



Intraoperative Period and Breast Cancer: Review

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ABSTRACT

Intraoperative radiation therapy in breast cancer (IORT) delivers a concentrated dose of radiation therapy to a tumor bed during surgery. IORT offers some of the following advantages with typically fewer complications like; maximum effect, sparing healthy tissues and organs, to help the patients finish treatment and get back to their normal activities. The goal of IORT is to improve local tumor control and survival rates for patients with breast cancer. IORT can both be performed with electron beams (ELIOT) and X-rays. Two main randomised trials testing intraoperative partial breast radiotherapy are TARGIT trial and the ELIOT (intraoperative radiotherapy with electrons) trial, but the techniques are fundamentally different. Whereas TARGIT delivers radiation from within the undisturbed tumour bed, for ELIOT, the mammary gland is mobilised, a prepectoral lead shield is inserted, the edges of the tumour bed are apposed, and radiation is delivered from without.

Key words: Intraoperative period, breast cancer, treatment

Introduction

Currently, breast cancer is one of the leading causes of cancer in women. Nevertheless, there are rapid developments and changes in the diagnosis, treatment and follow-up methods of this disease. Today breast cancer can be diagnosed at earlier stages, with a chance for cure with limited surgery, and the patients have improved quality of life. Today, based on recent studies, the type of breast cancer surgery that led to complete loss of the breast has been replaced by breast-conserving surgery (BCS) in all appropriate patients (1-4). According to the results from large multicenter studies on early breast cancer, there were no significant differences in terms of disease-free survival and overall survival between mastectomy, and BCS and whole breast radiotherapy (RT). Therefore, conserving surgery and whole breast irradiation has been accepted as the standard treatment in early breast cancer, and it has been reported that local control also plays an important role on survival. One of the most feared clinical situations in the treatment of breast cancer, especially after BCS, is local recurrence (LR) at the site of operation. Undoubtedly, one of the most important ways to avoid this dreaded complication is application of RT to the tumor itself and around the tumor bed. Most of the LRs usually occur at the same quadrant with the tumor area that has been operated, due to the microscopic tumor remaining after BCS. A number of risk factors have been identified for the occurrence of LR, including large tumor size, high tumor grade, young patient age, lymph node involvement, and presence of tumor deposit close to surgical resection margin (5,6). There is a decrease in LR rates due to earlier diagnosis of breast cancer patients, high quality standards in pathological examinations, better individual treatment planning, and increased awareness on breast cancer. The focus of the discussion regarding the causes of LR and the developments leading to decreased LR rates is centered around mostly the innovations and practices in the field of RT. In practice, it is an important fact that planning of the RT dose that will be applied to the tumor bed is the most effective way of preventing LR. Intraoperative radiotherapy (IORT) is a generic term covering ELIOT, which is irradiation of the tumor bed by using electrons especially after BCS for breast cancer surgery, and other RT techniques that utilize partial RT by using photons (7).

History

The first modern studies on intraoperative radiation therapy began in 1965 at the University of Kyoto in Japan. The patients were treated by electrons generated by betatron, and they advocated that when compared to other methods, IORT performed with electrons was more successful in terms of dose distribution, limitation of penetration to the surrounding tissues, and faster delivery of the required dose. The Japanese experience was followed by IORT with electrons (IOERT) at Howard University. The first IORT program in the United States was started at Massachusetts General Hospital in 1978(8,9).

