival and overall survival rates 94.05% and 91.39%, respectively.

Only 16 in-breast recurrences (IBR) were observed (9 invasive tumors, 3 DCIS, 4 without statement), yielding a local tumor control rate of 99.2% at the median follow-up time of 72 months. Eight of them accounted for true local recurrences within the index quadrant, the remaining eight were classified as out-quadrant relapses. Mean time to occurrence for true LR was 72.1 months (range 12.5–151), and 62.7 months (17–103) for out-quadrant relapses, respectively. Risk factors were analyzed with regard to all in-breast events and separately for true LR and out-quadrant relapses, respectively. To account for age as repeatedly reported strongest predictive factor for local control [1,2,13–15], analyses were performed along four age groups: <40 years, ⩾40 – <50 years, ⩾50 – <60 years and ⩾60 years, showing global total arc crude annual in-breast recurrence rates of 0.64%, 0.34%, 0.21%

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and 0.16%, respectively. This trend of decreasing LR rates with rising patient age was recorded for both: in-quadrant (IQ) and out-quadrant (OQ) relapses (Table 3). Cumulative incidences over time for each age group are illustrated in Fig. 1a–c and the number of patients at risk in (d).

To assess the role of the IOERT boost with regard to LR predicting risk factors we focused on all IBR and additionally tried to analyze IQ and OQ relapses separately. As to the total of all in-breast events, a significant negative impact of negative hormonal receptor-status and absent antihormonal therapy was present in univariate calculation only. For IQ relapses (true local recurrences), multivariate analysis reached significance for high tumor grading G3 ($p = 0.031$) (Fig. 2).

For OQ events, no predictive factor could be identified (Table 4). Nodal status was not associated with in-breast failure. Due to missing information in a third of all patients, a possible influence of Her-2 status was not statistically evaluable. To ascertain the role of a WBI delay following IOERT, three time slots were considered: WBI onset <70 days, $\geqslant 70 - \leqslant 140$ 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), in case of IQ relapses 8.5 weeks and for OQ – recurrences 6.6 weeks, respectively.

## Discussion

Frozen section histology as first estimation of resection margins [16] shows a specificity of 84% [17] and was in our study available in 79% of all cases. Final histopathological assessment might reveal discrepancies toward frozen section especially for in-situ tumor, leading to re-excisions in a second operation as necessary. In our series, this caused the vast majority of the 10% second resection rate. As to invasive components, frozen sections gave precise intraoperative informations on margin freedom regarding both dimension and direction.

Albeit the restrictions toward in situ components, a direct visualization of the tumor bed during surgery in addition to optimized preoperative tumor imaging [18] supports accurate dose delivery. While all other methods of a later reconstruction of the tumor bed's location (e.g. by clips) [19] finally remain indirect, a direct view to the tissue at risk has potential advantages. Yang et al. [19] reported that a distance between seroma and tumor bed clips of more than one cm to be predictive for a geographic miss, confirming previous data [20,21].

Furthermore, a growing number of surgeons use primary reconstruction techniques after lumpectomy to optimize cosmetic outcome, which inevitably hampers tumor bed localization unless for IORT, which is performed before breast tissue is mobilized for oncoplastic procedures. As a consequence of direct tissue exposure without distension by hematoseroma, IORT allows for small treatment volumes and complete skin sparing. Both should have a positive effect in late tissue tolerance.

In the present study, IOERT with 10 Gy was tested as anticipated boost modality in addition to whole-breast treatment. Taking into account the $\alpha/\beta$-model, which calculates values around 4 for tumor response in breast cancer, [22,23] this dose corresponds to about 23 Gy when administered in daily 2 Gy fractions. Together with WBI, this resulted in cumulative tumor bed doses equivalent to 73–77 Gy of standard fractionation.

A matter of debate is the classification of IBR as true recurrences (TR) or new primaries (NP). By definition, TR occur in or nearby the former index quadrant (<3 cm) with the same histologic subtype as the primary tumor, all other cases are classified as NP [24–26]. Of our eight TR, four showed up with at least one difference in histological characteristics and/or receptor status, three were consistent with the former primary tumor and in one case no information was available. For the eight OQ recurrences observed in our series, three showed different and two consistent features. In three patients, histologic information for reliable comparison was incomplete. Thus, to our opinion, some OQ-relapses might have originated from the initial tumor out of cell spread beyond the former Index-Quadrant which survived WBI.

