

# Intraoperative radiotherapy: Patient selection, management, and follow-up

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Intraoperative partial breast radiotherapy is an alternative or an adjunct to fractionated whole breast irradiation for the administration of adjuvant radiotherapy in breast cancer following breast conserving surgery. Establishing intraoperative radiotherapy as a therapeutic modality requires a multidisciplinary approach to patient selection, workup, surgery, radiation protocols, chemotherapy, and patient follow up. In this article, we review the published evidence for best clinical practice, as a guide to the introduction of intraoperative radiotherapy for breast cancer treatment.

## KEYWORDS

breast conserving surgery, breast irradiation, intraoperative radiotherapy

## 1 | INTRAOPERATIVE RADIOTHERAPY

Intraoperative Radiotherapy (IORT) has emerged as an alternative to fractionated whole breast irradiation (WBI) for administration of adjuvant breast radiotherapy following breast conserving surgery. As a strategy for delivering accelerated partial breast irradiation (APBI), the primary appeal of IORT to the patient is the receipt of the entire course of therapeutic breast radiation in a single fraction at the time of tumor resection.

Three IORT approaches are currently in common usage in the U.S: the TARGgeted Intraoperative radioTherapy (TARGIT) method using the Intrabeam System (Carl Zeiss Meditec, Inc., Oberkochen, Germany), the ELectronic Intra Operative Therapy (ELIOT method) using the Mobetron System (IntraOp Medical Corporation, Sunnyvale, CA), and the Xoft method using the Axxent System (iCAD, Inc., Nashua, NH). Each method utilizes a mobile radiation delivery system capable of administering IORT as a single fraction in a standard operating room setting without requiring structural modifications or bunkering of the surgical theater.

The TARGIT method utilizes a low-kilovoltage (50 keV) X-ray source that was proven non-inferior to conventional post-operative,

6-weeks fractionated WBI in the TARGIT-A trial, a prospective randomized controlled trial (RCT) of 3451 women with clinical node negative, T1-2 invasive breast cancer [5-year local recurrence rate (LRR) 3.3% (95% CI 2.1-5.1) for TARGIT vs 1.3% (0.7-2.5) for WBI,  $P = 0.042$ ].<sup>1</sup>

The Mobetron System utilizes a high-dose rate mobile linear accelerator that has not been directly compared to conventional WBI in a randomized controlled trial. However, the Mobetron method is comparable in technique, dose prescription, and energy levels (6-9 MeV) to the ELIOT method, which was shown to be non-inferior to WBI in the ELIOT Trial, a RCT of 1305 women with clinical node negative, T1-2 invasive breast cancer [5-year LRR 4.4% (95% CI 2.7-6.1) for ELIOT vs 0.4% (95% CI -0.0 to 1.0) for WBI  $P = 0.0001$ ].<sup>2,3</sup>

The Xoft method has also yet to be directly compared to WBI in a RCT. However, this method utilizes a low energy, 50 keV X-ray source and an intracavitary technique which is conceptually similar to the TARGIT method, despite use of a higher dose rate. In a non-randomized single center experience of 702 women with stage 0 and 1 breast cancer, the Xoft method achieved a 1.7% LRR at 24.2 months of follow-up.<sup>4</sup>

**Abbreviations:** ABS, American Brachytherapy Society; ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; AMAROS, After Mapping of the Axilla: Radiation or Surgery?; APBI, accelerated partial breast irradiation; ASBrS, American Society of Breast Surgeons; ASTRO, American Society of Therapeutic Radiation Oncology; ELIOT, Electronic Intraoperative Therapy; ESTRO, European Society of Therapeutic Radiation Oncology; HIOB, Hypofractionated Whole-Breast Irradiation Preceded by Intraoperative Radiotherapy Boost; IORT, Intraoperative Radiotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; SSO, Society of Surgical Oncology; TARGIT, Targeted Intraoperative Radiotherapy; WBI, whole breast irradiation.

## 2 | MULTIDISCIPLINARY MANAGEMENT

### 2.1 | Collaborative approach

As in other areas of breast oncology, IORT requires a multidisciplinary approach to patient care that calls for collaboration between surgery, radiation oncology, medical oncology, pathology, radiology, plastic surgery, and support team members.

### 2.2 | Specialist treatment policies

Each multidisciplinary team is expected to develop a written treatment policy establishing a consensus regarding the relevant aspects of patient management, including patient selection, treatment sequencing, and management of unfavorable or unexpected surgical pathology.

