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Intra-Operative Radiotherapy in Breast Cancer Treatment: A Literature Review

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Abstract

Context: The process of direct radiation to the tumor or tumor residue during surgery known as Intraoperative Radiation Therapy (IORT) is a new promising technique in the treatment of different cancers. For a detailed review of IORT application and effectiveness in breast cancer, we conducted a review of the present literature in the field.
Evidence Acquisition: In this study, the most important technologies for IORT were identified through a comprehensive study. Relevant, critical, and highly cited articles and studies were selected based on experts' opinions. Data were summarized in sections of technology and physics, protocols, and treatment outcomes.
Results: Electron beam and low-energy X-ray technologies were explained, and the physique of IORT was discussed. Due to the uncertainties of this modality and geometric complexities of post-excision treatment site, specialized treatment planning systems for IORT are necessary. In breast cancer treatment, regardless of the employed technology, IORT is applied with two main protocols: Partial Breast Irradiation and Intraoperative Boost Irradiation, each with their own advantages and disadvantages.
Conclusions: Despite the controversies in acceptance and effectiveness of IORT, this technique seems to be promising for increased survival of breast cancer patients.

Keywords: Breast, Neoplasms, Electron Beam, Low-Energy X-ray Technologies, Intraoperative Radiation Therapy, IORT, Outcome, Physics, Radiotherapy, Residual, Treatment

1. Context

Increased prevalence and burden of breast cancer are serious concerns for health service providers, policymakers, and people (1). Many research institutes have focused on developing new methods for decreasing the burden of breast cancer by improving treatment efficacy. Researchers are seeking modalities for more accurate diagnosis (2, 3), early detection (4), increased survival, reduced early and late treatment side effects, and cosmetic outcomes. Among the proposed techniques, Intraoperative Radiation Therapy (IORT) is a method that has received increased attention and applied for the treatment of breast cancer in the last two decades. This method is popular in breast cancer treatment due to accessible target, high efficacy, and improved long-term outcomes. This technique aims to reduce regional tumor recurrence by means of a single large radiation dose to the tumor bed during surgery, which is accompanied by reduced complications (5). Despite the promising results, IORT has not been well introduced in many health sectors, and limited providers are applying it in their practice. In this review, we aimed to investigate different aspects of IORT and its application in breast cancer treatment.

IORT is the process of direct radiation of the tumor during surgery (6, 7). After removing target tissues in surgery, cancer residuals are sterilized by irradiation before surgical closure. By directly exposing the lesion to irradiation, a lethal dose for cancerous cells can be delivered without affecting normal structures (8). The great advantage of IORT emerges in the treatment of lesions such as gastric cancers, located near radiosensitive organs, and radio-resistant tumors, such as soft-tissue sarcomas.

Carl Beck, MD, first documented IORT for the treatment of gastric cancer less than 20 years after the discovery of X-rays (9). It should be noted that although this method had a strong theoretical background, the low-energy beam modalities caused unsuccessful treatment at first attempts. Introducing megavoltage X-rays in medical radiation shifted the attitudes from the unsuccessful experience of radiotherapy to a new horizon of cancer treat-

ment in the 1950s (10). The first study of Intraoperative Electron Radiation Therapy (IOERT) was in the 1960s (11). In 1964, for the first time, megavoltage electron beams were used by Abe and Takahashi (6). In this method, high radiation was applied without additional exposure to healthy tissues (12). This experience in 1981 led to the publishing of the first review concentrated on IORT treatment beginning from their first attempt in 1964 at the University of Kyoto. In the 1970s, Howard University Hospital and Massachusetts General Hospital were equipped with conventional linear accelerators to perform IORT procedures (10).