### *Target volume and design of an IORT-boost*

The work of Holland et al. [27] still forms the essential background for the boost design. Without detailed consideration of risk subgroups, which have been published extensively [28] microscopic disease can be expected in up to 40% of the cases outside a distance of 2 cm apart the macroscopic tumor edge. The larger the distance, however, the smaller the probability: a safety margin of 3 cm will match over 80% of residual tumor cells, and a distance of 4 cm accounts for about 90% of possible remnant disease. These observations are at least partially consistent with pathologists' data and also MRI findings about the possible amount of microscopic spread throughout the breast, where incidences of out-quadrant tumor foci between 18% and 63% are reported [28–32] and multicentric foci would be left behind in 47% if the index tumor is excised by a margin of 2 cm [31,33].

The amount of tissue irradiated by IORT (or any other boost modality) should therefore consider the surgical extent of free margins in all directions. In the ISIORT treatment concept, tumor free margins of at least 5 mm for in-situ spread and 2 mm for invasive disease were demanded. IOERT encompassed an additional margin of at least 2 cm within all breast tissue directions, with emphasis of the tissue with closest margin status, thus hitting at least 60% of all subclinical tumor cells [27]. To further increase this amount, the use of larger tube diameters was pursued when technically possible. To date, four different techniques are frequently addressed by the term "IORT". However, from the point of dose distribution, these methods differ enormously [34], thus having massive implications on a targeting as described above. IOERT has been demonstrated to be the method delivering the utmost uniform dose distribution within a given target volume. Outcome analyses of local control rates after "IORT" must strictly be performed according to the used technique.

### *IORT: boost or single modality*

The idea of a "one-stop-shop" treatment by a single shot during the operative maneuver is tempting especially in lower risk patients. Critics to this approach point out that the applied doses of

**Table 3**
Local-recurrences depending on age separated in four groups.

| LR | Age | Pts/% | FUP: median/range (mths) | LR: pts/% | Annual |
|---|---|---|---|---|---|
| *IB* | | | | | |
| | <40 | 53/4.8 | 74.48 (16.50–126.00) | 2/3.7 | 0.64% |
| | 40–49 | 234/21.1 | 75.89 (4.80–187.90) | 5/2.1 | 0.34% |
| | 50–59 | 326/29.3 | 72.90 (3.80–208.50) | 4/1.2 | 0.21% |
| | ⩾60 | 496/44.6 | 73.03 (3.48–215.00) | 5/1.0 | 0.16% |
| *IQ* | | | | | |
| | <40 | | | 2/3.7 | 0.64% |
| | 40–49 | | | 2/0.85 | 0.14% |
| | 50–59 | | | 2/0.61 | 0.10% |
| | ⩾60 | | | 2/0.40 | 0.06% |
| *OQ* | | | | | |
| | <40 | | | 0/0 | 0 |
| | 40–49 | | | 3/1.27 | 0.21% |
| | 50–59 | | | 2/0.61 | 0.10% |
| | ⩾60 | | | 3/0.60 | 0.09% |