### 2.3 | Comprehensive treatment policy

The comprehensive treatment policy facilitates the informed consent process and promotes clear and consistent communication amongst clinicians and between clinicians and patients. In the following discussion, we will address common logistical and clinical concerns

that must be considered by any multidisciplinary treatment team initiating an IORT program, as well as strategies commonly employed by successful IORT programs. A sample treatment policy may be downloaded from this link: [www.targitcollaborative.org/samplepolicy](http://www.targitcollaborative.org/samplepolicy).

## 3 | PATIENT SELECTION

The most important decision for the multidisciplinary team is to establish a consensus on patient eligibility criteria for IORT. Presently, there are no universally accepted guidelines delineating the optimal population for IORT. Outside of an Institutional Review Board-approved clinical research protocol, most clinicians have utilized American Society of Therapeutic Radiation Oncology (ASTRO), European Society of Therapeutic Radiation Oncology (ESTRO), American Brachytherapy Society (ABS), or the American Society of Breast Surgeons (ASBrS) to identify suitable or low risk candidates for APBI/IORT (Table 1), although cautionary/intermediate risk groups are also identified by ASTRO and ESTRO.<sup>5-8</sup> At present, the ASTRO guideline specifically excludes the treatment of IORT in the treatment of DCIS, but no such restriction is specified by the ASBrS and ABS. Notwithstanding these recommendations, each

**TABLE 1** Comparison of four consensus guidelines for patients considered low risk or suitable for APBI

Study	ASTRO [5]	ESTRO [6]	ASBrS [7]	ABS [8]
Patient factors				
Age (years)	≥50	>50	≥45	≥50
BRCA ½ mutation	Negative			
Pathological factors				
Tumor size	≤2.0 cm IDC or ≤2.5 cm*	≤3.0 cm	≤3.0 cm	≤3.0 cm
T stage	Tis, T1	T1-2		
Margins	≥2.0 mm IDC or ≥3.0 mm*	≥2.0 mm	Negative	Negative
Grade	Any; DCIS: Grade I-II*	Any		
LVSI	Absent	Absent		Absent
ER status	ER+	Any		Any
Multicentricity	Unicentric	Unicentric	Unicentric	
Multifocality	Unifocal	Unifocal		
Histology	IDC or other favorable subsets; DCIS if screen-detected and all other criteria (*) are met. (IORT for DCIS excluded)	IDC, mucinous, tubular, colloid, medullary	IDC, DCIS	All invasive subtypes and DCIS
EIC	Absent	Absent		
Associated LCIS	Absent	Allowed		
Nodal factors				
N stage	pN0	pN0	pN0	pN0

Each guideline assumes that all criteria are present.

ASTRO, american society of therapeutic radiation oncology; ESTRO, european society of therapeutic radiation oncology; ASBrS, american society of breast surgeons; ABS, american brachytherapy society; IDC, infiltrating ductal carcinoma; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ER, estrogen receptor; pN0, pathologically negative node.

multidisciplinary team may opt to select narrower or more liberal criteria for IORT based on its own analysis of the available literature. A common strategy is to restrict IORT to the most favorable subset of patients at the launch of an IORT program and expand criteria as IORT experience grows.

#### 4 | PROTOCOL PARTICIPATION

IORT will be a new treatment modality for most institutions where the therapy is provided, and each institution must determine the context in which IORT will be made available to patients. For example, an institution may participate in a national, multicenter prospective clinical trial or may instead initiate its own institutional treatment protocol, with or without IRB-approval. Participation in an existing multicenter registry provides convenient access to an established research infrastructure, but might restrict the types of patients eligible for IORT (e.g., exclusion of infiltrating lobular cancers). Conversely, a single center protocol might take more effort to initiate, but could provide an opportunity to address novel research questions that might not be addressed in a multicenter trial (e.g., IORT in the setting of ductal carcinoma in situ).

##### 4.1 | Preoperative work-up

Most institutions consider clinical examination, bilateral diagnostic mammograms, and breast and axillary ultrasound sufficient for assessment of tumor size, tumor proximity to the skin, multifocality, multicentricity, and axillary adenopathy. Contrast enhanced breast MRI has the theoretical advantage of identifying mammographically occult lesions that might be left untreated by APBI. Although 10% of TARGIT-A trial participants underwent breast MRI prior to IORT, neither the TARGIT-A trial nor the ELIOT trial required breast MRI for patient selection or treatment planning. Breast MRI was also not required by NSABP B-39/RTOG 0413, the RCT comparing conventional WBI versus APBI for early stage breast cancer.<sup>9</sup> Ultimately, each multidisciplinary team will have to determine if and under what circumstances (e.g., mammographically occult malignancy) breast MRI may have a role in the preoperative work-up of IORT candidates.