Mobile linear electron accelerators and low-energy miniature X-ray machines were introduced to the clinical practice of radiotherapy worldwide in the 1990s (10, 13). In the last 30 years, significant progress has been achieved and expert multi-specialist hospital-based groups have proven the feasibility of IORT as a component of multimodal cancer therapy (14). The first pioneers in the field of IORT are Spain, Italy, Austria, and Germany (15). Although in the 1980s and the mid-1990s, the US was more active in formalizing IORT, Europe has concentrated on this subject since 2000 by grouping homogeneous cases (12).

2. Evidence Acquisition

Breast tumor treatment protocols get benefits from IORT as both main and adjuvant treatment modalities. In this study, we examined the role of IORT in the treatment of breast cancer with a chronological approach. In the period of 1975 up to 2018, most studies of IORT were done in the context of breast cancer. Originally, most studies were performed in Italy among other countries, but in recent years, the USA, England, and Germany added many studies to the literature in this field. France, Austria, Australia, Japan, Spain, and the Netherland also have some studies in this regard. By the end of 2018, more than 500 original studies were performed in this field.

3. Results

3.1. IORT Techniques

3.1.1. Low-Energy X-Ray Irradiation

In the low-energy X-ray irradiation method, after surgical excision of the tumor, the applicator of low-energy X-ray is inserted to the excised tumor cavity. The treatment time ranges from 20 to 40 minutes after finishing the surgical procedure. The appropriate dose is 20 Gy at the surface of the applicator and 5 - 6 Gy at the depth of 1 cm of the target tissue. The miniature X-ray source delivers up to 50 kV energy to the target, and the decreased dose preserves the nearby healthy tissue (16).

3.1.2. Intraoperative Electron Radiation Therapy (IOERT)

IOERT is another method in which electron beams are directly emitted to the tumor bed at the time of surgery. The electron energy range varies from 4 to 12 MeV in mobile accelerators, but the required energy to penetrate the breast tissue is 12 MeV. The irradiation procedure is completed in 2 minutes, and the delivered dose is 21 Gy with the depth of 90% isodose ranging from 13 to 24 mm depending on the electron energy (17). Cylindrical applicators are available in different diameters for breast irradiation. The chest wall protector, i.e., the shielding disk, must be inserted between the breast tissue and pectoral muscles.

3.1.3. Intraoperative Afterload Brachytherapy

High-Dose-Rate (HDR) intraoperative radiotherapy is used at the tumor cavity after surgical excision by a quadrangular Silastic applicator (Harrison-Anderson-Mick H.A.M.®). The Iridium^{192} (192Ir) source is loaded to the applicator by an HDR After-loader. To provide proper radiation, the size and the length of the applicator should be set down to the level of the target surface. Due to the rapid fall of the dose, tumor bed tissue should be in direct contact with the applicator to achieve the best result of the treatment (18). The most important limitation of this technique is the limited access to the totally shielded operating room for the treatment.

3.2. IORT Physique

3.2.1. Treatment Planning Systems for IORT

In the absence of a commercial treatment planning system for IORT, in the research era, there are some treatment planning system developments. Joining navigation systems and CT scan rendering packages is used to simulate the excised tumor cavity. After defining the applicator, its size and bevel angle for dose calculation, based on the type of irradiation, a Monte Carlo beam pencil or dose painting model is applied. There is a reporting and documentation application attached to the treatment planning system that can generate documents with the DICOM RT format. These systems need more maturity and competence for practical usage in patient treatment (19). Being able to connect to other equipment is crucial for these systems to receive and send needed data throughout the irradiation team network. In the IORT procedure, it is very hard to reconstruct the treatment at a later time to follow up and continue the treatment protocol. For this reason, it is necessary to have documentation and comprehensive reporting. This record should include geometry and anatomical relations of the treatment site, shielded areas, if any, and applicator definition such as shape, size, position, angle, and beam energy (20, 21). In short, we are at

the beginning of the journey in IORT treatment planning development.

3.2.2. Pre-Planned Dose in IORT, Uncertainties and Deviations

Uncertainty might have originated from the deviation from the desired value during radiation therapy.

