IORT with Electrons as Boost Strategy during Breast Conserving Therapy in Limited Stage Breast Cancer: Results of an ISIORT Pooled Analysis

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Introduction
There is common consensus that postoperative whole-breast irradiation with doses around 50 Gy remains the gold standard for local treatment after breast conserving surgery (BCS) [4,17–20]. A substantial benefit of an additional boost with 16 Gy to the tumor bed was recently confirmed by a re-analysis of the EORTC trial data: local recurrence rates were reduced by 50% in all age groups [1,2]. The idea of a Linac-based IORT with electrons (IOERT) during breast conserving surgery is the delivery of a single boost dose to the tumor bed with utmost precision, due to direct visualization [10,11]. However, the published data about boost-IOERT for breast cancer are scarce and rarely updated with only few centers participating [10,11,15,16]. Therefore, we initiated a collaborative analysis within the European Group of the International Society of Intraoperative Radiotherapy (ISIORT).

Methods
A pooled analysis has been performed by 6 institutions of the ISIORT-Europe using comparable methods, sequencing and dosage in intra- and postoperative radiotherapy during BCT. Between 10/98 and 05/05, 1131 patients were treated. Patients’ characteristics, histologic workup and tumor staging are summarized in Table 1. Sixty percent of all patients (671 pat.) presented with at least one risk factor for local recurrence in terms of tumor size > 2 cm, high grading, young age < 45 years and/or positive axillary nodes.

Breast tumor resection was primarily performed by circular incision. Surgical margins were assessed by frozen section after intraoperative sonography was performed for depth measurement allowing dose prescription, alternatively mobile CT or direct ruler measurement was used. During IOERT, median single fractionnal doses of 9.7 Gy (range 5–17) were applied to the 90% reference isodose, using round perspex tubes with 5–8 cm diameter and electron energies of mainly 6 and 8 MeV (range 4–15 MeV).

Whole-breast irradiation (WBRT) was prescribed with 50–54 Gy in single fractions of 1.7–2 Gy. Over 95% of the patients received additional systemic therapy, dependent on TN stage, menopausal and hormonal receptor status. The median time delay between IOERT to WBRT was 6.6 weeks (6.9, range 2.6–51); mainly 3 to 5 weeks for patients with either no systemic or adjuvant hormonal therapy, for patients undergoing chemotherapy the median delay amounted up to 18 weeks according to specific local protocol rules about the sequence of adjuvant regimen.

Results
43 patients were referred to immediate secondary mastectomy due to massive margin involvement in the final histologic work-up, which was not recognizable during frozen section assessments. No further follow up data were available for 57 patients, leaving 1031 patients for this analysis. As of April 2007, at a median follow up period of 52.3 months (range 1–108), only 5 in-breast recurrences were observed, yielding a local tumor control rate of 99.4%. Ninehundred-sixty-four patients are alive without evidence of breast cancer at 7 years follow up. Sixty-one patients developed metastases, 58 patients have died, 25 of them from breast cancer and 6 from a secondary tumor. The actuarial disease free survival rates at 7 years amount to 88%, disease specific survival and overall survival rates to 95.2% and 90.9%, respectively. In-breast recurrences (4 invasive tumors, one DCIS) occurred 20–37 months after primary treatment. Two of them accounted for true local recurrences within the index quadrant, the remaining three were classified as out-quadrant relapse. Prolonged timing of WBRT after IORT was not associated with local failure.

Key Words: IORT · Electrons · Breast cancer · Radiotherapy · Boost
### Table 1. ISORT Breast Boost Pooled Analysis: Patient’s Characteristics.

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<th>Grading</th>
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</table>

### Discussion

In the present study, IOERT with 10 Gy was tested as anticipated boost modality in addition to whole-breast treatment. According to the α/β-model, which calculates values around 8–10 for tumor response, this dose corresponds to about 17–20 Gy when administered in daily 2 Gy fractions.

**Target volume and design of an IORT-boost.** The work of Holland and colleagues [9] still provides the essential background for the boost design. Without detailed consideration of risk subgroups, which have been published extensively [6], microscopic disease can be expected in up to 40% of the cases further than 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 residual disease.

The amount of tissue irradiated by IOERT (or any other boost modality) should therefore consider the surgical extent of free margins in all directions. In our treatment concept, a surgical clearance of at least 5 mm for in-situ spread and 2 mm for invasive disease was demanded. IOERT encompassed an additional margin of at least two centimetres within all breast tissue directions with special emphasis of the tissue with the closest margin status.

To date, four different techniques are summarized by the term “IORT”. However, from the point of dose distribution, these methods differ considerably [13], thus having massive implications on a targeting as described above. Outcome analyses of local control rates as well as cosmetic results after “IORT” must strictly be performed according to the used technique.

**IORT: Boost or single modality.** The idea of a single shot treatment, as proposed by the Milan group, is tempting especially in low risk patients [12, 24]. Major criticisms point out that the investigated dose of 21 Gy is outside the tested dose ranges for equal tumor effects in the linear quadratic model. However, with regard to normal tissue tolerance, the same model predicts a significant increase in fibrosis and necrosis with long-term follow-up [3, 7, 22].

Moreover, any APBI-method, including single full-dose IOERT, bears the risk of mismatching parts of a relevant target volume, either in the periphery of a tumor bed, or outside the index quadrant. Both regions are now usually controlled by WBRT with doses around 50 Gy, due to the rarer and smaller tumor burden [5].

It is generally recognized that during the first years of follow-up, the vast majority of in-breast relapses occurs in the original tumor site. However, with prolonged follow-up, an increasing number of tumors is observed in growing distance from the primary area [2, 3, 8].

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 tumorfoci between 11 and 50% are reported [5, 6, 21, 23]. 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. The use of systemic and especially adjuvant hormonal treatment in these low risk patients prolongs the appearance of an in-breast recurrence, however, without definitive prevention [14]. As a consequence, follow-up periods far beyond five years are mandatory to provide definite evidence that both modalities yield equivalent long term tumor control.

### Conclusion

IOERT as anticipated boost during BCS guarantees optimal accuracy in dose delivery and thus outstanding local tumor control rates.

### References


