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Electron intraoperative treatment in patients with early-stage breast cancer: data update

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Intraoperative radiotherapy is a technique where a high, single-fraction radiation dose is delivered directly to the tumor bed during a surgical procedure, after the removal of a neoplastic mass, with minimal exposure of surroundings tissues, which are displaced and shielded during the procedure. Intraoperative radiotherapy has been used in the treatment of various malignancies, mostly in combination with external beam radiation therapy. The long-term results suggest a positive impact on local controls that appear to be associated with increased survival. Modern intraoperative radiotherapy can be performed either with electron beams or photons, and has been used recently in early-stage cancer as a boost or as an exclusive treatment, especially for breast tumors, with extremely promising results. The results of different clinical studies have demonstrated the feasibility of the technique and it is expected that its application will become more widespread in the immediate future. Intraoperative electron radiotherapy in the treatment of initial-stage breast cancer may be an excellent alternative to external beam radiation therapy in an appropriate selected group of patients. However, intensive long-term follow-up is required for a better evaluation of local control and possible side effects.

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Intraoperative radiotherapy (IORT) is a technique where a high, single-fraction radiation dose is delivered directly to the tumor bed during a surgical intervention, after the removal of a neoplastic mass [1]. Modern IORT is commonly carried out with electron beams (intraoperative electron radiotherapy [IOERT]) or photons. The use of electron beams allows the administration of a homogeneous dose to a selected layer of tissues surrounding the tumor, whereas photons achieve a high dose immediately adjacent to the applicator. An important technical advantage of IORT is the direct visual control of the target volume and the possibility of protecting healthy tissues by moving them out of the path of the radiation beam.

IORT has been used in the treatment of various malignancies, particularly in locally advanced stages, and usually in combination with external beam radiation therapy (EBRT).

Long-term results suggest a positive impact on local control and low toxicity, and seem to be associated with increased survival rates [2]. More recently, IORT has been used in early-stage cancer either as a boost or a sole treatment, especially for breast tumors, with extremely promising results. The European Institute of Oncology (IEO) in Milan have gained considerable experience administering IOERT using dedicated accelerators [3–16]. Photon devices are being used within the Targit trial, which is recruiting patients in several centers around the world [17]. The recently designed miniaturized mobile-linear accelerators have a variable range of electron energy (3–12 MeV) and their most important advantage is that they can be placed in any operating room without undue structural modifications.

IOERT is a technique in which the radiation oncologist has the full clinical responsibility (prescription and execution of the

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treatment), but which requires multidisciplinary collaboration between the surgeon, anesthetist, medical physics experts, radiation technologists and nursing personnel.

There is growing interest in the use of IOERT in early-stage breast cancer. Trials have been performed to investigate tolerance to increased IORT doses (10, 15, 17, 19 and 21 Gy) and to introduce the use of 21 Gy in the context of breast-conserving surgery without EBRT complement. This is a very significant contribution to IORT science in modern oncology in which both the concept tested (minimal efficient treatment) and methodology employed (prospective randomized trial) have been valuable and influential for some IORT experts [3,18], but controversial for others [19].

Intraoperative electron radiotherapy in early-stage breast cancer

Assuming equal cellular radiosensitivity, the probability of tumor control for a given absorbed dose decreases with an increase in the initial number of malignant cells. Therefore, the greater the tumor volume, the higher the dose required to achieve the same control rate. From this point of view, IOERT offers an important theoretical advantage in comparison with the conventional EBRT. In fact, in the latter case, the time-span between the surgical removal of the tumor and the radiotherapy (RT) may allow cellular repopulation from the neoplastic clones present in the microscopic remainder tissue. It is also necessary to consider the postsurgical phenomenon of the 'accelerated repopulation', where the first phases of neoplastic cellular growth follow an exponential-type course. IOERT, administered immediately after the intervention either as a boost or as sole treatment, may avoid the problem of the 'accelerated repopulation' on the irradiated area.

The dose-response relationship can be analyzed according to various mathematical models, with the linear quadratic model being the most commonly used, although this model presents higher validity at dose/fraction below 6–8 Gy. With the administration of a high dose in a single fraction in IOERT, the reduction of the rate of cell survival is achieved with smaller total dose (half to a third) in comparison with that achieved with conventional fractionated treatment. Assuming that the α/β ratio of tumor cells of the mammary glandular tissue is equal to ten, the administration of single-dose treatment, 12 Gy as a boost or 21 Gy as a sole treatment should result in the same local control as conventional fractionated doses of approximately 25 and 60 Gy, respectively. The potential disadvantage is represented by the higher risk of late effects, such as fibrosis, in late responding tissues (with α/β values of three or lower). An important area that should be explored is the influence of combined treatment (EBRT and/or chemotherapy [CT]) on IOERT tolerance.