Similar to conventional External Beam Radiotherapy EBRT, we have several sources of uncertainty in IORT. The major ones are uncertainty in measurement, reproducibility, and implementing the planned set-up. There is another source of uncertainty in IORT due to heterogeneous dose distribution. IAEA TRS-398 measured the calibration uncertainty of 2.1% for conventional external beam accelerators. In IOERT, this type of uncertainty should be considered marginally higher as a result of the non-reference positioning of applicators (22).

Angled irradiation results in an additional 2% - 5% uncertainty by a beveled applicator. Due to the uncertainty in detecting the correct clinical axis and the asymmetric and deviated dose distributions of the devices, an estimated uncertainty of about 2% should be added in quadrature for the output of beveled applicators. It is necessary to include an excessive uncertainty of 0.5% due to the variation of the recombination corrections for different ionization chambers, depending on the pulse dose and correction method for high-dose machines per pulse. The combined uncertainty in reference dosimetry can, therefore, be estimated to be 2.2% - 3.7% for straight irradiations and 2.9% - 6.2% for beveled dosimetry.

Uncertainty is also estimated based on standard deviations of in vivo dosimetry IVD values caused by setup errors, mainly due to inaccurate target size calculation, partial target coverage following application maladjustment or incorrect angle beam entry. Uncertainties are mostly not considered in the treatment of targets of just a few millimeters in depth such as lesion residues after excision. On the other hand, empty spaces or the collection of liquid/blood between the applicator and the tissue may also occur. Failure to correct this error in a 1 - 2 cm larger breast IORT applicator diameter can lead to a decrease of 50% or more in doses (23). Usually because it can be avoided easily, this is not taken into account in the total deviation calculation (22).

Various sources of uncertainty described above are included in an integral to achieve a total probable deviation from 4.1% to 11.7% of the applied dose. The variation in the application dose is partly due to its standard deviation, as well as the fact that the dose of treatment is determined at the 90% value of the homogeneous dose distribution. This situation results in an intentionally planned variation in the target dose, ranging up to 111%. It will result in a relatively large dose-effect than the prescription dose, as the prescription dose will be placed at the lower end of the range.

uncertainty in the electron therapy is between 5.3% (22) and 10.8% (15-17) and in X-ray therapy systems such as Intrabeam and Papillon, estimated to be about 10% continuously. Comparing four Photon RadioSurgery PRS sources, Armoogum et al. reported an internal radiation monitor reproducibility of 0.23% with mean dose differences of 0.49% at differential angles (16).

As discussed before, the incomplete adherence of the tissue to the applicator end may cause uncertainty in the set-up. A 1-mm air gap between a 40-mm diameter applicator and the tissue decreases the target tissue dose up to 9% based on the inverse square law. If the gap is filled with liquid, the dose will be reduced to 14%; a 2-mm air and liquid gap will reduce the dose values as high as 17% and 26%, respectively. Calibration and dose distribution uncertainties add to the total uncertainty of 7.2% - 13.4%. The gaps between the applicator and the target tissue might increase the overall difference to 10.5% - 15% and 20.1% - 28.2%.

The short distance for low-energy X-ray intensifies the tissue absorption, thus making the target dose variation more pronounced, reaching up to 34% and 25% decreases in the surface dose for 5-cm and 3.5-cm applicators, respectively. The target dose is as low as 15% for a 5-cm applicator and 10% for a 3.5 -cm applicator at a 20-mm gap.

it must be noted that the rest of the target dose variations should be considered.

Concerning the variation of the intended dose for breast cancer treatment with kV X-ray systems, one should recognize the doubled prescribed dose on the level of the applicator based on electron treatments.

As a result, in breast IORT with electron, a dose distribution of 111% and 100% of the prescribed dose with an uncertainty of about $\pm$12% for breast IORT would be considered (for 10-mm target thickness or 20% - 30% for 20-mm target thickness). Meanwhile a dose distribution of 200% and 66% - 75% of the prescribed dose with an uncertainty between 10.5% and 28.2% using kV X-ray for a same target is conceivable.

