Review Article

Review of current perspectives on low-energy X-ray intraoperative radiotherapy in early stage breast cancer

Yang-Hong Dai[1], Yu-Jen Chen[2], Chun-Shu Lin[1], Kuen-Tze Lin[1], Wen-Yen Huang[1], Chang-Ming Chen[1], Yu-Fu Su[1], Chao-Yueh Fan[1], Chen-Hsiang Lo[1], Yen-Fu Yang[1], Chih-Cheng Tsao[1], Ming-Yueh Liu[1], Po-Chien Shen[1], Hsing-Lung Chao[1], Kun-San Chao[3]

[1]Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [2]Department of Radiation Oncology, Mackay Memorial Hospital, Taipei, Taiwan; [3]Cancer Center building, Cancer Center, China Medical University Hospital, China Medical University, Taichung, Taiwan

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Correspondence to: Kun-San Chao, MD, PhD. Cancer Center building, Cancer Center, China Medical University Hospital, China Medical University, No. 2 Yude Road, North District, Taichung 40402, Taiwan. Email: d94032@mail.cmuh.org.tw; Hsing-Lung Chao, MD. Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, No. 325, Chengong Road, Sec. 2, Neihu, Taipei 114, Taiwan. Email: doc31217@yahoo.com.tw.

Abstract: In early stage breast cancer, intraoperative radiation therapy (IORT) is a form of accelerated partial breast irradiation (APBI) that provides attractive therapeutic effects while shortening the overall treatment time and sparing the normal tissue radiation exposure. This technique has been used in Taiwan for several years in selected patients with breast cancer. However, some randomized trials pointed out that IORT is associated with higher rate of recurrence, therefore impeding its wider use as one of the standard managements in breast cancer. Also, despite its theoretical benefits for smaller tumor after surgery, the problem of recurrence warrants the necessity of strict and careful patient selection. The purpose of this article is to comprehensively review the updated consensus and current opinions on the use of IORT for early stage breast cancer.

Keywords: Intraoperative radiation therapy (IORT); accelerated partial breast irradiation (APBI); breast cancer

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Introduction

Whole breast irradiation (WBI) has been widely used for decades to reduce the risk of ipsilateral breast tumor recurrence (IBTR) in breast cancer patients after breast-conserving surgery (1). The benefits of decreased local recurrence and improved long-term survival have been demonstrated in many randomized trials and meta-analyses (2-4). WBI is typically given in about 5 weeks and the duration may be further protracted to 6 or 7 weeks with additional electron boost depending on the institutional preference if there is any unfavorable postoperative feature (5-7). On the contrary, accelerated partial breast irradiation (APBI) offers decreased overall treatment time and has been increasingly attractive in the past several years (8). One of the most appealing theoretical advantages over WBI is its significant reduction of radiation dose to the uninvolved normal organs and tissues (9). Intraoperative radiation therapy (IORT) is an alternative form of APBI. One of the differences between IORT and other forms of APBI is the timing of intervention (10,11). As its name indicates, IORT is most often performed at the time of operation; other APBI techniques are done post-operatively. IORT requires well-organized radiotherapy system, and several

technologies are available for this type of partial breast irradiation, which deliver 50 kV X-rays or electrons (10,11). This type of radiation technique has gained growing interest as it provides patient convenience and theoretically decreases the possibility of normal tissue toxicities. However, the major concern of adopting APBI in early-staged breast cancer is its omission of occult cancer foci elsewhere in the residual breast tissue (12). Even though, due to its potential convenience and conceptual therapeutic effects, the use of APBI has increased markedly. Therefore, to further address these issues, the American Society for Radiation Oncology (ASTRO) published consensus statement about the criteria of patient selection and practice in breast cancer in 2009 (8). This consensus was partially updated in 2015 (13), but the exact role and indication of IORT were still controversial. In fact, the practice of IORT involves multidisciplinary teams led by radiation oncologists and surgeons. Therefore, it is of vital importance to establish treatment consensus. The purpose of the article is to comprehensively review the current evidence-based opinions, and aims to address some important issues related to the practice of IORT in early breast cancer.

The techniques of IORT in breast cancer

APBI can be delivered in many different forms, including multi-catheter brachytherapy, balloon-based applicators, external beam or intraoperative radiotherapy. All of them involve the treatment of limited and targeted volume of the breast in a shorter time period compared with conventional WBI. IORT is one of the techniques, which provides single fractionation of radiotherapy in the operating room.

