

# Is current clinical practice modified about intraoperative breast irradiation?

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**Abstract:** After the results obtained in the two randomized clinical trial, the ELIOT trial and the TARGIT-A trial, a heated debate is going on concerning the question of applying intraoperative radiotherapy (IORT) instead of postoperative whole breast irradiation (WBI) after breast conservative treatment. Currently, many centers are applying the IORT following the strict selection criteria dictated by the working groups American Society for Radiation Oncology (ASTRO) and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) and monitoring the oncological outcome together with radiation toxicity on breast tissue. The clinical experience of the Geneva University Hospital regarding the use of the Intrabeam system is evaluated and compared with current evidences.

**Keywords:** Breast cancer; intraoperative radiotherapy (IORT); radiation toxicity

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In recent time we are observing in the context of oncological breast surgery, an increasing trend towards the more effective treatment with minimum invasiveness, with the intent to combine the local control of the disease with the respect of patient's quality of life.

The introduction of conservative breast surgery, the debate on axillary nodes dissection in cases of sentinel node micrometastasis can be deemed to belong to this behavior.

The widespread use of accelerated partial-breast irradiation (APBI) after breast conservative surgery as an alternative to whole breast irradiation (WBI) can be considered also part of this approach (1). The procedure consists in the irradiation on the breast limited to the tissues surrounding the resected tumor, following the evidence of the higher incidence of local recurrence rate near the site of tumor bed with respect to the rest of the breast (2,3). A particular type of APBI is the intraoperative radiotherapy (IORT) that can be provided by electrons or with 50 kV X-rays (Intrabeam System) (4). IORT allows the patient with particular personal and tumor

characteristics to conclude the oncological treatment in one operating session with many consequent advantages; in particular allows a better comfortability for the patient avoiding delays related to logistical difficulties and above all permitting patients to forget shortly to be sick. The selection criteria for the application of APBI were defined by the two working groups of The American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) which delineated the risk categories and warned to apply the techniques in the context of clinical trials (5-8).

Two randomized phase III trials, ELIOT trial (9) and TARGIT-A trial (10), have been developed regarding the use of IORT with results at a medium follow-up of 5.8 and 2.4 years respectively. A heated debate is going on concerning the question of applying IORT instead of postoperative WBI after breast conservative treatment following the strict selection criteria dictated by ASTRO

and GEC-ESTRO. In TARGIT-A local recurrence rate at 5 years in the IORT group was 3.3%, while in ELIOT trial 4.4%. Although the findings of higher recurrence rate with respect to WBI, the pre-specified equivalence margins were respected. Therefore indication for IORT might be restricted to patients with low risk of local events and respecting very strict selection criteria (11).

In the clinical experience of Vinh-Hung *et al.* (12) 52 women received IORT after conservative surgery, but only the 65% as unique treatment. The rest of patients received further postoperative external radiotherapy, because inclusion criteria were not met for different unexpected findings. Despite the favorable result of no incidence of local events at 1 year follow-up in all patients treated, the short follow-up does not allow to make definitive and optimistic conclusions, considering the long-term local recurrences rate reported in the two randomized trials.

### Operating time

In Vinh-Hung study, patients following the preoperative selection criteria underwent IORT; however 35% of patients resulted to be not suitable for the treatment after receiving the definitive histopathological analysis, therefore required subsequent WBI. The frozen sections of resected tumor allow to evaluate during surgery if selection criteria regarding tumor characteristics are still respected such as sufficient resection margins and intraductal component and to plan the final appropriate radiotherapeutic treatment (13).

Mammographic and ultrasonographic exams prior to surgery are useful for non palpable lesions, however in accordance with our experience, an appropriate magnetic resonance imaging (MRI) examination is required in some cases before surgery to make a control of whole breast excluding the presence of multifocality. It has been reported a 9.6% of cases in which a variation in patients selection for APBI was necessary after performing an MRI, because of the identification of unexpected additional disease (14).

### Radiation toxicity

The greater total radiation dose delivered due to the addition of IORT boost to WBI is supposed to lead to an increased risk of radiation toxicity on breast tissues.