##### 4.2 | Definitive IORT and/or boost radiotherapy

Much of the attention regarding IORT has focused on the obvious appeal of administering IORT as definitive radiotherapy with the expectation that no additional radiation will be required. However, multiple prospective studies have demonstrated excellent rates of local control when IORT is administered as a tumor bed boost prior to planned WBI (Table 2).<sup>1,2,10-14</sup> Each institution will need to determine if it will introduce IORT as definitive therapy, restrict IORT to boost radiotherapy, or offer IORT as boost radiotherapy prior to expanding indications to include definitive therapy for selected patients. Most institutions have solved this dilemma by adopting a “risk-adapted” approach for low risk patients in which IORT is offered as definitive therapy with the stipulation that WBI

**TABLE 2** Selected trials of Intraoperative Radiotherapy boost prior to planned whole breast irradiation

Study	N	Age (years)	Size (cm)	cN	Histology	Dose (Gy)	Device	Median follow up (months)	LRR	OS	DFS
<sup>10</sup>	72	33-81		N0-1	Not specified	10-15	Hard-dock collimator based	24-204	11yr: 1.39%	Not specified	Not specified
<sup>11</sup>	378 (190*)	57	≤5.0	N0-1	IDC/ ILC/ DCIS	9	Phillips Electra	81	5yr: 0.0% vs 4.3%*	Not specified	5yr: 95.8% vs 90.8%*
<sup>12</sup>	50	54.4*	≤3.0	N0-1	IDC/ ILC	10	Saturne 20	109	10yr: 4%	10yr: 94%	10yr: 83%
<sup>13</sup>	197	61.8*	≤5.0	N0-3	Not specified	20	Intrabeam	37	5yr: 3%	5yr: 91.3%	5yr: 81%
<sup>14</sup>	299	57	≤5.0	N0-1	IDC/ ILC	20	Intrabeam	60.5	5yr: 1.73%	Not specified	Not specified
<sup>2</sup>	52	98% > 50	≤5.0	N0	Not specified	10	Mobetron	79	7yr: 2%	6yr: 89%	6yr: 96%

IDC, infiltrating ductal carcinoma; cN, clinical nodal status; ILC, infiltrating lobular carcinoma; DCIS, ductal carcinoma in situ; LRR, local recurrence rate; OS, overall survival; DFS, disease-free survival. \*subset of patients receiving external beam boost.

would be added if unfavorable histopathological findings (e.g., EIC, LVI, or a positive node) were detected in the surgical pathology specimen. At the same time, patients identified as high risk at presentation may be offered either conventional WBI with an external beam boost or IORT boost followed by planned WBI.

Compared to conventional external beam techniques, IORT boost has the added advantage of eliminating the potential “temporal miss” and “geographical miss” associated with conventional post-operative external breast boost that is typically administered weeks or months after significant tissue changes may have taken place. The main advantages of an IORT boost are that it is administered under direct visualization to the anatomical area of greatest risk of recurrence at a time when radiobiologically the treatment has the greatest potential to inhibit repopulation of residual tumor cells.<sup>15–17</sup> The benefit of an IORT boost may be even more pronounced in patients receiving chemotherapy due to the long interval between lumpectomy and WBI. The comparative effectiveness of TARGIT boost and conventional external beam boost is currently being evaluated in the TARGIT-B trial (NCT01792726), an international RCT of 1796 lumpectomy patients at high risk of local recurrence and for whom definitive APBI is considered suboptimal local therapy.<sup>18</sup> The TARGIT-B trial remains open for accrual for women with one or more high risk criteria, including age <45, history of neoadjuvant chemotherapy, multicentric or multifocal cancer, LVI, EIC, or gross nodal disease.