There have been several photon beam-based IORT devices to date. The most popular two systems are Intrabeam system (Carl Zeiss Meditec, Dublin, CA, USA) and Axxent system (Xoft Inc., Sunnyvale, CA, USA) (14). The Intrabeam system is a miniaturized mobile linear accelerator that produces electron beam to the tip of a drift tube, creating 50 kV, low-energy X-rays. This unit has been designed for IORT and single-fraction radiation is delivered through a spherical applicator with size ranging from 1.5–5 cm in diameter. The Axxent system comes to clinical use in 2009. The source is generated from a X-ray tube that is integrated into a flexible catheter, producing low-energy X-ray at the tip. In contrast to the Intrabeam system, the source and balloons (the spherical applicator) in Axxent system are disposable, and can be used up to 10 fractions in fractionated balloon-based partial breast irradiation. Both of these techniques can be operated in a standard surgical room with appropriate shielding.

In Taiwan, the experience of electron-based IORT is insufficient. Generally, the electron energy used ranges from 3 to 12 MeV (14), with electron delivered through a cone inserted in the lumpectomy cavity. Since electrons penetrate more than low-energy X-rays, shields have to be placed to the posterior border, preventing unwanted scatter into the chest. This technique is often called the intraoperative electron radiation therapy.

Evidence-based feasibility of IORT

In 2014, a work group was summoned to review the available literatures and recommended that the consensus statement of APBI should be revised and updated. The proposal was approved in 2015 and the updated consensus was completed in 2016. The updated consensus aimed to further elucidate the inclusion criteria of the 'suitable' and 'cautionary' patient groups, regarding the age and pure ductal carcinoma *in situ* (DCIS) (*Table 1*). In addition, key question about the use of IORT for PBI in early stage breast cancer outside the context of clinical trial was formed and discussed. Furthermore, this work group consisted of two IORT experts from the TARGIT and ELIOT trials (10,11), emphasizing the significance of these two trials and a need to focus on this single-fraction radiation.

The ELIOT trial

ELIOT trial enrolled 1,305 patients who were aged ≥48 years old with a tumor size ≤2.5 cm. The patients were randomized to receive either a single fraction of 21 Gy intraoperative radiation or 50 Gy of WBI with a 10 Gy boost over 6 weeks. This trial adopted electron technique with energy from 6 to 9 MeV and 21 Gy was prescribed to the lumpectomy cavity with 90 % isodose. This trial showed significantly higher 5-year IBTR in the arm of intraoperative electron beam compared the WBI (4.4% *vs.* 0.4%, P=0.0001). However, for low-risk patients that met the APBI 'suitability' criteria (tumor size ≤2 cm, ≤3 positive nodes, grade 1 or 2, estrogen receptor positive, and not triple negative disease), there was lower IBTR (1.5%, 3/294) in this subgroup. The findings pointed out that patient selection is crucial and the ASTRO consensus is applicable to selected cases. In terms of the toxicity profile, the overall toxicity was lower in the IORT arm, including the skin erythema, dryness, hyperpigmentation, pruritus

Table 1 ASTRO consensus on accelerate partial breast irradiation

Patient group	Risk factors	2009 consensus	2016 consensus
Suitable	Age	≥60	≥50
	Margin	At least 2 mm	Unchanged
	T stage	T1	Tis or T1
	DCIS	Not allowed	All of the followings: • screen detected; • low to intermediate nuclear grade; • size ≤2.5 cm; • margin at least ≥3 cm
Cautionary	Age	–	• 40–49 if all other criteria for "suitable" are met; • ≥50 if patient has at least 1 of the pathologic factors* below and does not have any "unsuitable" factors
	Margin	Close (<2 mm)	Unchanged
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50	• <40; • 40–49 and do not meet the criteria for cautionary
	Margin	Positive	Unchanged
	DCIS	>3 cm	Unchanged

*, pathologic factor: size 2.1–3.0 cm; T2; close margins (<2 mm); Limited/focal LVSI; ER (–); Clinically unifocal with total size 2.1–3.0 cm; Invasive lobular histology; Pure DCIS ≤3 cm if criteria for "suitable" not fully met; EIC ≤3 cm. ASTRO, American Society for Radiation Oncology; DCIS, ductal carcinoma in situ; LVSI, lymphovascular invasion; EIC, extensive intraductal component; ER, estrogen receptor.

and pulmonary fibrosis, as compared with WBI. However, the rate of fat necrosis was higher in the IORT arm (17% *vs.* 7%, P=0.04).