Herskind's Radiobiological Models (18) attempt to explain why the distribution of kV dose can provide comparable treatment to electrons. TARGIT's final results (20-22) and perchance additional studies can also help in proving the equivalence.

It can be concluded that although the uncertainties in IORT dosimetry are comparable to those in external beam therapy (when IORT calibration problems are clarified), there are other unexpected dose deviations due to set-up uncertainties such as inaccurate target dimension calculation, applicator spacing, accumulation of blood, etc., which are reported as approximately 4% - 12% for electrons

and 10% - 28% for low-energy X-ray.

The values extracted in-vivo suffer from possible variations in the stability of calibration and output, which can be decreased through physical improvements in dosimetry. Target assessment and applicator location uncertainties can also be decreased using online imaging and treatment planning, which hopefully will result in more useful tools (19).

There are difficulties in prediction and comparison of the dose-effect associations in breast cancer due to the deviations from the intended prescription dose, as well as radiation dose gradients. Although IORT is believed to have clear benefits due to increased target dose and simultaneous reduction of adjacent healthy cells, reduced geographical error, early application of therapy on the remnant tumor cells, and potential biological benefits of single-high-dose irradiation (16), the need for clinical trials of IORT efficacy is still highlighted due to the inherent uncertainties. Overall, the frequent evaluation for assuring the quality of treatment is considered an important step in the appropriate application of IORT in practice (24).

3.2.3. Partial Breast Irradiation (PBI) Versus Intraoperative Boost Irradiation

There are two different applications of IORT in breast cancer treatment. The first one is the Intraoperative Boost Irradiation that starts radiation therapy immediately after surgical tumor reduction, followed by a Whole Breast Irradiation (WBI) course. The rationale for boosting is to reduce the period of the rapid proliferation of the tumor residue that theoretically happens due to the rest interval between surgery and WBI in conventional treatment (25). The second application of IORT is Partial Breast Irradiation (PBI), which is a single fractionated radiotherapy applied immediately after tumor excision but not followed by WBI. Photon therapy and electron therapy are applicable in both applications. Both major techniques of IORT (low-energy X-ray and IOERT) have almost identical processes in PBI and Boost, except for the insertion of shielding disk in IOERT PBI while it is not used in IOERT Boost (26).

Extensively reviewing the literature, the outcomes and results of these two applications of IORT in breast cancer treatment are summarized in Tables 1 - 4. Patient survival, cosmetic outcome, and overall patient satisfaction are measured based on the variables considered in the surveys (27). The term IORT is currently used for various techniques that show huge differences in dose delivery and coverage of the tissue at risk.

3.3. IORT PBI

There are many overlaps among studies that used IORT as single-fraction radiotherapy treatment. Because of the youthfulness of this meditating therapy, the lack of research data, and short follow-up times of research groups, the researchers will update their findings as soon as new information is available. We selected 15 studies for review, of which seven used electron therapy and eight used low-energy X-ray.

In 2007, Karaus-Tiefenbacher et al. performed electron-therapy on 17 patients between 51 and 80 years of age whose tumor sizes were 2.5 cm or less, with a dose of 19 to 21 Gy. In 2008, Reitsmer et al. performed this type of treatment at a dose of 10 to 16 Gy for 156 patients. Kimple et al. published their study on 56 patients aged over 48 years with tumors smaller than 3 cm treated with the X-ray dose of 15 Gy. In all of the above-mentioned studies, the cosmetic outcome was evaluated well to excellent and the state of patients' satisfaction was reported well although there was no information about patients' surveillance. This may be due to the variability of follow-up times in these studies. One of the most important studies of electron-therapy was conducted by Veronesi et al. in 2010 on 1822 patients with tumor sizes of equal to or greater than 2.5 cm. All of the patients were treated at a dose of 21 Gy and the mean follow-up time was 36 months. The surveillance rate of the patients was 97.4% and the cosmetic results were mentioned well (30). In 2007, Holmes et al. published their report of 569 patients treated with X-rays at 20 Gy. The average follow-up period was 12 months and the patients had great cosmetic outcomes (35).

