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Review Article

Update on intraoperative radiotherapy for early-stage breast cancer

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Abstract: Intraoperative radiotherapy (IORT) is a practical and feasible alternative or an adjunct to whole-breast external beam radiation therapy (EBRT) for adjuvant treatment of breast cancer. A large number of experiments have proved IORT is non-inferior for treating early breast cancer due to its advantages, including precise radiotherapy, protection of healthy tissues and organs and sound cosmetic effects. IORT can use both electron beams and X-rays. Some aspects of the clinical use of IORT are still controversial, and extensive trails are ongoing. In this article, we review the published evidence and some ongoing clinical practice to introduce IORT in breast cancer treatment.

Keywords: Early-stage breast cancer, breast-conserving surgery, intraoperative radiotherapy

Introduction

Breast cancer is the most common malignancy for women worldwide. Due to the widespread implementation of mammography screening, a majority of breast cancer patients are diagnosed at an early stage [1]. Thus more and more patients and doctors attach great importance to the cosmetic effects. The current standard care for this group of people is breast-conserving surgery (BCS) followed by whole-breast external beam radiation therapy (EBRT) [2, 3].

The EBRT method is typically administered postoperatively as 45-50 Gy for 3-7 weeks, and 1.8~2 Gy every time and additional exposure to 10-16 Gy to the tumor bed usually followed to suppress local recurrence [3]. Due to the long-term duration, the economic burden increases and the quality of life decline, so in many countries patients cannot complete it, especially those living a far distance from radiation centers. Besides, the large irradiation area and a high dose of EBRT will cause pigmentation and atrophy of the skin, affect the cosmetic effect of patients, and damage organs adjacent to the irradiation site, such as potential lung and cardiac toxicities of radiation treatment and other adverse radiotherapy reactions [4]. A series of observations confirmed that the majority of locally recurrent cancers develop at or near the site of the original breast cancer.

All the above drove the emergence of the accelerated partial breast irradiation (APBI), which can shorten the courses of radiation and decrease the size of the irradiation field. Nowadays, APBI has developed into an alternative to EBRT in the setting of early breast cancer. Intraoperative radiotherapy (IORT) is a form of APBI that can deliver a large, single dose of radiation to the lumpectomy site and tissue adjacent to the resection cavity at the time of surgery.

Recently, the clinical application of IORT has gradually increased. This article reviews the advantages and mechanisms of IORT in breast cancer; discusses the side effects and challenges in the applications and trails of IORT and explores perspectives for future applications of IORT in early-stage breast tumors.

The advantages of IORT [2, 5-7]

IORT is mostly used in 2 approaches, including the targeted intraoperative radiotherapy (TARGIT-IORT) delivering low-voltage X-rays of 30-50

kV directly and the intraoperative electronic radiation therapy (ELIOT) using large-dose electrons (3-12 MeV).

Precise radiotherapy

Intraoperative radiotherapy irradiates the tumor location directly during breast-conserving surgery so it can ensure the accurate positioning of the tumor margin, site, and the accuracy of radiation dose, ensuring that it is accurately delivered.

Protecting health tissues

Radiotherapy destroys cancer cells by ionising high-dose radiation so that it may also cause potential damage to healthy peripheral cells at the same time. IORT can select different-diameter tubes according to the size of the tumor and the area of tumor bed to make tumor site get high dose irradiation and protect the healthy peripheral tissues. Thus IORT significantly reduces postoperative radiotherapy complications such as pulmonary fibrosis and skin contracture.

Avoiding delay

Radiotherapy does not need to be delayed until after chemotherapy to reduce the possibility of tumor cell expansion after an operation or during curative interventions. Besides, doctors cannot accurately locate the original location and margin of the tumor as the residual site may have local changes such as edema, fibrosis, and atrophy after the tumor is removed for a few weeks or even more.

IORT is given at the time of surgery rather than after a few weeks' delay before a three or four-week course of daily doses of traditional radiotherapy. Thus, IORT is more economical and time-saving [6].