The TARGIT-A trial

The TARGIT-A was essentially different from the ELIOT trial in that the TARGIT-A trial used photon beam, rather than electron technique (10). The 3,451 patients included in the TARGIT-A trial had age ≥45 years old with a ≤3.5 cm unifocal invasive ductal carcinoma. The patients were randomized to receive 20 Gy IORT or 50 Gy WBI over 3–5 weeks with or without a tumor bed boost depending on the physician's direction. X-rays with energy of 50 kV was given via an Intrabeam device (Carl Zeiss Meditec, Jena, Germany). An implant with spherical applicator was dedicated to deliver the radiation to the volume surrounding the surgical cavity. The dose to the surface of tumor bed is 20 Gy and it attenuates to about 5–7 Gy at 1 cm depth below the surface. The 5-year IBTR in TARGIT-A trial was 3.3% in the IORT arm and 1.3% for WBI (P=0.042). The overall recurrence risk was also higher in the IORT arm [hazard ratio (HR) =1.44, P=0.053]. However, the shorter median follow-up time (2.4 years) in this trial limited the accurate estimate of 5-year recurrence risk even though the initial 1,222 patients have a median follow-up up to 5 years. The TARGIT-A trial also divided the balloon brachytherapy into prepathology (IORT delivered at the time of breast-conserving surgery) and postpathology (IORT after the final pathology was available) arms. In the prepathology arm, WBI was added if there were close margins (<1 mm), extensive *in situ* component, or unexpected invasive lobular carcinoma. Finally, 21% of patients received another 50 Gy of WBI without boost due to the presence of risk factors. Although patients receiving IORT in the prepathology group didn't show increase in IBTR, the attention should be focused on the pre-specified overall patient population. Similar to the ELIOT trial, the skin toxicities were less in the IORT arm (0.2% *vs.* 0.8% in WBI group, P=0.029). The non-breast cancer-related death was also reported to be lower in the IORT group as compared to the WBI (1.4% *vs.* 3.5%, P=0.0086). The authors thought that the cardiac events and other cancers contributed by WBI causes this difference.

Moreover, the breast and arm symptoms were significantly lower in the IORT alone arm.

Updated ASTRO consensus statement for APBI

Age

In the original ASTRO consensus, patients with age ≥60 were considered suitable for APBI (8). The updated consensus modified the limitation and revised the age criteria to ≥50. The evidence came from three prospective trials that enrolled patients for APBI with ages meeting the inclusion criteria. In these three trials, most of the patients had T1, N0, and hormone-receptor positive disease, which partly corresponded to the APBI consensus as 'suitable'. In the GEC-ESTRO trial (Groupe Européen de Curiethérapie of the European Society for Radiotherapy and Oncology), 1,184 patients were randomized to WBI with a tumor bed boost or APBI (15). The 5-year IBTR was similar in both arms (<2%). The enrolled patients in GEC-ESTRO trial were >40 years, and there was no evidence of increased IBTR with APBI below the age of 50. In the second trial from Budapest, 128 patients received APBI in the form of multicatheter brachytherapy (16), same as the GEC-ESTRO trial. Among these patients, 23% of them were <50 years old, and those <40 were excluded, based on an early analysis that the risk of IBTR was higher in these patients. After a median follow-up of 10.2 years, the rate of IBTR was 5.5%. In the third trial conducted by the University of Florence (17), age was not reported to be associated with recurrence. The in-breast recurrence rate was only 1.5% after a median follow-up of 5 years. Different from the mentioned trials, this study used intensity-modulated radiation therapy as the form of APBI, rather than multicatheter brachytherapy. In the Austrian multi-institutional study, the 274 stage I, hormone-sensitive breast cancer patients who received APBI had higher 5-year IBTR for ages <50 years (7.5% *vs.* 1.1% for patients ≥50 years, P=0.030) (18), supporting some previous reports that younger age was more likely to be associated with higher recurrence rate. Nevertheless, despite the evidence indicating relatively lower rate of IBTR for patients ≥50 years old, there still lacks high-level data addressing the indication for IORT in terms of age stratification. As we will see in the following sections that discuss the evidence for IORT, the age was confined to ≥48 and ≥45 years old in the ELIOT and TARGIT-A trials (10,11), and none of these trials well elucidated the impact of age on the IBTR. Therefore, the adoption of age ≥50 as the criteria for IORT is still controversial.