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IORT Techniques

Intraoperative radiotherapy is used to give a single fraction radiation in the operating room during BCS (one-time treatment). There are three main IORT techniques; linear accelerator technique that provides RT with electrons, brachytherapy and photon radiosurgery. Mobile linear accelerators using X-ray or electrons are Liac (Info & Tech, Rome, Italy), Novac7 (Hitesys Srl, Aprilia, Italy), Mobetron (IntraOp Medical Corp., Santa Clara, California). Also Intrabeam (Zeiss, Inc., Oberkochen, Germany) system is a miniature, electronic, mobile platform with X-ray source that can be used in selected patients via specific applicators either for irradiation of the tumor cavity intraoperatively with single and high dose radiation, or irradiation before whole breast irradiation to reduce RT duration. These equipments can be easily transported to the operating room (10-12). All linear accelerators act in a similar way. For the electron technique, a mobile linear accelerating electron applicator that generates 3-10 MeV electron beam is used. The applicator is placed over the surgical cavity to give a single dose of 21 Gy to the tumor bed with a 1.5-3 cm margin. An aluminum disk is placed on the pectoral muscle to protect thoracic tissues from irradiation, the skin is moved away from the applicator by as much retraction as possible. The total administered dose of 21 Gy is considered biologically equal to 60 Gy radiation applied for 5 weeks (13-15). Axxent Electronic Brachytherapy (Intracavitary systems) System (Xoft Inc., Fremont, CA) is a balloon-based brachytherapy system, and uses a 50 kilovoltage electronic radiation source. This system simplifies the process of interstitial brachytherapy. A single lumen balloon catheter similar to MammoSite catheter is used together with a system that has two additional ports, one serves to give air or fluid and the other is for discharge. During or after surgery, the balloon is inserted into the surgical cavity by ultrasonographic guidance. Then the balloon is connected to a radioactive source with a high-dose rate. It is important that the skin thickness should be 5-7 mm in order to achieve good cosmetic results. Therefore, this technique is not suitable for patients with small breast sizes or in tumors located at the upper inner quadrant. Risk of fat necrosis is a side effect. Generally, 34 Gy is implemented in 5 days over 10 fractions (twice a day) to 1 cm from the surface of the balloon. Axxent electronic brachytherapy catheter was approved in 2006 by FDA (Food Drug Administration). It seems to be superior to MammoSite system due to the increased protection provided to normal tissues with a similar target volume. Long-term clinical results are necessary. Early results of single and multi-center studies indicate no recurrence and good cosmetic results (16, 17).

Which diseases are suitable for application of the IORT Technique?

Coma and Prio made the first application of intraoperative radiotherapy in endometrial cancer. Another area of use is rectal cancer, and it is aimed to improve local control especially in the treatment of tumors with pelvic recurrence and high-risk locally advanced disease, that are accepted as causes of failure. It has been reported that IORT provides local control in selected patients with sarcoma limited to the trunk and extremities. Early information on the use of IORT in prostate cancer came from Kyoto University. In locally advanced prostate cancer, IORT was applied without prostatectomy (18-21). In the study by the Italian group, IORT was implemented before or after surgery together with radical prostatectomy and regional lymph node dissection. It has been presumed that utilization of IORT may be beneficial in achieving local control in locally advanced pancreatic cancer, and positive outcomes have been reported. However, since many treatment regimens are used in combination for pancreatic cancer, it is difficult to extract the specific effects of IORT technique.

IORT was usually applied following adequate resection in locally advanced disease (22-24).

Breast cancer and IORT

All the developments in breast cancer are associated with improvements in less radical, less invasive and more patient-friendly techniques. Due to increased public awareness and screening programs, patients can be diagnosed at early stages allowing the possibility of BCS. Moreover, now we have scientific data with results from 20-years of follow-up, showing that BCS and breast irradiation is as effective as mastectomy in early breast cancer. However, patients may not complete radiotherapy for various reasons, and expose their selves with the risk of recurrence on the same side, so some patients prefer mastectomy rather than BCS, and avoid RT. That is why, by the development of IORT it is planned to reduce the standard 6-week course of treatment (25).

The LR rate decreases with IORT after breast-conserving surgery. An increase in LR, radiation toxicity or other side effects was not detected after IORT, in studies with five year follow-up. The IORT technique also brings many advantages compared to conventional RT in which all breast is irradiated. A single dose of external beam RT instead of the six-week-long therapy is more preferable, both economically and in terms of time (26). In the IORT process there is no invasive entry to the body, which makes this technique easier to accept. It is also thought that the distribution in the tumor bed and usefulness of RT is increased due to the proangiogenic environment occurring in the early post-operative period. IORT immediately sterilizes the tumor cavity, and potentially reduces residual tumor cell proliferation. It has been advocated that high dose IORT can block the potential stimulating effect of wound fluid on tumor cell proliferation and invasion, *in vitro* (27). It is thought that probable residual tumor cell re-population that may appear in the period between surgery and adjuvant RT will also be prevented by the IORT technique. Another hypothesis supporting IORT is that the good oxygenation in the tumor bed during surgery also may increase the bioavailability of RT, but this hypothesis has not been evaluated so far. Despite all these hypotheses cellular and intracellular reactions in the irradiated tissue, and their effects on local tumor recurrence are not clear, with requirement of further studies in this regard. Although a definite rate has not been determined, the common feature of the majority of recurrences is that they are poor differentiated. Another important point is that recurrence are more frequent in younger patients. Annual LR rates vary according to different RT techniques and age; the lowest rates are in 41-50, 51-60 and > 60 years of age (1.8%, 1.5%, 1%). The annual recurrence rates have decreased with advances in the fields of diagnosis, surgery and pathology in the last 10 years, together with an increase in the use of modern systemic therapy and advances in RT. The 5-year local recurrence rate was reported as 0.7% in the ELIOT study, which is not recruiting new patients anymore (28, 29).