The radiobiological advantage of the high dose disbursed in single fraction with IOERT is the avoidance of repopulation by eliminating the surgery to RT interval (SRI) or the interval between RT fractions, during which tumor cells could proliferate. Moreover, tissues under surgical intervention have a

rich vascularization, with aerobic metabolism, which makes them more sensitive to the action of the radiation (oxygen effect).

Intraoperative electron radiotherapy as a boost

The most common scheme of adjuvant RT used for the conservative treatment of initial-stage breast cancer after surgery is the administration of 45–50 Gy on the gland as a whole, followed by a boost of 10–16 Gy to the tumor bed. The role of this boost on the reduction of the incidence of local recurrences has been confirmed widely by the results of the European Organization for the Research and Treatment of Cancer (EORTC) 'boost versus no boost' randomized trial, which demonstrated a significant increase in local control with the administration of 16 Gy on the tumor bed after microscopically complete tumorectomy, compared with the sole irradiation of the whole breast [20]. These results were more evident in women aged under 50 years. Similar results have already been obtained in another randomized trial in Lyon, France, on more than 1000 patients comparing those treated with a boost dose of 10 Gy with those not treated with a boost, with a follow-up of 3.3 years [21].

There are several techniques for the administration of the boost [22]. The main constraint is the localization of the tumor bed after the surgical intervention. This can be difficult, particularly when the mammary gland has been reconstructed, when clips of reference have not been inserted or when there is no radiological evidence of the area of fibrous scar or the exeresis cavity. These inaccuracies could be responsible for the increase of local recurrences. Often, to avoid errors of location, the area of radiation is widened, but the increase of the radiated volume can correspond with a greater risk of late tissue reactions with cosmesis compromise.

Previously, there had been very few cases of published experiences on the use of IOERT as a boost [23,24]. More recently, results based on a wide number of patients with invasive breast cancer have been published [25]. A total of 188 patients had been treated with breast-conserving surgery and postoperative radiation therapy to the entire breast (51–56.1 Gy in 1.7 Gy fractions) either with conventional external beam electron boost in group one (fractionated dose of 12 Gy) or with IOERT in group two (single dose of 9 Gy). With a different median follow-up period (55.3 months in group one and 25.8 months in group two), the results of this sequential study demonstrated that the IOERT boost yielded excellent local control (local recurrence rate of 4.3% in group one and 0% in group two) and appears to be superior to the conventional postoperative boost.

A recent pilot randomized study in 234 women with T1–T2 breast cancer, comparing IORT boost after quadrantectomy versus conventional treatment with external electron beam boost, confirmed the efficacy of IORT on esthetic valuation and toxicity, with a slight trend to local control. No recurrences were present after 3 years follow-up. More results are expected at the end of the study. The use of mobile machine makes the IORT procedure easier and reduces the

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total external RT time [26]. Another study at the Montpellier Cancer Institute, although with a small number of patients (50 women), has a relevant follow-up time (median 8.3 years, range: 5–15 years) and reports two recurrences (one at 8 years and one at 8 years after initial treatment), good quality of life (QoL) and good to excellent cosmesis in 86% of the evaluated women [27]. In another study, using a special low energy x-ray device as opposed to electrons, the feasibility and safety of this technique have been tested. With a median follow-up of 22 months (maximum 72 months), only two out of 227 patients receiving a boost dose presented a local relapse. With the exception of two patients treated early in this study, wound healing and cosmetic outcome have being reported as excellent and good, respectively [17].

In conclusion, IORT results illustrate that it can be a valid and reliable alternative to the conventional external-beam boost. With the administration of the boost in a single intraoperative session, with just a modest extension of the surgical time (15–20 min) using a dedicated unit, the total time of external treatment is reduced by 1–2 weeks with consequent economic advantage and improvement of the general well-being of the patient. Moreover, the direct exposure of the operating bed may eliminate the possible inaccuracy of location, allowing treatment of a more limited volume of glandular tissue.