Pure DCIS

The other major update of the ASTRO consensus statement for APBI is the revision of the criteria for DCIS. Based on the RTOG 9804 trial, DCIS detected via screen, with low to intermediate grade, ≤2.5 cm in size and negative margin at least ≥3 mm, was considered to be low-risk (19). After a median follow-up of 7.2 years, the risk of IBTR was 6.7% in the observation arm and 0.9% in the WBI arm. Also, in ECOG 5194 trial, patients meeting similar criteria as the RTOG 9804 trial had 6.1% risk of IBTR at a median follow-up of the 6.7 years (20). According to these two trials, the absolute risk of IBTR in the observation arm is relatively low compared to the addition of adjuvant WBI. On the other hand, the advantage of WBI over observation for the low-risk DCIS is quite small with only measurable absolute benefit. Therefore, the enrollment criteria in fact define a low-risk group of patients. For APBI, one pooled analysis from the data in the MammoSite registry and a single institution showed a 2.6% 5-year risk of IBTR, comparable with other separate analyses (21). Moreover, a single-institution study that evaluated the use of balloon brachytherapy, interstitial brachytherapy or external beam APBI showed a 1.4% 5-year risk of IBTR. When applying the ECOG 5194 low-risk criteria, the risk of IBTR was 2%. Prospective data from randomized trials comparing APBI and WBI in patients with DCIS have not yet published. Given the lower risk of IBTR in selected DCIS patients and favorable outcomes when applying similar low-risk criteria for APBI, the updated consensus recommended inclusion of low-risk DCIS as 'suitable' candidate.

On the contrary, for IORT, it was recommended that electron beam or photon beam should be restricted to women with invasive rather than *in situ* diseases (recommendation rated as 'Strong' for electron beam and 'Weak' for low-energy X-ray) (13).

Current controversy about IORT and future direction

In Taiwan, the practice of IORT is currently based on the ASTRO consensus statement and its update in 2016. However, the main body of evidence comes from studies of APBI using multicatheter brachytherapy or external beam. The reference for IORT using photon beam as the radiation source is quite lacking. TARGIT-A trial is the single large study using photon-based radiation (10). Although it is a

prospective phase III trial, this trial is subject to several criticisms. In addition, its inclusion criteria for IORT were not strictly based on the ASTRO consensus, making the direct extrapolation to our breast cancer patients difficult. One of the criticisms is the short median follow-up time (2.4 years) in the TARGIT-A trial. Some experts thought the shorter period of time was insufficient to assess the local failure since most failures happened after 5 years, and 5 years of follow-up at least is required to evaluate the late toxicities caused by the single high-dose focal irradiation (22). Another argument was that 15% of patients in the IORT arm received WBI according to the trial's protocol, suggesting a great portion of patients in the IORT arm, especially the prepathology group, were poorer in prognosis at the time of inclusion. However, Vaydia *et al.* responded that patients even with tumors that were grades 2–3, >1 cm, and with nodal involvement, still had good local control without WBI. Together with the noninferior results from several APBI trials, it raises a question about whether the inclusion criteria for IORT can be expanded. One possible explanation of similar results between APBI and WBI is that the actual tissue at risk is much less than the entire breast; therefore, the use of APBI sounds theoretically and biologically appropriate in this context, However, in the ELIOT and TARGIT-A trials, the IBTR was found to be significantly higher than the WBI arm. According to the primary results, IORT might be considered inferior to WBI, though the follow-up time in the TARGIT-A trial was not long enough to reach noninferiority. In addition, the combination of surgery and IORT technique is another important factor in treatment failure. Besides strict patient selection, which is the first priority before IORT, the perfect mutual communication and cooperation between surgeons and radiation oncologists are of vital significance. The surgical findings and the extent of cancerous tissue in the breast should be discussed with the radiation oncologist at the time of radiation. Since there have been no studies about the comparison of dosimetric distribution between balloon brachytherapy and multicatheter brachytherapy, the practice of IORT depends entirely on the skill of the radiation oncologist. In order to sharpen the skills and avoid off target in the field of radiation, the detailed evaluation of the preoperative imaging reports, histologic results and surgical findings become increasingly important.

In addition, this inter-team cooperation could be further facilitated by sophisticated image guidance, which was a major limitation in ELIOT and TARGIT-A trials. One technique called precision-based IORT attempts to acquire intraoperative computed tomography (CT) scan, aiding the position adjustment before radiation is delivered (23). Indeed, in one study, the intraoperative CT helps identify the immediate condition in breast, residual tumor and errors of applicator positioning in 24% of patients (24). On the other hand, preoperative or intraoperative magnetic resonance imaging (MRI), though not currently in standard use, showed potential in the evaluation of breast condition and surgical findings. In a study done by Tallet *et al.*, the preoperative MRI identified ipsilateral second breast cancer in 4% of patients. Therefore, this imaging modality might help improve patient selection and reduce the rate of IBTR.