Radiation toxicity was investigated in Vinh-Hung study using the LENT-SOMA scale, resulting a not significant difference ( $P=0.631$ ) on the grades of toxicity in the 18

patients requiring WBI in addition to IORT, considering 90 days time interval between the two treatments. However follow-up was almost 1 month in all patients, therefore there are no data regarding possible increasing in the fibrosis rate in the long time period.

There are evidences that subcutaneous fibrosis tends to increase with a longer follow-up. The EORTC 22881-10882 trial showed a statistically significant higher rate of fibrosis after 10 years follow-up for the boost group rather than the no-boost group (15), however there are no evidences at 5 years (16).

Furthermore the rate of fibrosis and late toxicities, such as edema, telangiectasia, breast retraction, hyperpigmentation and pain, seem to be related to the time interval of adjuvant WBI delivery after IORT boost, with data showing a high toxicity rate within 36 days (17) and possible no incidence of tissue toxicity after 5–6 or more weeks of delay (18).

Higher frequency of postoperative wound seroma was found after IORT in Vinh-Hung study, in accordance with the evidences of TARGIT-A, however it was not significantly associated with the rate of fibrosis, that was observed to be higher in the IORT boost group together with toxicity grade 3/4. The minor rate of fibrosis in the IORT group can be correlated to the evidences of less breast and arm symptoms (19).

Two cases of grade 4 skin toxicity requiring re-operation were found after IORT in the study of Vinh-Hung; no heart toxicity was found, though lung symptoms were diagnosed in six cases after IORT and one after further WBI. However the short follow-up does not allow a clear evaluation of long-term effects of radiation. In TARGIT-A, more cases of pulmonary fibrosis occurred after WBI (38 out of 83) than after IORT (4 out of 95).

Regarding patients treated with IORT respect to WBI in terms of skin side effects, no significant differences were seen in TARGIT-A trial (20), while in ELIOT trial is reported a significative higher incidence in the WBI group.

Another evidence to emphasize is the higher rate of subcutaneous fibrosis seen in patients treated with IORT boost using the Intrabeam System rather than external electrons or intraoperative boost with electrons (21-25).

Concerning the use of IORT, at present time it is not clear about what happens after application of a single high dose of 20–21 Gy. This dose might correspond to a fractionated dose of 65 Gy, therefore a greater incidence of severe fibrosis should be expected; on the contrary there are

not definitive results supporting this hypothesis (26).

The incidence of fibrosis might influence the final cosmetic result and the subsequent psychological comfort of the patient. A cosmetic result and patient's satisfaction analysis should be performed when considering the application of postoperative WBI or IORT. Techniques of reduction mammoplasty can be associated to conservative surgery and IORT in cases of mammary hypertrophy or ptosis with the great advantage of obtaining a good cosmetic result in the same surgical session of oncologic treatment without the need to re-operate the patient afterwards.

The application of oncoplastic techniques allows a greater surgical access with the advantage of performing a more comfortable wide excision of the tumor and applying a greater shielding disk when there is necessity to protect underlying vital structures, with deliver of radiotherapy on more extent of glandular tissue. Subsequently glandular flaps can be harvested and mobilized to refill the defect and recreate the volume of the breast (13).

After surgery the rearrangement of the mammary gland should be taken under control by expert radiologists in order to distinguish benign findings benign calcifications or fat necrosis from malignancies (27).

The removal of a larger extent of glandular tissue and the gland remodeling in cases of application of oncoplastic techniques is associated with a more favorable aesthetic global judgement either with IORT or WBI (28).

Therefore in the clinical cases of lower risk of recurrence and respecting the strict selection criteria, IORT should be taken into account, considering also the advantage of a good quality of life and the less chronic skin toxicities especially after IORT alone identified in IORT patients (20).

Furthermore, if patients conditions result favorable, oncoplastic techniques should be offered after a direct and precise preoperative conversation with the objective to get the patient involved with the surgical options.

The complexity in surgical techniques and oncologic treatment involves a multidisciplinary team and require a continuous dynamic communication between oncologic surgeon, plastic surgeon and radiotherapist to carry out a successful breast cancer treatment that satisfy the patient and ensure an adequate local control of the tumor.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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