Intraoperative electron radiotherapy as an exclusive treatment

The rationale for the use of this segmental radiation therapy in place of whole-breast irradiation (WBI) is based on the results of some long-term studies reporting that local relapses after conservative surgery and EBRT occur at the original tumor site at a rate of 80% or more, with few exceptions [28–31]. Also, the results of the Milan III trial, which compared quadrantectomy alone with the same conservative surgery plus EBRT on the whole breast, have confirmed that the 85% of local relapses were in, or close to, the previous index quadrant [32]. Moreover, the incidence of local relapses are found to be significantly lower in patients younger than 55 years and equal in both arms (with or without RT) in patients older than 65 years.

Therefore, with IOERT it could be possible to reduce the radiation field only to the involved quadrant of the breast and change the RT course from 5–7 weeks to one single, intensive dose in the operating theater immediately following surgical resection of the tumor. This may allow patients to have breast-conserving therapy even in the case of difficult access to a RT center and also reduce the social and economical burden of prolonged treatment. IOERT could minimize some potential side effects since the skin and the subcutaneous tissue are not irradiated, and the spread of irradiation to lung and heart is reduced significantly.

Another important advantage is the avoidance of interactions with systemic therapy that may determine delays in the initiation or in performing conventional EBRT when CT, and particularly anthracyclin-based cycles, are given. There is conflicting available information regarding the optimal sequencing of

CT and RT after surgery. A recent update of a prospective randomized trial confirms that the optimal integration of CT with radiation for patients with early-stage cancer remains uncertain [33]. The trial included 244 patients with a median follow-up time of 135 months. No significant differences were observed between the CT- or RT-first arms in time to any event, distant metastasis or death. Sites or first failure were also not significantly different. The authors concluded that there is no advantage in administering RT before adjuvant CT; however, the study does not have enough statistical power to rule out a clinically important survival benefit for either sequence. Delay in the initiation of RT may be associated with an increase in the rate of local recurrence and there are concerns regarding delaying the initiation of CT in patients at high risk of metastases. It is considered that it may be possible to deliver RT and CT simultaneously in a safe and effective manner, but data from randomized clinical trials are necessary to confirm this.

With regards to patients receiving WBI alone, there are contradictory opinions concerning whether the SRI modifies the meaning of margin status. A large retrospective study from British Columbia found that the risk of local failure was not affected by the increase of SRI of up to 4 months, regardless of margin status [34]; however, most guidelines suggested that a longer period could increase this risk.

Moreover, IOERT could be specifically applied when post-operative fractionated RT is not safe or feasible, such as in the case of severe cardiopathy, large hypertrophic scarring from skin burns or vitiligo, and in particular in patients previously irradiated for Hodgkin's disease. The use of IOERT can avoid repeat irradiation of the entire breast, permit breast-conserving surgery and decrease the number of avoidable mastectomies [35].

Together with other techniques, IOERT belongs to the modern treatment philosophy of partial breast irradiation (PBI) of treating only the excision site and the adjacent tissues [36]. This technique should not yet be used as standard treatment, but its use should be limited to a subgroup of patients at low risk of local recurrences with some of the following characteristics: age above 45 years, tumor diameter below 3 cm, infiltrating ductal histology, no mammographic evidence of multifocality, negative resection margins, negative or no more than three positive axillary nodes and of extensive intraductal component.

Intraoperative electron radiotherapy in nipple-sparing mastectomy

The present consensus on surgical treatment of breast cancer is to limit mutilation as much as possible, therefore lumpectomy or quadrantectomy are the selected procedure for breast-conserving surgery. However, a mastectomy is still required in patients with large or multifocal infiltrating tumors, in some cases of local recurrence after conservative treatment and in diffuse *in situ* carcinoma. Skin-sparing mastectomy allows immediate breast reconstruction; however the removal of the nipple–areola complex (NAC) dramatically increases the feeling of mutilation [37]. To reduce such psychological impact,

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nipple-sparing mastectomy (NSM), associated with IOERT, could be proposed to the remaining glandular tissue behind the areola [38]. The aim of this technique is to maintain the blood supply and the sensitivity of the NAC while reducing the risk of recurrence in the central area of the breast.