The mechanisms of IORT

There are usually 4-6 months between surgery and traditional adjuvant radiotherapies, such as WBI and EBRT. During this interval, adjacent lesions in tumor beds may proliferate or reproliferate, while IORT can avoid this interval, thus reduce local tumor recurrence. Also, a single high-dose intraoperative irradiation can effectively destroy the tumor microenvironment where the tumor is located, such as reduce microvessels and change the recognition and killing effect of immune cells such as CD8+ T on tumor cells.

Based on the fact that 90% of the local recurrence after BCT occurred in or close to the primary tumor, some studies focused on the mechanism of local relapse of breast cancer and the biological and molecular effects of radiation procedures on tumor bed. Several studies [8-10] have shown that surgical wound fluid (WF) is one of the factors that promote tumor proliferation, and wound fluid after intraoperative radiotherapy (RT-WF) can reduce the local recurrence rate of breast cancer. Belletti [8] found that WF can stimulate proliferation, migration, and invasion of breast cancer cell lines. RT-WF can abrogate the stimulatory effect. Segatto [11] further indicated that WF strongly induced stem-like phenotypes of BC cells, mainly relying on STAT3 signalling, which was crucial for the tumorigenicity and formation of local relapse of breast cancer after surgery. Kulcenty [12] demonstrated that RT-WF induces apoptosis in breast cancer cell lines to reduce the proliferation rate and invasiveness of tumor cells. WF can active the extrinsic apoptotic pathway in the MCF7 cell line while RT-WF can suppress the activation.

Besides the proven mechanisms by RT-WF, Uhlig [13] discovered that IORT inhibits breast adipose tissue-derive mesenchymal stromal cells (bMSC) function to suppress tumor relapse and metastases, as IORT abolishes the adhesion and proliferation potential of bASC.

Indication for patients

Different countries and organisations have different indication of IORT. To this date, there is no generally accepted guideline for the treatment of the IORT of breast cancer patients. Consensus statement or guidelines from American Society of Therapeutic Radiation Oncology (ASTRO) [14], European Society of Therapeutic Radiation Oncology (ESTRO) [15], American Brachytherapy Society (ABS) [3], or the American Society of Breast Surgeons (ASBrS) are most generally accepted. The criteria of different studies may be somewhat different, and a common strategy is to restrict the most favourable subset of patients at the beginning of a research and expand criteria as more experience of IORT obtained. The com-

parison of eligibility criteria of patients low risk or suitable for APBI in different guidelines is listed in the table below (**Table 1**), and IORT is only applied in those appropriate patients suggested by ASTRO consensus statement. Moreover, the ASTRO consensus statement specifically restricted the use of IORT in the treatment of DCIS to patients with invasive breast cancer.

Trials of IORT

At present, a large number of clinical trials study the application of IORT in patients with early breast cancer, and the patients' local recurrence, complications, adverse reactions, quality of life, and cosmetic effects have been followed up for a short or long time. However, most studies are mainly retrospective, the sample size is small, and long-term follow up data is lacking. Thus, the therapy may be applicable only in specific populations.

TARGIT-IORT

According to its form, TARGIT-IORT is divided into simple intraoperative radiotherapy (TARGIT-A) that completely replaces EBRT, and as a tumor bed supplement for APBI, combined with EBRT after surgery target-boost.

TARGIT-A: The Lancet published the largest international, multicenter, prospective, randomised non-inferiority phase III trial--TARGeted Intraoperative radiotherapy - Alone (TARGIT-A) trial, using Intrabeam® IORT. Vaidya [16] reported the up-date data of the TARGIT-A trial in 2013 in The Lancet, which enrolled 3,451 patients over 45-years old, from 33 clinical centres and 11 countries, with clinically T1-T2 ≤ 3.5 cm, N0-1 invasive tumors. After a follow-up of 2 years and 5 months, the 5-year risk of local recurrence was 3.3% (95% CI 2.1-5.1) for TARGIT versus 1.3% (0.7-2.5) for EBRT (P= 0.042). Breast cancer-related deaths were almost the same between the two groups (2.6% [1.5-4.3] for TARGIT vs 1.9% [1.1-3.2] for EBRT; P=0.56), but there were much more non-breast-cancer deaths with EBRT (1.4% [0.8-2.5] vs 3.5% [2.3-5.2]; P=0.0086), due to deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% (2.7-5.8) for TARGIT versus 5.3% (3.9-7.3) for EBRT (P=0.099). Moreover, the complications were much the same between groups while TARGIT had significantly fewer grade 3 or 4 skin complications (four of 1720 vs 13 of 1731, P=0.029).