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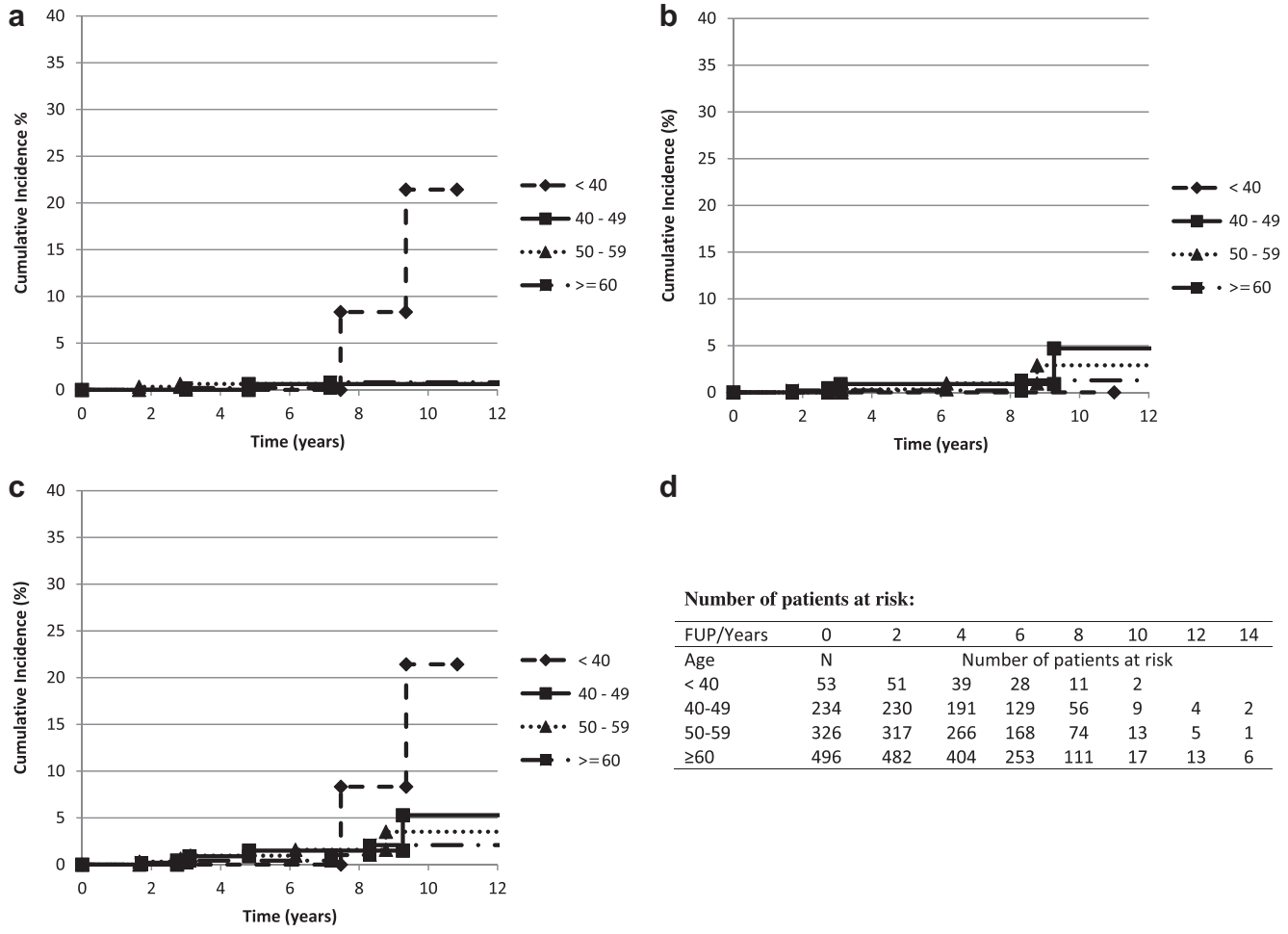


**Number of patients at risk:**

| FUP/Years | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 |
|---|---|---|---|---|---|---|---|---|
| Age | N | Number of patients at risk | | | | | | |
| < 40 | 53 | 51 | 39 | 28 | 11 | 2 | | |
| 40-49 | 234 | 230 | 191 | 129 | 56 | 9 | 4 | 2 |
| 50-59 | 326 | 317 | 266 | 168 | 74 | 13 | 5 | 1 |
| ≥60 | 496 | 482 | 404 | 253 | 111 | 17 | 13 | 6 |

**Fig. 1.** (a–c) Local recurrences dependent on age – cumulative incidences over time. (a) in-quadrant events, (b) out-quadrant events, (c) total in-breast events and (d) number of patients at risk

21–24 Gy are outside the tested dose ranges for equal tumor effects in the linearquadratic model. However, as to normal tissue tolerance, the same model predicts significant increase in fibrosis and necrosis with long-term follow-up [35]. In principal, any APBI-method, including single full-dose IOERT, bears the risk of missing parts of a relevant target volume, either in the periphery of a tumor bed, or outside the index quadrant. Both regions are usually controlled by WBI with doses around 50 Gy because of the smaller tumor burden [29]. There is little controversy that during initial follow-up, the vast majority of in-breast relapses occurs in the original tumor site. The longer the follow-up, however, the more tumor recurrences are reported with increasing distance from the primary area [1,35,36]. If effective radiation treatment is restricted to the very center of a tumor bed, this might lead to a higher frequency of in-breast recurrences at sites which are not reported up to now. Gujral et al. [37] described that WBI can reduce the occurrence of ipsilateral NP to less than half of the incidence of contralateral breast cancer (CLBC). They assume that current trials of APBI will presumably record more IBR after long-term follow up than after WBI. The widespread use of systemic and especially adjuvant hormonal treatment of these low risk patients postpones the appearance of an in-breast recurrence, however, without definitive prevention [38].