Review of clinical studies at the European Institute of Oncology

Experience with IOERT (electron intraoperative therapy [ELIOT]) started at the IEO on July 1999. The first step has been a dose escalation trial to define the maximum tolerated dose in a single fraction and establish equivalence between the reached value of single dose and the conventional fractionated EBRT, followed by a Phase I–II trial to test ELIOT feasibility and tolerance. Other related clinical studies include a prospective randomized Phase III trial and a NSM study.

Dose-escalation & Phase I–II trial

From 1999 to 2000, 99 patients with infiltrating breast carcinoma up to a diameter of 2.5 cm received 101 ELIOT treatments (two women presented bilateral carcinoma) after quadrantectomy. An informed consent was signed by the patient every time ELIOT treatment was proposed and accepted. The trial was based on a dose escalation starting from 10 Gy. ELIOT was administered at 10, 15, 17, 19 and 21 Gy. Patients in the two initial dose levels (10 and 15 Gy) received further conventional EBRT (44 and 40 Gy, respectively). Patients were evaluated 1, 3, 6 and 12 months after surgery and thereafter every 6 months to look for early, intermediate and/or late complications and cosmesis. The mean age of the patients was 58 years (range: 33–80).

Prospective randomized Phase III trial

This is an ongoing study with more than 900 patients, comparing standard EBRT (50 Gy on the whole breast and 10 Gy electron beam boost on the tumor bed) with a single dose (21 Gy prescribed at 90% isodose) of ELIOT, in a group of patients older than 48 years affected with invasive cancer with a diameter of 2.5 cm or less. All women received quadrantectomy, followed by sentinel biopsy (and axillary dissection just in the case of positive node). The aim of the study is to evaluate effectiveness in terms of local control, disease-free survival, distant metastases, overall survival, cosmetic outcome and cost.

Nipple-sparing mastectomy study

This study was initiated in 2002 testing the above described new technique to preserve the NAC during mastectomy. A total of 300 NSMs were performed. Invasive (58%) and *in situ* (42%) carcinomas were included. When frozen sections of the retroareolar tissue proved to be cancer free, ELIOT was performed with 16 Gy to the NAC. The mean patient age was 45 years (range: 26–73). A total of 75% of patients had a mean follow-up time of 10 months (range: 1–33). Clinical complications, aesthetic, oncological and psychological results were recorded.

Results of The European Institute of Oncology studies

Dose-escalation & Phase I–II trial

The single dose of 21 Gy at 90% isodose (corresponding to an average dose of 22.53 Gy) has proved to be feasible and equivalent to a full dose of conventional EBRT, and has been selected as the new standard dose for ELIOT at the IEO. Results have been published recently [39]. After a mean follow-up time of 42 months (13–59 months), 16 patients developed breast fibrosis (mild in 15, severe in one) of transitory duration, two patients postoperative infection and four developed lymphonecrosis, complications that did not affect the cosmetic result of surgery. Lymphonecrosis related to IOERT deserves more clarification based on further follow-up.

With regard to local control, three patients treated with ELIOT developed ipsilateral cancer (one received 17 Gy and two received 19 Gy), only one of them was a true recurrence (in field) detected at 36 months, while the other two were located on other quadrants of the breast. Regarding the other detected events, two patients presented with contralateral cancer (one patient treated with IOERT at 10 Gy and EBRT at 44 Gy and the other with ELIOT alone at 17 Gy) and five patients developed distant metastases.

Prospective randomized Phase III study

Final results are not yet available.

Nipple-sparing mastectomy study

The results of this study have been updated in a recent publication [40]. The NAC necrosed totally in ten cases, partially in 29, and was removed in 12. Nine infections were recorded. Two local recurrences occurred outside the radiated field. Three metastasis are reported and no deaths occurred. No local recurrence was observed but longer follow-up is required in order to prove the efficacy of ELIOT. From the psychological point of view, the preliminary results report a high level of patient satisfaction.

Expert commentary & five-year view

We need to wait for the results from ongoing clinical trials in order to further demonstrate IOERT's therapeutic benefits. The two main trials of IOERT are the ELIOT trial and the Targit trial. It will now require coordination and discipline among institutions to generate data that will influence clinical practice on a larger scale. In the clinical setting, clear guidelines, including the best available methodology to improve the therapeutic index, should be developed. The use of IOERT was handicapped previously by the need for patient transportation at the time of surgical operation. Nowadays, portable Linac can overcome this limitation increasing its potential use by allowing movement from one surgical room to another. Three models, the Mobetron[®], the Novac[™] and the Liac[™] are currently available and in clinical use. In addition, there is another device called Intrabeam[®], which produces x-rays at 50 kVp. With its use, a typical dose of 5 Gy at 1 cm, 10 Gy at 0.5 cm or 20 Gy next to the applicator over 25–30 min can be administered [41].