TARGIT-boost: TARGIT-IORT can also be used as a boost to the tumor bed, followed by EBRT.

IORT-boost has been studied by the TARGIT-B trial in 2013 and it is still ongoing. As a multicentre randomised clinical trial, it is to test whether TARGIT-IORT as a tumor bed boost (TARGIT-B) is superior in terms of local relapse within the treated breast compared with standard postoperative EBRT boost in women undergoing breast-conserving. Patients are randomised into the boost group and the EBRT group. The endpoints include local tumor control, site of relapse, five years' relapse-free survival, overall survival (OS), local toxicity and morbidity, and quality of life.

*TARGIT-retrospective:*TARGIT-Retrospective(TARGIT-R) trial [17] is the most extensive retrospective study in North America to analyse the frequency of use, patient selection, and outcomes of IORT. Seventy-nine percent of them received primary IORT at the time of surgery and 7% had secondary IORT as a delayed procedure, 14% for boost followed by EBRT. After a median follow-up of 23.3 months, local recurrence was 2.3% for all patients treated. And they finger out that IORT performed concurrently at the time of lumpectomy is the preferred approach as the recurrence rate for primary IORT versus secondary IORT was 2.4 vs 6.6%.

TARGIT-elderly: Chesney [18] demonstrated RT after surgery can reduce the local recurrence rate from 6% to 1% (95% CI 6-20), women, aged 70 and over, however, tend to refuse the radiotherapy treatment after BCS because most of them have serious co-morbidities or physical inconvenience or the financial problems. IORT needs to work it out for elderly patients with breast cancer. TARGIT-Elderly (TARGIT-E) trial [19] is a prospective, international, multicentric, single-arm phase II study based on the protocol of TARGIT-A. It recruited 538 elderly low-risk patients (≥ 70 years, cT1 and small cT2, cN0, cM0, invasive ductal) to confirm the efficacy and toxicity of a single dose of IORT (20 Gy) in these elderly patients. The expected local relapse rates are 0.5%, 1.0% and 1.5% after 2.5, 5.0 and 7.5 years, respectively. Launched in 2011 and its first outcome released in 2016 with local relapse-free survival of 99.4% and overall survival of 98.6% [20].

Table 1. Comparison of eligibility criteria of patients low risk or suitable for Apbi in four guidelines

Criterion	ABS	ASTRO	ASBrS	GEC-ESTRO
Age (years)	≥ 45	≥ 50	≥ 45	≥ 40
Histology	All invasive subtypes and DCIS	All invasive subtypes and low-risk DCIS*	All invasive subtypes and DCIS	All invasive subtypes and DCIS
Tumor Size	≤ 3.0 cm	≤ 3.0 cm	≤ 3.0 cm	≤ 3.0 cm
T Stage	Tis, T1, T2	Tis, T1	Tis, T1, T2 (≤ 3 cm)	Tis, T1, T2
Margins	Negative, ≥ 2 mm for DCIS	Negative	Negative, ≥ 2 mm for DCIS	≥ 2 mm, ≥ 5 mm for DCIS and LCIS
Nodal status	Negative	Negative	Negative	Negative
ER status	Any	Any	Any	Any

Each guideline assumes that all criteria are present. DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ER, estrogen receptor. Low-risk DCIS*: screen-detected, low to intermediate nuclear grade, size ≤ 2.5 cm, resected with margins negative at ≥ 3 mm.

Delayed TARGIT-IORT: During the TARGIT-IORT trial, another randomised clinical trial was performed simultaneously. In 2004, Vaidya [21] launched an additional study comparing delayed TARGIT-IORT with postoperative EBRT in low-risk patients after breast-conserving to test whether delayed TARGIT-IORT is non-inferior to EBRT in terms of local control. This international multi-centre prospective non-inferiority randomised controlled clinical trial included 1,153 patients over 45-years old from 28 centres in 9 countries with low-risk invasive ductal breast carcinoma smaller than 3.5 cm treated with breast conservation surgery. Five hundred eighty-one patients were randomised to the delayed TARGIT-IORT group. They reopened the breast lumpectomy wound for a median 37 days after the first breast lumpectomy for targeted radiotherapy.