By using intraoperative radiotherapy, problems related to access to conventional RT centers for treatment is eliminated, and the patients have to opportunity to receive their treatment at the center where they had surgery. Certain anatomical sites, such as the brachial plexus, heart, lungs, that cannot be protected by conventional RT regimes can be protected by IORT techniques, and unnecessary exposure to radiation are avoided in these areas. In addition, seroma occurring after lumpectomy likely does not influence the radiation field in IORT (30-32).

In intraoperative radiotherapy, the surrounding skin is protected with potentially better cosmetic results, and the risk of radiation-dependent

angiosarcoma is probably eliminated. One of the most important benefits is the elimination of the possibility of delays in RT due to side effects of systemic chemotherapy, which is a factor that increases LR. IORT technique can be used instead of conventional RT in patients who have been previously irradiated due to diseases like Hodgkin's disease or cancer, and therefore are not appropriate for this technique. However, more scientific studies and results are required in this regard (33, 34).

Which Breast Cancer Patients Can Undergo IORT?

Younger patients are at a higher risk of LR. For this reason, partial breast irradiation studies were selected from patients 45 years and older. One of the major risk factors for LR is tumor size, the tumor size appropriate for partial breast irradiation is recommended as tumors less than T3. Patients with extensive intraductal component should be treated with caution. Partial breast irradiation can be used in patients who have clinically unifocal or multifocal tumors, no larger than 2 cm. Patients who will not be surgically assessed for lymph node involvement, or those with pathological evidence of lymph node involvement are at a significant risk for ipsilateral breast cancer, and these patients do not appear to be suitable for partial breast irradiation techniques. There is no consensus on the exact ideal population for the application of IORT in modern breast cancer treatment algorithms. IORT is still considered as an experimental treatment protocol, and this technique is not performed in patients with serious co-morbidities or those with a history of previously performed RT, and it is limited to older patients with early stage breast cancer (35, 36).

The TARGIT-A (Targeted Intraoperative Radiotherapy) study, which is one of the two most important studies on the field of intraoperative radiotherapy, included patients over the age of 45 years, with unifocal invasive breast cancer who are eligible for BCS. The European Institute of Oncology (EIO) study included patients over the age of 48 years, with unifocal, small invasive (maximum tumor diameter of 2.5 cm) tumors. The Montpellier study included patients over 65 years, with unicentric stage I cancer (37, 38).

Which breast cancer patients are not suitable for IORT?

Partial breast irradiation should be avoided in patients with multicentric tumors, tumors in different quadrants, because of the extent of tumor foci. The American Society of Radiation Oncology (ASTRO) has determined certain criteria and guidelines to differentiate between the patients suitable for Accelerated Partial Breast Irradiation (APBI) and those who are not. These criteria also serve as a guideline for patients in whom IORT technique can be used. Bilateral, multifocal or multicentric breast cancer patients with clinical positive lymph nodes or patients with extensive ductal carcinoma in situ are not candidate for IORT. Contraindications for standard RT such as connective tissue diseases, and pregnancy (although in the EIO preliminary study potential fetal radiation exposure was found to be negligible) are also contraindications for IORT (39,40).

One of the main limitations of intraoperative radiotherapy technique is whether the definitive pathological analysis of surgical lumpectomy and surgical margin control is done properly. To overcome this issue a quadrangectomy can be performed with removal of a larger volume and negative surgical margins, or alternatively the surgeon may use intraoperative frozen section to verify resection margins prior to IORT. It should be kept in mind that in case of re-resection after IORT due to positive surgical margins on definitive pathology, there are risks of delayed wound healing and poor cosmetic results (41, 42).

Patients with breast cancer that are located very close to the skin or axillary tail are unsuitable candidates for IORT, since they lack enough breast parenchyma to protect the skin or the chest wall. Lobular cancers are not suitable candidates for IORT because of the possibility of occult tumor spread areas at the time of lumpectomy. One of the major drawbacks of IORT is not knowing the involvement status of sentinel lymph node or axillary lymph nodes during the implementation of the technique, for certain. IORT is a local treatment method and normally local lymph nodes should not be involved into the treatment in anyway. However, during the planning of whole breast irradiation, lymph node involvement is known for certain, and the treatment plan is shaped according to the situation. One of the most important barriers in promoting the IORT technique is its being more expensive in every aspect. Nevertheless, when it is considered that some patients live in far away from RT centers, their access is difficult or impossible, and there is a longer duration of external RT time, then IORT technique may be more advantageous (43-45).