Specific dosimetric treatment planning systems, virtual simulation, preplanning, 2D and 3D real-time isodose distribution, documentation of final dosimetric treatment characteristics and

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integration of IOERT boost into the external beam component of treatment are valuable developments in radiation physics emerging as research projects in expert institutions pending definitive validation and commercial availability.

Over the past 20 years, many changes have occurred in relation to both the characteristics of breast cancer and the impact of therapy. Around 20 years ago, approximately a third of patients had T1-stage tumor at the time of diagnosis and no more than 1% had a nonpalpable disease. Currently, thanks to the available screening program, more than two-thirds of patients have T1-stage tumor and about 1% have a nonpalpable disease. In addition, breast cancer therapy has achieved a substantial success rate with a continuing decrease in the annual breast cancer death rate over the past 10 years. Morbidity associated with treatment has also been reduced. A series of studies have shown that breast conservation therapy achieves equivalent survival rates to that of mastectomy for patients with early-stage breast cancer. Sentinel lymph node surgery is used for lymph node-negative breast cancer patients. With regard to radiation treatment, the approach is to reduce both the volume irradiated and overall treatment time. In this context, PBI could represent a significant advancement in the treatment of selected patients with early-stage breast cancer [36]. External beam 3D conformal irradiation, dedicated balloon catheter (Mammosite®), multicatheter interstitial brachytherapy technique and Intrabeam device

have been tested in several American and European studies with extended follow-up [27,42–45]. However, large clinical trials with long-term follow-up are needed in order to properly define treatment techniques and patient selection criteria in order to avoid suboptimal therapies, disease recurrence or normal tissue damage [46]. Hence, the results of two prospective, randomized, ongoing studies, one in the USA and the other in Europe, will be important. The NSABP B-39/RTOG 0413 Phase III study of 3000 women aims to evaluate the effectiveness of PBI performed with three different techniques (interstitial brachytherapy, Mammosite and conformal 3D radiation therapy) compared with WBI in providing equivalent local tumor control in the breast following lumpectomy for early-stage breast cancer [45]. The European study of the Breast Cancer Working Group of the GEC/ESTRO plans 1170 patients with the same aims, although they aim to compare just interstitial brachytherapy with WBI [44].

In conclusion, in the treatment of initial-stage breast cancer, IOERT, as well as other treatment modalities of PBI, may be excellent alternatives to the traditional postoperative RT. Some caution is needed in the selection of patients while, with the results of new studies, the specific characteristics of the target group are defined. Moreover, further intensive long-term follow-up is required for a better evaluation of local control and possible side effects.

Key issues

- Some of the advantages of the use of intraoperative electron radiotherapy (IOERT) in the conservative management of initial-stage breast cancer compared with conventional external beam radiation therapy (EBRT) are:

Radiobiological:

- Single high dose to the operative bed.
- Elimination of the time span between the surgical intervention and the EBRT (eliminating neoplastic-cellular repopulation).
- Radiosensitization action due to the oxygen effect in the presence of rich vascularization characteristic of tissues under surgical intervention.

Physical–technical:

- More accurate administration of the treatment owing to the elimination of geographic misses.
- Homogeneous distribution of the dose in the target.
- Protection of normal tissues with special methods (mobilization and shields).

Clinical:

- Avoidance of the need to delay the start of radiotherapy until chemotherapy is completed, or vice versa.

Psychological and social/economical:

- Decrease of patient's stress due to the total or partial elimination of EBRT with a positive impact on the quality of life.
- Positive impact on the cost and global demand of both the patient and the radiotherapy center.
- IOERT is a technique in which the radiation oncologist has the full clinical responsibility but which requires multidisciplinary collaboration.
- Some caution is needed in the selection of patients while, with the results of new studies, the specific characteristics of the target group are defined.
- Further intensive long-term follow-up is required for a better evaluation of local control and possible side effects.
- IOERT may be an excellent alternative to the traditional postoperative radiotherapy for the treatment of initial-stage breast cancer. However, currently, it should only be used within a clinical trial until results on long-term randomized studies are available.

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