3.4. IORT Boost

There were 10 articles assessing the use of IORT as boost treatment, seven of which used IORT electron therapy and the rest was related to X-ray therapy. As seen in the boost electron table, Lemanski et al. in 2006 examined 45 patients aged 66 - 80 years. The mean size of the tumor in these patients was 1 cm and the treatment dose was 21 Gy. The patients were followed for 30 months; the author did not mention the surveillance of the patients, but reported good to excellent cosmetic outcomes (53). In 2012, Forouzannia et al. observed 50 patients aged between 32 and 76 who had tumor sizes of smaller than or equal to 2 cm. The patients received 10-Gy electron therapy followed by a 24-month follow-up. The outcomes of these patients were evaluated well (45). In another study performed by Piorth et al., 53 patients with a tumor size of 2 cm or smaller were to receive the radiation dose of 10.8 Gy, followed by 24-month followed-ups (46). The poor cosmetic result was reported due to complicated fat necrosis. In 2013, two separate multicenter studies of this surveillance method were published. Fastner et al. followed up 1,009 patients between the ages of 40 and 60 for 72.4 months after IORT. The surveillance rate of the patients was reported as 99.20%

Table 1. A Summary of Main Studies in the Whole IEORT for Breast Cancer

First Author	Year of Publication	Research Center	Number of Patients	Age Range	Tumor Size, cm	Radiation Dose, Gy	Follow-up period (months)	Surveillance, %	Cosmetic Outcome	Patient Satisfaction
Kraus-Tiefenbacher (28)	2007	-	17	51-80	≤ 2.5	19 to 21	60	-	Excellent	-
Reitsamer (29)	2008	-	156	-	-	10 to 16	24	-	Excellent	-
Veronesi (30)	2010	-	1822	-	≤ 2.5	21	36	97.40	Excellent	-
Kimple (31)	2011	-	56	≥ 48	≤ 3	15	36	-	Good to excellent	Satisfied
Dessena (32)	2011	-	30	38 - 75	≤ 2.5	21	11	-	Good	-
Wang (33)	2014	-	36	-	-	-	28	100.00	Good to excellent	-
Hanna (34)	2015	Rambam Health Care Campus in Haifa	31	-	≤ 2	-	36 - 48	91	Good	-

Table 2. Characteristics of Low-Energy X-Ray Whole IORT Publications

Author	Year of Publication	Research Center	Number of Patients	Age Range	Tumor Size, cm	Radiation Dose, Gy	Follow Up Period, mo	Surveillance, %	Cosmetic Outcome	Patient Satisfaction
Holmes (35)	2007	Zeiss Inc, Germany	569	-	-	20	12	-	Excellent	-
Sawaki (36)	2009	-	-	≥ 50	≥ 2.5	21	26	-	Very good	-
Chua (37)	2011	-	60	-	≥ 3	5	-	97	-	-
Ruano-Ravina (38)	2011	-	-	-	2	10 - 24	24	99	Excellent	-
Sawaki (36)	2009	-	-	≥ 50	≥ 2.5	21	26	-	Very good	-
Neumaier (39)	2012	-	540	≥ 70	2	20	24	96	Good	-
Merdad (40)	2013	King Adulaziz University Hospital, Jaddeh, Saudi Arabia	45	27 - 79	≤ 3.5	20	24	-	Acceptable	Acceptable
Keshtgar (41)	2013	-	342	59 - 68	-		60	-	Excellent	Satisfied
Osti (42)	2013	-	110	-	-	21	27	97.30	-	-