After five years of follow-up, compared with the postoperative EBRT group, the local recurrence rate of delayed TARGIT-IORT group was 3.96% compared to 1.05%, a difference of 2.91% (90% CI, 4.4%). After median 9-year long-term follow-up, the rates of local recurrence-free survival, mastectomy-free survival, distant disease-free survival (DFS), and OS were no statistically significant differences between the above two groups.

Though delayed TARGIT-IORT has a higher 5-year local recurrence rate, the long-term local recurrence-free survival rate, mastectomy-free survival rate, distant disease-free survival, and overall survival rate were similar, compared with postoperative EBRT.

ELIOT

ELIOT is a radiotherapy technique, administering large-dose electrons (3-12 MeV) in one session after tumor resection during surgery.

ELIOT trails: The most famous clinical is the ELIOT trails. The European Institute of Oncology launches the first ELIOT trail in 1999, and the first result was published in 2010 [22]. In 2013 Veronesi [23] published a randomised equivalence study to compare local recurrence and overall survival after ELIOT with traditional EBRT. One thousand three hundred five patients were enrolled between 2000 and 2007 and divided into two groups, the IORT group and the EBRT group. With a medium follow-up of 5.8 years, the local recurrence rate (LRR) was 4.4% and 0.4%, of the IORT group and EBRT group, respectively. There were no differences in terms of five-year survival rates between the two groups (96.8%, IORT group vs 96.9%, EBRT group). The IORT group showed significantly less skin-related side effects (P=0.0002). The researchers stated that the LRR may decrease with more careful inclusion criteria.

Since no data is available on IORT in Asian breast cancer patients, Sawaki [24] launched a series of clinical trials on Japanese patients. After the dose-finding phase I and II studies, they performed the one single-arm, non-randomized, phase II trial to evaluate the efficacy and safety of IORT using three kinds of ELIOT institutions. The primary endpoint was LRR and the secondary endpoints were safety for five years and cosmesis. A total of 129 patients underwent IORT at 21 Gy from 2010 to 2015, and after a follow-up of 59.5 months, the LRR is 3.1%, and they found all recurred cases had luminal A-like features. 83.0% of patients followed up by three years after IORT received good to excellent cosmetic outcomes [25].

ELIOT-boost: Sedlmayer [26] launched a pooled analysis of 1031 patients from 21 centres, seven countries with T0-3N0-x breast cancer treated by ELIOT as a boost instead of EBRT [27]. The median follow-up was 52.3 months. The local control rate of tumors was 99.4% and the 7-year DFS, disease-related survival rate and OS were 88%, 95.2%, and 90.9%, respectively. This result verified the effectiveness of ELIOT as a boost.

Fastener [28] initiated the largest-scale retrospective analysis of ELIOT-boost (ELIOT-B) and published data in 2013. The ELIOT-B enrolled 1109 patients from 7 research institutions in Europe. The median follow-up was 72.4 months and the local tumor control rate was as high as 99.2% with only 16 local recurrence cases.

ELIOT for Chinese Han population: Wang [29] launched the study on ELIOT for the Chinese Han population. In this study of Cancer Hospital of the Chinese Academy of Medical Sciences, Beijing, China, 50 patients were incorporated and 28% of them had IORT as a boost followed. In contrast, 72% of them had IORT as their sole radiation treatment. The median follow-up is 51.8 months. There were no metastases and

no deaths and only two patients developed local relapses. No myonecrosis or hematomas or radiotherapy related acute haematological toxicity was observed. The evaluation of cosmetic outcome showed 88.0% of them graded as excellent or good.

IORT with NSM

Nipple-areola complex-sparing mastectomy (NSM) is increasingly accepted as a desirable option for patients with breast cancer, as it can preserve the integrity of the external breast for post-mastectomy breast reconstruction. The European Institute of Oncology (EIO) performed the study of IORT with NSM since 2002 [30]. EIO included 1,001 patients receiving NSM from 2002 to 2007, of which 800 received IOERT and 201 received delayed IORT, whose postoperative pathology confirmed breast cancer. The primary wound was reopened and IORT was performed for those 201 patients. After 20 months, the local recurrence rate was only 1.7%. Of the 14 cases of local recurrence, ten recurrences occurred near the primary tumor site and no recurrence near the nipple-areola complex (NAC).