To date, two major "full-dose" IORT studies are promoted: the TARGIT approach using ortovoltage X-rays, and the ELIOT trial respectively, testing single-shot electron treatment. In 2010, a first interim analysis was published from the TARGIT trial at a median follow up time of 24.6 months [39]. The Kaplan Meier estimate of local recurrence at 4 years was 1.2% in the APBI arm and 0.95% in the WBI group.

The frequency of any complications and major toxicity was similar with both treatment modalities (3.3% TARGIT vs. 3.9% WBI). The ELIOT trial [40] has reached its accrual goal, Formatted: Underline 651 ELIOT-patients were randomly compared to a cohort treated with standard EBRT, with a first publication awaited. Outside from this trial setting, another 1822 pts were treated by the ELIOT concept [41]. After a median follow-up of 36 months, altogether 3.63% in-breast recurrences were observed. Predictive factors for LR were age <50 years, tumor size, grading, involved nodes and negative hormone receptors. When analyzed along current ASTRO.

Consensus Statement Guidelines for the Application of Accelerated Partial Breast Irradiation, the 5-year rate of ipsilateral breast recurrence for suitable, cautionary, and unsuitable groups were 1.5%, 4.4%, and 8.8%, respectively ($p = 0.0003$) [42]. Applying GEC-ESTRO risk criteria, the 5-year rate of in-breast tumor reappearances for "good candidates" amounted to 1.9%, for "possible candidates" and "contraindication" 7.4% and 7.7%, respectively ($p = 0.001$) [43].

In the light of the existing literature, interpretation of the results following sole IORT – by any means – to be isoeffective toward standard treatment is premature. True local recurrences are presumed to occur between 40 and 65 months after primary

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**Table 4**
Hazards ratio (HR) and 95% confidence intervals (CI) obtained from univariate and multivariable Cox proportional hazards regression model were calculated for all patients (pts) and groups of local recurrences (LR) located in-quadrant (IQ), out-quadrant (OQ) or in-breast (IB).