Table 3. Characteristics of IEORT Boost Publications

Author	Year of Publication	Research Center	Number of Patients	Age Range	Tumor Size, cm	Radiation Dose, Gy	Follow-up Period, mo	Surveillance, %	Cosmetic Outcome	Patient Satisfaction
Ivaldi (43)	2008	-	204	-	-	37.05	36	-	Acceptable	-
Lemanski (44)	2010	-	45	66 - 80)	1	21	30	-	Good to excellent	Maximal
Forouzannia (45)	2012	National Cancer Institute	50	32 - 76	≤ 2	10	24	-	Good	-
Piroth (46)	2012	-	53	-	2	10.8	24	-	Poor	Fat necrosis
Fastner (47)	2013	7 centers	1109	40 - 60	-	-	72.4	99.20	Excellent	Satisfied
Veronesi (48)	2013	European Institute of Oncology, Milan, Italy	651	48 - 75	≤ 2.5	21	60	96.80	Good to excellent	-
Welzel (49)	2013	-	230	3 - 84	-	-	32	-	-	Acceptable
Ivaldi (43)	2008	-	204	-	-	37.05	36	-	Acceptable	-

Table 4. Characteristics of Low-Energy X-Ray IORT Boost Publications

Author	Year of Publication	Research Center	Number of Patients	Age Range	Tumor Size	Radiation Dose, Gy	Follow-up Period, mo	Surveillance, %	Cosmetic Outcome	Patient Satisfaction
Kraus-Tiefenbacher (50)	2006	-	73	-	-	20	24	-	Good	-
Blank (51)	2010	Carl Zeiss Surgical Center	197	30 - 84	-	20	60	97	-	-
Sperk (52)	2014	-	305	≥ 50	-	20	40	-	Excellent	Satisfied

(47). Veronesi et al. examined 651 patients aged 48 - 75 years followed for 60 months, and reported the surveillance rate of 96.8% (48).

In the years 2006, 2010, and 2014, radiation boost treatment with X-ray was studied by researchers. As demonstrated in Table 4, all the three studies used X-ray doses of

about 20 Gy, and followed up the patients from 24 to 60 months.

As shown in Tables 3 and 4, the electron-therapy technique was more relevant to IORT boost treatment and more accurate information was available on how it was tracked and its outcomes. Most therapies were performed with a dose of 10 Gy. The greatest benefit of IORT boost is the improvement of the cosmetic outcome and satisfaction of the patients. This treatment not only has good local tumor control, but also has good surveillance results.

3.5. Clinical Trials

As mentioned earlier in this study, not only the IORT therapeutic results were highly acceptable in terms of patient satisfaction and cosmetic outcomes, but also its surveillance was evaluated well in studies with measurable follow-up periods. It should be noted that the data regarding surveillance are not still conclusive. However, in order to find the alternative modality to be placed as an ideal choice in therapeutic protocols, it is necessary to demonstrate the superiority of this therapeutic approach to conventional methods, or at least non-inferior effects with other therapeutic approaches (54). For this purpose, several clinical trials have been designed around the world. Some of these trials are still ongoing. In this section, we will review two main clinical trials, including the ELIOT trial based on electron-therapy and the TARGIT trial based on low-energy X-ray therapy (48, 55).

3.6. ELIOT Clinical Trial

In 1999, Veronsei et al. at the European Institute of Oncology, Milan, Italy, started the ELIOT clinical trial. They used a mobile linear accelerator (LINAC) with a robotic arm to deliver electron beams that could produce energies from 3 to 9 MeV (56). In 2001, the first article was published with 17 patients receiving an IORT dose of 10 to 15 Gy as an anticipated boost to external radiotherapy while 86 patients received discrete doses of 17, 19 or 21 Gy as their main irradiation treatment (10). The follow-up time ranged from 1 to 17 months for 101 patients, and the mean follow-up time was eight months. Initially, Vernoesi et al. hypothesized that IORT, due to its simplicity and rapidity, was very well accepted by patients receiving IORT either as a whole or as an anticipated boost. The ELIOT trial was designed at the European Institute of Oncology, Milan, Italy, to evaluate this hypothesis (51). Therefore, 1,305 patients were randomized to receive external radiotherapy (n = 654 patients) or intraoperative radiotherapy (n = 651 patients). Women were aged 48 - 75 years with early breast cancer, and the maximum tumor diameter was up to 2.5 cm.