Pan [31] firstly introduced Intrabeam® IORT in NSM with breast reconstruction in 2014. In their latest study in 2019 [32], 41 patients who underwent NSM surgery with Intrabeam® IORT (16 Gy) followed by breast reconstruction were enrolled. After a median follow-up of 26 months, no IORT-reduced lung or cardio injury, local recurrence, or metastasis was observed.

Other studies

Juan Lei [33] used the surveillance, epidemiology, and end results (SEER 18) database to investigate the survival outcomes and factors significantly associated with clinical outcomes of IORT compared to whole-br [31] east EBRT for women with early-stage breast cancer. The study enrolled a total of 477,353 patients diagnosed with first primary breast cancer between 1998 and 2013. It segregated them into two groups based on whether they received IORT or EBRT after surgery. The results indicate that there is no substantial statistical difference between the cancer-specific survival (CSS) and overall survival (OS) of the two groups (OS: aHR=0.84, 95% CI 0.42-1.71, P=0.634; CSS: aHR=0.51, 95% CI 0.12-2.07, P=0.343).

A meta-analysis [40] published in 2016 obtained an identical conclusion, confirming the survival benefit of IORT versus EBRT. All the trails mentioned above are listed in **Table 2**.

Side effects of IORT

IORT technique is thought to result in tissue fibrosis and necrosis in long-term follow-up [38, 39]. Engel [34] suggested that we should pay attention to the fat necrosis and incision calcification of patients after TARGIT treatment. And IORT did not significantly alleviate the patients' pain in their assessment of persistent pain after radiotherapy.

All APBI techniques, including the single-dose ELIOT technique, carry the risk of overlooking peripheral tumor beds or areas outside the target volume. The main causes include the proximity of the tumor to the skin and the oversize of the target volume. Except for the right anatomical conditions, accurate preoperative ultrasound, and strict interdisciplinary application of preoperative management of intraoperative radiotherapy are also very important [36, 37].

Some studies are exploring IORT under the assistance of other image guidance techniques to give accurate positioning. Hassinger [35] developed Precision Breast IORT (PB-IORT), which utilises intraoperative computed tomography (CT) images for confirmation of brachytherapy applicator placement and treatment planning.

Conclusion and perspectives

Although the application of IORT in patients with early breast cancer is still in the exploratory stage, IORT plays an essential role in early-stage breast cancer treatment, and its application prospect is worth looking forward to. IORT has become accepted as an alternative or an adjunct to EBRT following breast-conserving surgery. Clinical research is still needed to explore the safety and applicability of IORT, and decisions have to be made about patient selection. The development of PB-IORT might address the technical limitations of conventional breast IORT.

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Table 2. Comparison of studies of IORT