Advantages of the IORT Technique

The main idea on Linac-based IORT with electrons during breast-conserving surgery is based on utilization of a single high dose RT directly to the tumor bed. This process is carried out under direct observation during surgery. The studies with intraoperative electron radiation therapy technique defined this treatment as a procedure with better cosmetic results without additional morbidity when compared to standard treatment. In the ISIOR study, the analyses of patients from separate European institutes that used their own prospective programs were combined. Patients received an average single dose of 10 Gy IOERT and 50-54 Gy fractioned doses of whole breast RT. The mean interval between surgery and RT was recorded as 6-8 weeks. Intraoperative frozen section analysis or postoperative definitive histopathological examination was used for negative surgical margins. The accuracy rate of frozen section for the invasive component showed compatibility with definitive histopathology. On the other hand, the assessment of in situ lesions with frozen section is not reliable and patients may require re-excision after definitive treatment (46, 47).

An increasing number of surgeons are using reconstruction techniques during BCS according to oncologic principals. The mobilization of surrounding tissues towards the tumor bed might lead to difficulties in detection of the actual bed of the tumor after surgery despite marking with clips, or to the formation of seroma that affects the RT field by increasing the thickness between the tumor bed and seroma. IORT is applied prior to reconstruction, even in patients with reconstruction in the same session, ensuring irradiation of the tumor bed more accurately, and optimizing the cosmetic result. For these reasons, in tissues without distension due to hematoma or seroma, IORT may be administered directly to the tissue, providing small treatment volumes and full skin protection. IORT is regarded as a highly effective technique in terms of destruction of microscopic residual tumor cells (48).

Side effects of the IORT Technique

The technique is thought to result in tissue fibrosis and necrosis in long-term follow-up. All accelerated partial breast irradiation method including single-dose IOERT technique carry the risk of overlooking peripheral tumor bed or areas outside the target volume. Due to the risk of tumor recurrence, these areas are usually attempted to be controlled by 50 Gy whole breast irradiation. Undoubtedly, tumor recurrence occurs in the original tumor bed in the early follow-up period, while, the long-term tumor recurrences tend to be more distant from the primary area. In the IORT technique findings such as redness,

warmth, and hyper-pigmentation can be seen at the irradiation field (49,50).

IORT Studies

Although intraoperative radiation therapy studies are conducted with limited follow-up durations, all by the same institute, initial results on IORT technique in carefully selected patients are comparable to results on whole breast irradiation. There are two major full-dose IORT studies to date. One of them is TARGIT and the other one is ELIOT. The technique in the TARGIT study used orthovoltage X-ray, and the ELIOT study tested the single dose electron treatment (51).

The EIO study that published the largest patient series on this issue has reported good outcomes. In that prospective study, 1822 patients were administered a single intraoperative dose. In this series, the mean follow-up time was 36 months, with a necrosis rate of 4.2% and fibrosis rate of 1.8%. The LR rate was detected as 3.63%, and the rate of new primary breast cancer in the ipsilateral breast was reported as 1.3%. These ratios confirm that the technique is efficient and reliable in terms of oncology. Veronesi and colleagues have presented recent data from the ELIOT study in their manuscript on November 2013, in the *Lancet*. According to this report, 1305 patients were included in the study and at a mean follow-up period of 5.8 years, the ipsilateral recurrence rate of the tumor was 4.4% in the IORT group whereas this rate was found to be 0.4% in the external RT group, and a statistically significant difference was detected. There were no differences between the two groups in terms of five-year survival rates. Less skin related side effects were noted in patients from the IORT group. The researchers believed that the LR rate may be reduced with more careful selection of patients, and perhaps with the addition of new criteria. They stated that randomized trials focusing on this issue are required, and that the ELIOT technique provided an irradiation equal to whole breast irradiation (52).

One of the interesting studies conducted at the European Institute of Oncology is the application of IORT during nipple-sparing mastectomy. In the study, the LR was 1.4% in 1,001 patients who were followed-up for 20 months, and none of the recurrences was in the nipple-areola complex (53).