Women were aged 48 - 75 years with early breast cancer, and the maximum tumor diameter was up to 2.5 cm and appropriate for breast-conserving surgery, randomly assigned in a 1:1 ratio for either full-breast external radiotherapy or intraoperative electron radiotherapy. During surgery, patients in the group of intraoperative radiotherapy received one dose of 21 Gy in the tumor bed. Patients in the group of external radiotherapy received 50 Gy in 25 fractions of 2GY, followed by a 10-Gy boost in five fractions. There were 35 patients in the group of intraoperative radiotherapy and four patients in the group of external radiotherapy that had an ipsilateral breast tumor recurrence IBTR ($P < 0.0001$) after a median follow-up of 5.8 years (52). The five-year IBRT event rate was 4.4% (95% CI: 2.7 - 6.1) in the intraoperative radiotherapy group and 0.4% (95% CI: 0.0 - 1.0) in the external radiotherapy group (95% CI: 3.3 - 26.3). Although the IBTR rate was within the clearly predefined equivalence margin in the intraoperative radiotherapy group, the rate was significantly higher in this group than in the external radiotherapy group; however, there was no difference in overall survival between the groups (35).

Having studied 1,822 patients in Italy from 1999 to 2008, Veronesi again indicated in 2010 that ELIOT appears to be a promising feature in early breast cancer treated with breast-conserving surgery, which reduces normal tissue exposure to radiation and shortens the radiation course from six weeks to one session (21). According to the ELIOT trial findings, a single dose of IOERT is a way to avoid mastectomy, decrease the risk of possible toxicity, improve the quality of life, and increase the patient's treatment accessibility (57).

3.7. TARGIT-A Trial

In the TARGIT-A (TARGeted Intraoperative Radiotherapy Alone) trial, 3,451 patients were enrolled starting from 2000 for a period of 12 years with the propose of Intention-to-Treat and non-inferiority of IORT modality in breast cancer treatment. All the cases were $\geq$ 45-year-old women diagnosed with invasive ductal carcinoma of the breast, undergoing breast-conserving surgery from 33 centers in 11 countries. To make it more feasible for facilities to follow the protocol of the trial, randomizations were applied both before lumpectomy (pre-pathology) and after lumpectomy (post-pathology) in which irradiation was given by reopening the wound (58).

In this trial, 1721 patients were randomized to TARGIT and 1730 to EBRT. Randomization was done for 2,298 patients before lumpectomy and for 1,153 patients after lumpectomy. In the TARGIT arm, 239 out of 1571 (15%) patients were given both TARGIT and EBRT (59).

TARGIT-A trial used a risk-adapted protocol. Some patients allocated to TARGIT, who proved to have the characteristics of high-risk disease post-operatively, received TAR-

GIT and EBRT as per the protocol. In all cases receiving intraoperative radiotherapy and EBRT, TARGIT was considered as a boost treatment, and they entered another trial called TARGIT-B (60).

The main objective of the TARGIT-A trial was to compare the non-inferiority of IORT with whole-breast external beam radiotherapy. In the first publications of this trial, due to immature results, making the decision about the trial intents in primary reports was not attainable (55). In the final report, it was found that the five-year risk of local recurrence for TARGIT was 3.3% compared to EBRT with the rate of 1.3%, which was non-inferior (61).