Study	Number of Patients	Eligibility	IORT Equipment	Follow-up	Result	Conclusion	Ref.
TARGIT-A	3451	Age ≥ 48 and < 75 Unifocal invasive breast carcinoma ≤ 2.5 cm. No previous therapy (biopsy included) for breast cancer in other institutions.	INTRABEAM	5 years	1) TARGIT vs EBRT: OS: 96.1% vs 94.7%; LRR: 3.0% vs 1.3%; 2) Non-breast-cancer deaths rate: 1.4% vs 3.5%; 3) Overall mortality rate: 3.9% vs 5.3%; 4) Grade 3 or 4 skin complications rate: 0.2% vs 0.8%.	IORT can be used as an alternative for EBRT in the treatment of patients with early breast cancer, but it is necessary to restrict the criteria of suitable patients.	[23]
TARGIT-B	still recruiting patients	Age < 45 years Lobular carcinoma Post-neo-adjuvant systemic therapy Age ≥ 45 years with • G3 tumor • ER-negative, PR-negative • Positive margins • Lymphovascular invasion • Gross nodal involvement (not micrometastasis) • More than one tumor in the breast but still suitable for BCS • Patients with either HER2 positive or HER2 negative.	INTRABEAM	ongoing	unknown.	unknown.	
TARGIT-R	822	Eligibility was determined by the individual institutions.	INTRABEAM	23.3 months	The median patient age was 66.8 years; 90% had a tumor that was < 2 cm in size; 91% was estrogen positive; 68% had invasive ductal cancer; 89% had negative sentinel lymph nodes; 79% primary IORT; 7% secondary IORT; In-breast recurrence was 2.3%.	IORT with Intrabeam is a rational option for selected patients with early-stage breast cancer.	
TARGIT-E	853	Age ≥ 70 years; Unilateral and unifocal breast cancer; cT1c N0 M0; Invasive ductal carcinoma; Absence of lymphovascular invasion.	INTRABEAM	14.0 months	The local recurrence-free survival rate was 99.4%, and the overall survival rate after 2.5 years was estimated to be 98.6%.	This trial supports the use of IORT in selected elderly patients.	
delayed TARGIT-IORT	1153	Age ≥ 45; Unifocal invasive ductal carcinoma ≤ 3.5 cm, cN0-N1; Primary tumor already excised; Suitable for BCS.	INTRABEAM	Five years	delayed TARGIT vs EBRT: LRR: 3.96% vs 1.05%; No significant difference in recurrence-free survival, mastectomy-free survival, distant disease-free survival, and overall survival.	Although LRR is higher than EBRT, there is no significant difference in recurrence-free survival, mastectomy-free survival, distant disease-free survival, and overall survival.	
ELIOT	1305	Age ≥ 48 and < 75 Unifocal invasive breast carcinoma ≤ 2.5 cm. No previous therapy (biopsy included) for breast cancer in other institutions.	Mobetron	5.8 years	IORT vs EBRT: LRR: 4.4% vs 0.4%; OS: 96.8% vs 96.9% Fewer skin side-effects.	ELIOT is non-ferior to EBRT and improves the selection of patients can reduce the LRR of ELIOT.	
ELIOT-B	1109	Unselected patients of any risk group.	Mobetron	72.4 months	Local tumor control rate: 99.2%; Disease-free survival rate: 88% OS: 90.9%.	A 10 Gy IOERT boost before WBI provided outstanding local control rates, comparing favourably to all trials with similar length of follow up.	

ELIOT for Chinese Han population	50	Exclude multifocal cancer and any evident axillary lymph node involvement. More than three axillary lymph node metastases were eliminated from the study; Tumors were ≤ 3 cm in size without invasion of the skin, adjacent muscles or chest wall.	Mobetron	51.8 months	No metastases and no deaths and two patients developed local relapses. No myonecrosis or hematomas or radiotherapy related acute haematological toxicity was observed. The evaluation of cosmetic outcome showed 88.0% of them graded as excellent or good.	In the Chinese Han population, IORT is safe and reliable and has resulted in very acceptable cosmetic outcomes.
ELIOT with NSM	1101	Primary tumors located at least 1 cm outside the areola margins, absence of nipple retraction or bloody discharge and lack of retro areolar microcalcifications. Multifocality that all tumor sites were distant from the areola. DCIS included.	Novae-7	20 months	LRR was only 1.7%. 10 recurrences occurred near the primary tumor site and no recurrence near the nipple-areola complex. The excellent and good rate of cosmetic effect was 88.0%. There were 3 cases of wound infection, 5 cases of delayed healing and 2 cases of wound edema. No noticeable side effects were found.	NSM combing IORT is proposed.
Intrabeam-IORT with NSM	41	Breast carcinoma T0-2N0-1M0 (including DCIS and LCIS); Bilateral breast carcinoma; Multifocal and multicentric tumors; unifocal or unicentric tumor unsuitable for BCS; Primary tumor or microcalcifications located in the central portion of the breast, at least 1 cm away from the NAC skin.	INTRABEAM	26 months	No recurrences or metastases; Radiation doses at different sites in the NAC flap varied considerably and were about 10 Gy at the areola surface; No Intrabeam IORT-related acute or chronic radiation injuries of the lung, heart or bone marrow.	Intrabeam-IORT during NSM combined with breast reconstruction is safe and feasible.

Disclosure of conflict of interest

None.

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