## 5 | SURGICAL CONSIDERATIONS

### 5.1 | Surgical margins

The optimal surgical margin width in the setting of BCT has been a subject of longstanding debate in the surgery and radiation oncology communities. Fortunately, for patient receiving WBI, the margin width controversy was largely settled by the publication of the Society of Surgical Oncology (SSO)-ASTRO joint consensus guideline on surgical margins, which defines a negative lumpectomy margin for invasive breast cancer as “non-transection” or “no ink on tumor” and a negative margin for pure DCIS as “ $\geq 2$  mm,” whereas the ASTRO APBI Consensus Statement defines a negative lumpectomy margin as “ $\geq 2$  mm” for invasive breast cancer and “ $\geq 3$  mm” for pure DCIS for patient undergoing APBI.<sup>5,19–20</sup>

Contrary to the data supporting the SSO-ASTRO BSC-WBI invasive margin guidelines, which are based on “moderate”-“strong” levels of evidence, ASTRO characterizes as “weak” its consensus statement recommendations regarding minimum margin requirements among APBI candidates. Moreover, ASTRO’s ABPI guidelines are at odds with the margin requirements of the TARGIT-A trial, which defined a negative invasive cancer margin as  $\geq 1$  mm, as well as the recently completed NSABP B-39/RTOG 0413 trial, which defined negative margin for invasive ductal carcinoma and DCIS as “tumor free margins”. Although the NSABP B-39/RTOG 0413 trial did not include IORT as an APBI treatment modality, there is no evidence-based rationale for requiring wider margins for IORT than for other forms of APBI.

Irrespective of the source of radiotherapy, margin re-excision is generally recommended for patients not meeting minimum margin requirements adopted by the treatment team. Thus, in addition to establishing a consensus on minimal accepted margin width, each multidisciplinary team must outline a protocol for managing patients requiring margin re-excision. For example, some institutions require WBI in all cases where re-excision is performed, even if re-excision achieves clear surgical margins or reveals no residual disease. On the other hand, some institutions apply a more measured approach by adding WBI only if re-excision reveals residual disease (assuming final margins are negative), but omit WBI if no residual disease is found in the re-excision specimen, as is often the case. There is widespread consensus that WBI does not compensate for margins that are persistently positive following attempted re-excision, and that such patients should be managed with mastectomy. There are also no published data supporting repeat IORT of the lumpectomy site at the time of margin re-excision.

### 5.2 | Management of Axilla

Surgical management of the axilla has evolved considerably over the last 10 years with the publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, the After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) study, and the International Breast Cancer Study Group 23-01 trial evaluating the use of WBI +/- regional nodal radiotherapy instead of axillary lymph node dissection (ALND) in the management of patients with clinically node negative but histologically positive sentinel nodes.<sup>21,22</sup> Each of these trials demonstrate decreased rates of axillary and arm morbidity in the radiotherapy group compared to the ALND group, but no significant difference in the regional nodal recurrence rate. Although each of these studies have contributed to a dramatic decline in the rate of ALND among sentinel node-positive women treated with breast conserving surgery and WBI, the study results are not applicable to women treated with IORT alone because each trial excluded patients treated with APBI. Consequently, sentinel node positive IORT recipients are generally advised to undergo ALND, WBI or both to minimize the risk of locoregional recurrence.

Each multidisciplinary team must establish a strategic plan for managing the axilla, including the intraoperative management of sentinel nodes. The most common strategy is for a patient to undergo lumpectomy and sentinel node biopsy followed by IORT regardless of the ultimate sentinel node findings. If the sentinel node is found to be positive, the patient could be referred for WBI without further axillary surgery if all other criteria for ACOSOG Z0011 are met. In this case, the IORT dose would serve as the boost replacement, obviating the need for external beam boost. Another approach is to perform microscopic analysis of the sentinel node intraoperatively prior to lumpectomy followed by IORT only if the sentinel node analysis is negative. After recovering from surgery, and typically after completing chemotherapy, the patient would subsequently receive WBI with or without an external beam boost. Patients with more advanced sentinel node pathology (e.g.,  $> 2$  positive nodes and gross extracapsular extension) would be expected to undergo ALND, chemotherapy, followed by WBI +/- regional nodal irradiation.

## 6 | TIMING AND SEQUENCING OF WBI, IORT, AND CHEMOTHERAPY

### 6.1 | Timing of WBI after an IORT boost

Consideration must be given to the optimal timing of WBI with respect to an IORT boost. In an analysis of 48 women receiving 20 Gy TARGIT boost followed by 46-50 Gy WBI, significantly higher rates of grade II and grade III fibrosis, telangiectasia, retraction, and hyperpigmentation were observed among women receiving WBI within 36 days of TARGIT boost compared to those receiving WBI after 36 days.<sup>23</sup> Although the authors did not make a distinction between surgical induration and radiation fibrosis, grade II/III fibrosis was reported in 42% of women receiving WBI within 36 days of TARGIT compared to 17% of those treated beyond 36 days. Based on these observations, it is suggested that WBI be withheld until at least 5 weeks after TARGIT boost. This is in contrast with the ELIOT trial, in which WBI was withheld for 8-12 weeks in the subset of IORT recipients that subsequently required WBI. The NSAPB B-39/RTOG 0413 trial did not define the temporal parameters under which WBI could be administered following APBI.