When it comes to toxicity, the TARGIT-A trial showed an increase in non-breast cancer-related deaths in the WBI arm. The authors attributed this to the cardiac events conferred by WBI. However, this might be unlikely in this case since the techniques in WBI nowadays has greatly reduced the mean heart dose; a meta-analysis investigating the comparison of APBI and WBI showed a significant reduction in non-breast cancer death (1.1–1.3%) (25). Additionally, the shorter follow-up time also precluded observation of such toxicity. Another concern about the TARGIT-A trial was the depth-dose in the IORT arm, which was lower when compared with other APBI plan using multicatheter brachytherapy. Even though the relative biological effectiveness increases with depth, the lower total dose to the tissue at risk likely caused higher local recurrence.

With the patient convenience and satisfaction offered by IORT, the practice of single-fraction radiation therapy at the time of breast surgery has greatly increased in the United States. While the role of IORT may go beyond breast conserving surgery, the use of IORT in the setting of mastectomy has to be further addressed. In mastectomy, nipple-sparing technique is often done to obtain cosmetic purpose. However, recurrence over the nipple-areolar complex is concerned. In a study performed by Pan *et al.*, the utilization of electron beam with 16 Gy IORT in 800 patients receiving nipple-sparing mastectomy showed 1.6% locoregional recurrence (39/800) (26), with an increase of complete or partial necrosis of the nipple-areolar complex (10%). These findings suggest that further investigational study has to be done in mastectomy to identify the suitable criteria as for the breast-conserving surgery.

One last common concern raised against IORT is the timing before final pathology is available. Therefore, some groups prefer radiation delivery shortly after surgery for optimal treatment planning and dosimetric coverage of all

Table 2 IORT guideline in Tri-Service General Hospital

Patient factor	Clinicopathologic factor
Age	Postmenopause and ≥50
Histology	IDC (DCIS not allowed)
Tumor size	≤2 cm (EIC not allowed); (≤1 cm preferred)
T stage (invasive size)	≤ T1 (≤ T1b preferred)
Margin	Negative and ≥2 mm
Grade	Low grade (grade I preferred)
LVSI	Negative
Multicentricity or multifocality	Not allowed
ER status	Positive (luminal type A preferred)
N stage	pN0
Nodal surgery	SNBX or ALND (≥6 nodes)
M stage	M0
Others	• Distance from applicator to skin ≥1 cm • also excluded: autoimmune disease, synchronous or prior breast cancer, pregnancy, lactating women or prior history of breast radiotherapy

IORT, intraoperative radiation therapy; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER, estrogen receptor; LVSI, lymphovascular invasion; SNBX, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

possible tissue at risk. Although in the TARGIT-A trial there was no increased IBTR in the prepathology arm, this might be due to the adjuvant WBI for the 21% patients who had high-risk tumor pathologies. Also, the shorter follow-up time was likely not powerful enough to prove inferiority to the WBI arm, which was also true in the postpathology arm. Despite these limitation mentioned above, the author pointed out the post-operative tissue microenvironment differed from that at the time of surgery; this would more or less affect the biological effectiveness of radiation (27,28).

Taken together, even though IORT has advantages such as patient convenience and cosmetic preservation, the determination of eligible patients remains the most crucial prerequisite. The notation that 'Less is good' is faced with several questions that have to be answered. Although there are two prospective trials describing the use of IORT in early-stage breast cancer patients, the enrollment criteria, statistical evaluation, and the authors' viewpoints are not flawless. Based on the unsolved limitations and the ASTRO recommendations, the practice of IORT as a form of APBI is only encouraged for highly selected patients and in the setting of prospective clinical trials. Several ongoing studies such as National Surgical Breast and Bowel Project-coordinated prospective trial evaluating APBI (B-39/RTOG 0413) will assist with treatment decisions regarding APBI; data from randomized trials of APBI versus WBI with selection criteria including patients with DCIS are also pending.

At our hospital, the practice of IORT is not in the setting of clinical trials and is based on the in-hospital guideline, which is the modification and extension from the ASTRO consensus (*Table 2*). Briefly, our guideline has more strict inclusion criteria to define 'suitable' for IORT. Similar to the recommendation in the updated ASTRO consensus, DCIS is not allowed.

Conclusions

IORT is a promising radiation technique that brings convenience to patients with early stage breast cancer and is characterized by sparing the normal tissue radiation exposure. However, current evidence is still scarce and the practice of IORT is largely based on consensus statement and the experience of separate studies. Both of the ELIOT and TARGIT-A trials showed higher local recurrence, and the salvage EBRT was conducted in 21% of patients in

the prepathology arm (TARGIT-A), though the follow-up duration in TARGIT-A trial was subject to many criticisms. Additionally, the adoption of IORT for patients with DCIS should be carefully evaluated and would better be avoided when photon beam is used. Based on the absence of high-evidence randomized trials coming out, strict inclusion criteria are generally recommended to minimize any unwanted outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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