| Characteristics | Pts ($n$ = 1109) | LR | Univariate IQ $p$-value | Univariate HR (95% CI) | Multivariate IQ $p$-value | Multivariate HR (95% CI) | LR | Univariate OQ $p$-value | Univariate HR (95% CI) | LR | Univariate IB $p$-value | Univariate HR (95% CI) | Multivariate IB $p$-value | Multivariate HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Size* | | | | | | | | | | | | | | |
| T1 | 771 | 5 | | 1.0 | | | 6 | | 1.0 | 11 | | 1.0 | | |
| T2 | 298 | 3 | 0.4 | 1.8 (0.4–7.7) | | | 2 | 0.84 | 0.85 (0.17–4.2) | 5 | 0.7 | 1.24 (0.43–3.6) | | |
| Others | 20 | 0 | | | | | 0 | | | 0 | | | | |
| ns | 20 | 0 | | | | | 0 | | | 0 | | | | |
| *Grading* | | | | | | | | | | | | | | |
| G3 | 292 | 7 | | 1.0 | | 1.0 | 1 | | 1.0 | 8 | | 1.0 | | |
| G2 | 595 | 1 | 0.01 | 0.07 (0.01–0.6) | 0.031 | 0.09 (0.01–0.8) | 7 | 0.25 | 3.41 (0.42–27.9) | 8 | 0.163 | 0.49 (0.19–1.32) | | |
| Others | 155 | 0 | | | | | 0 | | | 0 | | | | |
| ns | 67 | 0 | | | | | 0 | | | 0 | | | | |
| *Nodes* | | | | | | | | | | | | | | |
| N0 | 697 | 8 | | 1.0 | | | 7 | | 1.0 | 15 | | 1.0 | | |
| N+ | 374 | 0 | 0.26 | 0.26 (0–14.2) | | | 1 | 0.24 | 0.27 (0.04–2.3) | 1 | 0.05 | 0.14 (0.02–1.03) | | |
| ns | 38 | 0 | | | | | 0 | | | 0 | | | | |
| *IORT-WBRT* | | | | | | | | | | | | | | |
| <70 d | 600 | 5 | | 1.0 | | | 6 | | | 11 | | 1.0 | | |
| 70–140 d | 179 | 0 | | | | | 0 | | | 0 | | | | |
| >140 d | 107 | 2 | 0.09 | 4.8 (0.8–28.6) | | | 0 | | | 2 | 0.43 | 1.88 (0.39–8.99) | | |
| ns | 223 | 1 | | | | | 2 | | | 3 | | | | |
| *Age* | | | | | | | | | | | | | | |
| <40 | 53 | 2 | | 1.0 | | 1.0 | 0 | | | 2 | | 1.0 | | |
| 40–49 | 234 | 1 | 0.05 | 0.09 (0.01–1.01) | 0.24 | 0.23 (0.02–2.7) | 3 | 0.4 | 2.03 (0.4–10) | 4 | 0.29 | 0.4 (0.07–2.18) | | |
| 50–59 | 326 | 2 | 0.1 | 0.22 (0.04–1.37) | | | 2 | 0.92 | 1.09 (0.18–6.55) | 6 | 0.34 | 0.46 (0.09–2.3) | | |
| ⩾60 | 496 | 3 | 0.01 | 0.07 (0.01–0.57) | 0.23 | 0.28 (0.03–2.27) | 3 | | 1.0 | 4 | 0.06 | 0.19(0.03–1.08) | | |
| *HR-status* | | | | | | | | | | | | | | |
| Pos | 905 | 4 | | 1.0 | | 1.0 | 6 | 0.52 | 0.6 (0.12–2.9) | 10 | | 1.0 | | 1.0 |
| Neg | 171 | 4 | 0.019 | 5.3 (1.31–21.07) | 0.6 | 0.54 (0.06–5.38) | 2 | | 1.0 | 6 | 0.029 | 3.1 (1.12–8.54) | 0.82 | 1.27 (0.17–9.74) |
| ns | 33 | 0 | | | | | 0 | | | 0 | | | | |
| *Histology* | | | | | | | | | | | | | | |
| IDC | 605 | 7 | | 1.0 | | | 4 | | 1.0 | 11 | | 1.0 | | |
| Mixed | 90 | 1 | 0.94 | 1.08 (0.13–9.09) | | | 1 | 0.94 | 1.079 (0.13–9) | 1 | 0.74 | 0.71 (0.09–5.6) | | |
| Other | 188 | 0 | | | | | 0 | | | 1 | 0.98 | 1.03 (0.13–8.04) | | |
| ns | 226 | 0 | | | | | 3 | | | 3 | | | | |
| *CTX* | | | | | | | | | | | | | | |
| Yes | 392 | 4 | | 1.0 | | | 3 | | 1.0 | 7 | | 1.0 | | |
| No | 689 | 4 | 0.23 | 0.4 (0.09–1.8) | | | 5 | 0.87 | 0.89 (0.21–3.7) | 9 | 0.34 | 0.61(0.22–1.68) | | |
| ns | 28 | 0 | | | | | 0 | | | 0 | | | | |
| *AT* | | | | | | | | | | | | | | |
| Yes | 872 | 3 | | 1.0 | | 1.0 | 6 | | 1.0 | 9 | | 1.0 | | 1.0 |
| No | 201 | 5 | 0.01 | 6.3 (1.5–26.6) | 0.098 | 7.32 (0.7–77.6) | 2 | 0.76 | 1.28 (0.26–6.38) | 7 | 0.032 | 2.96 (1.01–7.99) | 0.47 | 2.01 (0.29–13.83) |
| ns | 36 | 0 | | | | | 0 | | | 0 | | | | |

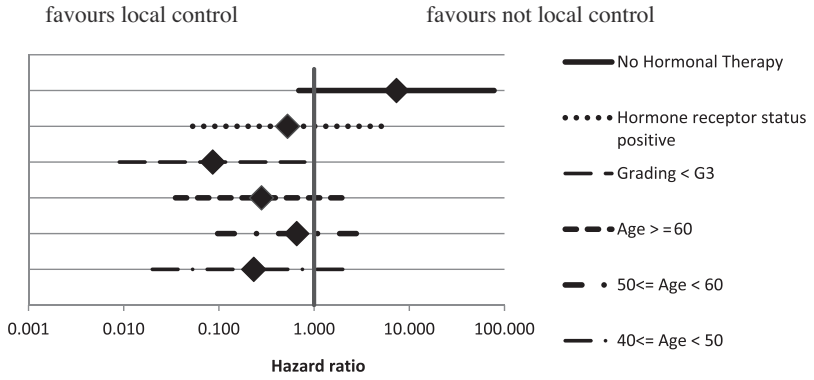


**Fig. 2.** Forrest – Plot: negative predictive factors for development of in-quadrant local recurrences.

treatment [37,44], out-quadrant relapses even later than that [36] 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 [45].