### 6.2 | Timing of chemotherapy after IORT

The multidisciplinary team must also determine when to initiate chemotherapy among IORT recipients. Currently, there is no consensus on the optimal timing of chemotherapy after IORT, which must balance the oncological benefits of chemotherapy with the potential cosmetic and adverse effects of early chemotherapy initiation. However, analysis of the Mammosite Registry showed significantly worse cosmesis when chemotherapy was initiated  $\leq 3$  weeks after APBI compared to  $>3$  weeks after APBI.<sup>24</sup> There was also a statistically non-significant trend toward greater radiation recall when chemotherapy was initiated  $\leq 3$  weeks after APBI. Consequently, participants in NSABP B-39/RTOG 0413 trial for whom chemotherapy was recommended were advised to begin chemotherapy no less than 2 but no more than 8 weeks following APBI. In the absence of precise guidance regarding the timing of chemotherapy with respect to IORT, it is reasonable to delay the initiation of chemotherapy for a minimum of 2-3 weeks after IORT.

### 6.3 | Sequencing of WBI and chemotherapy

The optimal timing of WBI with respect to chemotherapy among IORT recipients has yet to be fully elucidated. Analysis of the treatment sequence in the TARGIT Boost cohort study demonstrated no relationship between the sequence of WBI and chemotherapy and LRR, overall survival, and morbidity.<sup>1</sup> However, the non-randomized nature of the study and its low overall event rate suggest that these findings should be considered hypothesis-generating rather than conclusive. The TARGIT-B trial aims to determine the optimal treatment sequence by requiring each study site to pre-specify its preferred sequence (e.g., WBI before or after chemotherapy) among

TARGIT boost recipients, which will permit stratification and analysis of outcomes by timing of WBI delivery. Pending further guidance, most institutions favor administration of chemotherapy prior to WBI to avoid delays in the initiation of chemotherapy, followed 2-4 weeks later by WBI. When WBI is initiated prior to chemotherapy, evidence supports delaying WBI for a minimum of 5 weeks after IORT, followed by chemotherapy a minimum of 2-3 weeks after WBI.

### 6.4 | Hypofractionated WBI following IORT

Several institutions utilize hypofractionated WBI administered in 15-16 fractions as a strategy to expedite completion of WBI without delaying initiation of chemotherapy.<sup>25</sup> The largest experience is reported by the Hypofractionated whole-breast irradiation preceded by IORT with electrons as anticipated Boost (HIOB) trial (NCT01343459), an ongoing single-arm multicenter study of IORT using intraoperative boost with electrons followed 6-8 weeks later by 15 fractions of hypofractionated WBI.<sup>26</sup> A 2015, interim analysis of 481 HIOB trial participants showed low rates of severe skin reaction (grade 0-I in 96% of patients) and overall good-to-excellent cosmesis ( $\sim 80$ -90%) at 4-5 months, 1, 2, and 3 years, and no in-breast recurrences at median follow-up of 12.6 months—outcomes comparable to conventional WBI.<sup>27</sup> Currently, studies examining the safety and efficacy of hypofractionated WBI after TARGIT boost are limited to single institution series with similar short-term follow-up. However, the favorable preliminary findings of the HIOB trial provide justification for ongoing studies evaluating the combined use of hypofractionated WBI and IORT.

## 7 | PATIENT FOLLOW-UP

### 7.1 | Clinical follow-up

A treatment policy should define the expected post-operative follow-up of the IORT recipient. In general, IORT recipients exercise the same follow-up protocol as patients treated with WBI, including routine post-operative follow-up visits with the surgeon, radiation oncologist, and medical oncologist. Clinical examination should exclude the presence of a symptomatic seroma, which might benefit from aspiration, and document any potential complications of radiotherapy and/or surgery, including cellulitis, radiation dermatitis, fibrosis, telangiectasia, and wound dehiscence.<sup>28</sup> However, with the exception of recurrent seromas (2.1% TARGIT vs 0.8% WBI,  $P = 0.012$ ) and grade III/IV fibrosis (0.5% TARGIT vs 2.1% WBI,  $P = 0.002$ ), the TARGIT-A trial revealed no significant difference between TARGIT and WBI in the rate of infection, hematoma, skin breakdown, or delayed wound healing<sup>1</sup>. Similarly, the ELIOT trial reported no difference in the rate of major toxicity, but observed a higher rate of skin erythema, dryness, hyperpigmentation, and pruritis among WBI recipients.<sup>3</sup>