The TARGIT-A study was initiated in 2000. It is a multicentric, international, randomized, controlled clinical trial comparing a single dose of IORT by intrabeam radiotherapy method and conventional external RT in early breast cancer patients. This study reported similar complication and morbidity rates, as well as offering Level I data that IORT can be used in selected patients with early breast cancer, and is valuable in this regard. Low energy radiation (50 kV) is used. Jayant S Vaidya and colleagues from University College London have designed this technique in 1998. This method prevents the delay in chemotherapy, and enables BCS. This study that was conducted with women undergoing lumpectomy, initial results of 2232 patients who were included in the TARGIT study and were randomized to standard whole breast irradiation or IORT by Intrabeam System were published by Vaidya and colleagues (6). According to the 4-year follow-up results, the LR rate in both arms was statistically equal (0.95% versus 1%). Complications and local toxicity rates were also similar, in fact were even less in the IORT arm. Evidently, these early results should be validated with long-term outcomes. The presence of higher LR rates in the IORT study, which during the initial phase appear to be higher than the conventional RT, should not lead to negative opinions on IORT. (54,55).

In the up-date of TARGIT-A randomized trial data that was published in the *Lancet* in November 2013, Vaidya et al reported that 1721 patients in 33 centers from 11 countries received TARGIT, and 1730 patients received external breast RT. The five-year LR ratio in the TARGIT group was determined as 3.3% and as 1.3% in the external RT group. The risk of breast cancer related death was found to be 2.6% in the TARGIT group, and similarly 1.9% in the external RT group. Grade III and IV skin complications were significantly lower in the TARGIT group. According to this study, the authors stated that TARGIT can be considered as an alternative to external RT method in well selected patients with BCS. In a large systematic review of 15 studies on IORT, local control in patients with IORT at 1 and 4-year follow-up was calculated as 95%, and 5-year survival as 99%. In the most recent study published in 2013 in the *Lancet*, according to 5-year results of lumpectomy and TARGIT in combination, it has been reported that mortality rates related to rare causes like cardiovascular disorders and other cancers due to RT are less in the TARGIT method and the results remained stable in longer follow-up (56).

In the study by the Mannheim group, impacts of IORT on quality of life have been questioned and it has been reported that IORT was superior to whole breast irradiation in terms of quality of life. IORT patients stated less restriction in daily activities due to pain, breast and axillary symptoms. New studies are planned with more patients, and longer follow-up period, by using specific toxicity and cosmetic scores (58).

In the Montpellier study, 42 patients with a mean age of 72 years received IORT and the mean 5-year disease-free survival rate was reported as 92.7% with a mean follow-up of 72 months, and both good cosmetic results and good quality of life were reported (57).

Normally, in cases of recurrence where a mastectomy is necessary, the patient can be a candidate for re-BCS by the application of IORT, without any fear of side effects. These results show that in a very carefully selected patient population, an average of 10 years disease-free survival can be achieved by re-RT. According to the results of the ELIOT study that was presented earlier this year, the rate of tumor recurrence within the same breast was higher in the IORT group. Direct comparison with accelerated partial breast irradiation techniques has not been studied so far. The 5-year follow-up results will not be obtained until 2017 (59, 60).

General Evaluation

Currently, IORT is still in the experimental stage, except clinical trials, until its long-term effects and safety are proven. IORT is applied in EIO since 1999. Prospective studies investigating tolerance to increased IORT doses are required. The most recently adopted state is that the implementation of 21 Gy IORT is biologically equivalent to whole breast irradiation dose. Because it is applied during surgery, a more sensitive environment to RT is created without giving tumor cells the chance to proliferate. IORT dose is applied during surgery under direct observation enabling correct irradiation of the surgical bed and with the right dose. The radiation dose received by the heart and lungs are reduced by IORT. The early application of RT by IORT prevents any delay in the delivery of chemotherapy. In some countries, it is argued that the single dose administration of IORT reduces health care costs as compared to conventional RT. Shah et al conducted a study in 2014, and compared IORT with whole breast irradiation, and accelerated partial breast irradiation methods in terms of prices and costs. The IORT method was more advantageous with respect to

expenditures only in early-stage breast cancer patients, and apart from this, the other two methods have been reported to be more economical as compared to IORT (61).

Intraoperative radiotherapy enables good cosmetic results. The skin and subcutaneous tissues are not irradiated; therefore, a change in the appearance of the breast is not expected. However, information on this subject is limited. Evaluation of late stage changes after IORT is significant and results in this regard are also pending (62-64).

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