In contrast, when used as boost modality, IOERT seems to yield local control rates in every risk group which has not been shown before by any other method in trials with comparable size and follow-up. The effect was reproducible in every participating center. Interestingly, even long time delays between IOERT and WBI – mainly caused by adjuvant chemotherapy – did not compromize local control. For breast tumors, a postulated low $\alpha/\beta$ ratio around 4 was clinically corroborated by the British and Canadian hypofractionation trials [4,5,46,47]. Applied to a 10 Gy IOERT dose, this corresponds to an iso-effect of about 23 Gy in conventional fractionation, which could well be responsible for the remarkably low LR-rates especially when administered under optimal conditions of visual CTV control. In addition to dose–effect extrapolations of high single doses, 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 [48]. Another obvious 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 transcellular 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 [23,49,50].

Although low in absolute number, most of the observed recurrences showed poor differentiation. This very feature was also reported to be the only one associated with worse outcome in hypofractionated WBI arms [51]. Whether this indicates a different biological behavior of G3 – tumors, reflected by a higher $\alpha/\beta$ ratio and thus lower efficacy of hypofractionation (including the value of a high single dose) is unclear.

Beside all these biological considerations, age has unanimously been reported to be of strong influence on local control: the younger the patient, the higher the risk for recurrence. Several international societies proposed to categorize different risk for relapse situations following ABPI, with slightly varying emphasis on diverse adverse features, but all of them with age as most important risk-determining factor [52–54]. Annual local recurrence rates are frequently used to benchmark the efficacy of different RT strategies. To date, when reported along usual age cohorts of $\leqslant$40, 41–50, 51–60 and >60 years, lowest annual LR rates for the respective groups amount around mean values of 1.8%, 1.5%, 1% and 0.6% respectively [1,13]. Best published data derived from prospective hypofractionation trials accounted for 0.72% at age $\leqslant$50 [4] and 0.4% for patients >50 years [5]. Compared to all these data, the results of our pooled analysis underbid these figures by a factor of up to 4 in every age group.

Annual recurrence rates decreased steadily during the last ten years, due to quality progress in diagnostics, surgery, pathologic work up, frequent use of modern systemic therapy and of course, progress in radiotherapy. Interim reports of the ongoing prospective "Young Boost Trial" (NCT0021212) or closed ELIOT-trial (WBI-group) describe low recurrence rates of estimated 0.5 % after 4 years (age group <50 years) and 0.7% after 5 years, respectively [55,56], pointing at the value of further dose augmentation in the tumor bed. In our analysis, we were able to demonstrate the validity of this concept in a long term follow up, suggesting boost-IOERT as a highly effective asset in the radio-oncologic portfolio.

### *Study limitations*

Nevertheless there are some limitations of this analysis: first, this is not a randomized trial, but is compared to historical controls only. However, a previously published matched-pair analysis [8] and a first interim report [11] were hypothesis-generating that boost IOERT could be superior to previous standard treatments.

IOERT is frequently criticized to be a time-consuming and hence, expensive procedure. The first was overcome by the development of dedicated mobile devices, where IOERT is performed within the operation theater. As to the cost argument, prolonging an operation time by 15–30 min while saving up to two weeks of daily outpatient treatment have to be offset. Reimbursement for IOERT is highly different within EC and US countries, impeding broader application and hence, quicker scientific appraisal of its potential. In our study, this is reflected by unbalanced patient referral, where 67% of all patients derived from one institution, building a potential bias in interpretation of the results. However, within all participating institutions, reported recurrence rates were equally low.

Finally, nearly half of the study patients were older than 60 years of age, where – especially in the absence of other adverse features – the absolute benefit from a boost is lowest and therefore frequently questioned. On the other hand, dose escalations to the tumor bed half local recurrence rates in every age group [2,57] which is important especially for long term survivors [58,59]. For these lower risk age groups, clinical investigation during the last decade rather focused on the potential of partial breast irradiation strategies including IOERT to replace the classical WBI +/− boost approach, emphasizing the primacy of local dose intensification.

Another aspect of any medical intervention is the consideration of patients convenience and hence compliance toward treatment.

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Boost IOERT is able to shorten adjuvant RT up to one and a half weeks compared to external boost RT. To further optimize overall treatment time, and in the light of upcoming evolvement of hypofractionated WBI, the impact of boost IOERT in combination with a 3-week accelerated WBI schedule is currently investigated within a prospective ISIORT multicenter trial (HIOB).

## Conclusion

IOERT during BCS as preceding boost strategy has possible advantages in terms of precision, patient comfort and in theory, also a potential beneficial influence on late cosmesis. Long term results provide outstanding in-breast tumor control rates in every risk group.

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