### 7.2 | Breast imaging follow-up

The multidisciplinary team should also establish a policy for breast imaging follow-up of the IORT recipient. Breast imaging after IORT

should generally mirror the protocol used for women treated with WBI. Most often, this consists of a 6-months post-operative/post-radiation diagnostic mammogram followed by annual bilateral diagnostic mammography. However, clinicians new to IORT may choose to continue semi-annual mammography and/or ultrasound of the treated breast for a 2-3 year period to familiarize themselves with the typical temporal imaging changes of the IORT-treated breast. There is no standard role for routine follow-up breast MRI, but MRI may be considered when physical or imaging findings are not resolved by mammography and/or ultrasound.

The majority of local recurrences develop within the first 5 years after breast conserving therapy. Consequently, radiologists face the challenge of distinguishing between the seminal parenchymal changes associated with cancer recurrence and the usual radiographic changes that may evolve in the initial years following surgery and radiotherapy. IORT and other forms of APBI are commonly associated with mammographic and ultrasound evidence of fat necrosis, parenchymal scarring, hematoma/seroma, and circumscribed masses, which may cause concern and occasionally lead to unnecessary diagnostic core biopsies.<sup>29-31</sup> This underscores the importance of the radiologist's experience in interpreting post-IORT/ABPI imaging studies. Several reports have documented a higher risk of radiographic fat necrosis in patients treated with IORT.<sup>32-34</sup> In a retrospective analysis of 30 randomized participants in the TARGIT-A Trial for whom at least 4 years of mammograms were available, a radiologist blinded to the treatment allocation observed a significantly greater degree of mammographically-detected fat necrosis in the TARGIT group (36% TARGIT vs 13% WBI), but no difference in the frequency of architectural distortion, skin thickening, skin retraction, or mass density between the two groups.<sup>35</sup> Similarly, a higher incidence of fat necrosis and prolonged parenchymal scarring was reported after 3 years among 40 TARGIT boost recipients and 54 TARGIT alone recipients compared to a non-randomized cohort of 48 patients receiving WBI alone.<sup>36</sup> In contrast, Elsberger et al observed no significant difference in the appearance of calcification (a surrogate for fat necrosis) in a non-randomized study of 141 TARGIT-A Trial participants (61 TARGIT, 80 WBI) with 4-5 years of follow-up, but observed a greater degree of ipsilateral breast density (31.3% WBI vs 9.8% TARGIT,  $P = 0.002$ ) and skin thickening (32.5% WBI vs 16.4% TARGIT,  $P = 0.030$ ) among WBI recipients.<sup>37</sup>

## 8 | CONCLUSIONS

IORT has become accepted as an alternative or an adjunct to fractionated WBI following breast conserving surgery. There are several published protocols which can be adapted for application in treatment centers. The most salient features of these protocols have been discussed and compared, providing a rationale for the introduction of this new treatment modality. Decisions have to be made about patient selection and preoperative workup. There is a choice to be made concerning the use of IORT alone or as an intraoperative boost of radiotherapy prior to WBI. IORT has the advantage of delivering the

course of radiotherapy as a single fraction during breast surgery. If the boost approach is used, the timing between IORT and WBI should be more than 5 weeks to minimize radiation morbidity. The initiation of chemotherapy, likewise, should be delayed for at least 2 weeks to reduce the risk of radiation recall and poor cosmesis.

Improved breast cancer outcomes with the use of IORT strongly justify the widespread adoption of this APBI approach which can be aided by the adoption of standardized patient selection, management, and follow-up protocols based on best practices supported by published literature.

## DISCLOSURES

D.H. is President of the TARGIT Collaborative Group and Co-Principal Investigator of the TARGIT U.S. Registry Trial. R.Z. has no conflicts of interest to declare.

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## SYNOPSIS

Intraoperative Therapy (IORT) may be used alone or as an adjunct to whole breast irradiation in patients undergoing conservative surgery for breast cancer. Multiple studies have addressed issues such as patient selection, preoperative workup, definitive application of IORT, its interaction with whole breast irradiation and chemotherapy, and patient follow-up after IORT treatment. This article reviews these studies as an aid to protocol and policy development for the introduction of IORT.