The results of the trial were reported for patients who received TARGIT or TARGIT plus EBRT treatment in the pre-pathology group and patients with post-pathology receiving TARGIT treatment. It should be noted that since there were number only 20 post-pathology patients who received the TARGIT plus EBRT treatment, the researchers did not mention the outcomes of this group. Patients were categorized in terms of tumor size, tumor grade, and presence of lymph nodes. The risk of five-year local recurrence was 5.9 (3.3 - 10.5) in post-pathology patients who received TARGIT alone compared to the risk of 0.9 (0.1 - 6.1) for pre-pathology patients who received TARGIT plus EBRT and 2.7 (1.3 - 5.5) for pre-pathology patients who received TARGIT alone. The risk of five-year death due to breast cancer was highest in pre-pathology patients who received TARGIT plus EBRT (8 (3.5 - 17.5)), followed by the risk of 1.8 (0.7 - 4.6) in pre-pathology patients who received TARGIT alone and 0.6 (0.2 - 2.5) in post-pathology patients who received TARGIT alone. The risk of five-year death for any other reason was highest in pre-pathology patients received TARGIT alone (1.9 (0.9 - 4)) while it was 1.5 (0.6 - 4.3) for post-pathology patients who received TARGIT alone and zero in pre-pathology patients who received TARGIT plus EBRT (58).

In this report, non-inferiority was calculated individually for the primary cohort, mature cohort, and all patients. The number of patients in the mature cohort was 2,232 patients whose information was published in 2010. Patients in the early cohort were those who were enrolled in the cohort during the first eight years of the study and patients recruited in the last four years of the study were not included in this population. Local recurrence was intended for patients who had not had a mastectomy before tumor recurrence. It should be noted that the number of mastectomies was not significantly different between the TARGIT and EBRT groups. For this trial, non-inferiority was acceptable with a margin of 2.5% (59).

International societies initially recommended that patients older than 60 years having a minimal negative margin of 2 mm with T1 staging and without DCIS were suitable for IORT (62). However, international societies have lately recommended that patients older than 50 years having a minimal negative margin of 2 mm with Tis or T1 staging are suitable candidates, if they are screen-detected, for whom the tumor shows low to intermediate nuclear grade and has a size less of than 2.5 cm. On the other hand, while patients younger than 50 years who had a positive margin and DCIS of larger than 3 cm were considered unsuitable for IORT, the new recommendations remark that the patients are unsuitable if they are younger than 40 years or they are between 40 and 49 and do not meet any of the cautionary criteria. Cautionary cases are now 40 - 49-year-old patients with no other contraindication, or those older than 50 years with at least one risk factor (tumor size between 2 and 3 cm, T2 staging, a margin close to 2 mm, limited or focal LVSI, ER-negative, Clinically unifocal with total size of 2.1 - 3 cm, invasive lobular histology, and Pure DCIS $\leq$ 3 cm) (26).

In recent years, a body of literature has been added on long-term results and survival and mortality of the patients. One important issue is the sociodemographic differences in patients' willingness to adopt IORT as their treatment choice, which has had a determining effect on short and long-term outcomes (63). In many cases, patients' choices are not attributable to any known determinant (64). The researchers mostly highlight the importance of proper case selection in achieving appropriate outcomes (65, 66). Some researchers consider the benefits of IORT beyond conventionally evaluated pathways, such as its role in altering the tumor microenvironment through radiation-induced bystander effect (67). Also, due to the exclusion of the skin from radiotherapy in IORT, it is crucial to reevaluate the applied surgical techniques (68).

4. Conclusions

Despite controversies in the acceptance and effectiveness of IORT, this technique seems to be promising in breast cancer treatment, as well as improved cosmetic outcomes and non-cancer-related deaths (69). The success of IORT technique depends on three main features: rational patient selection, well-performed quality assurance process of devices, and appropriate treatment plan. The aim of these measures is to reduce the innate uncertainty associated with IORT. These measures require approved guidelines and protocols for health service providers.

Footnotes

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