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Intraoperative Radiotherapy in Breast Conserving Surgery

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Intraoperative radiotherapy (IORT) of the breast is the administration of a single fraction of radiation to the tumor bed while shielding low risk and uninvolved tissues from the effects of radiation. The TARGIT A and ELIOT trials demonstrate efficacy of IORT when administered at the time of lumpectomy to post-menopausal women with low to intermediate grade, lymph node negative, invasive ductal carcinoma, consistent with international guidelines defining suitable candidates for accelerated partial breast radiotherapy.
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INTRODUCTION

The current standard of care for the management of conservatively treated breast cancer is a 3.5- to 7-week course of radiotherapy administered to the entire affected breast and adjacent tissues (skin, pectoralis muscle, and lower axilla) using a 1.8–2.0 Gy per day fractionation regimen for a total dose of 45–50 Gy. Numerous randomized trials and meta-analyses have confirmed the effectiveness of whole breast external beam radiotherapy (WB-EBRT) at achieving two-thirds reduction in the frequency of local recurrence. For women with early stage breast cancer, this translates into 20-year local recurrence rates of 8–14% and improved overall survival in the longest running randomized controlled trials [1–3]. Among the minority of women that experience ipsilateral breast tumor recurrences following breast conservation therapy, over 80% will develop a recurrence within or adjacent to the original tumor site due to progression of premalignant or residual occult disease [4].

The protracted course of standard radiotherapy and the propensity for breast cancer to recur at the original tumor site have provided a logistical and biological rationale for the innovation of breast radiotherapy techniques aimed at achieving two main goals: (1) accelerating the delivery of radiotherapy by reducing the number of required treatments and (2) targeting the radiation dose to the tumor site while minimizing radiation exposure of the remaining breast and adjacent tissues. Acceptance of accelerated partial breast irradiation (APBI) has been facilitated by a growing desire to reduce the inconvenience and morbidity of breast radiotherapy combined with increased detection of smaller, localized breast cancers from widespread use of screening mammography. Multicatheter interstitial breast radiotherapy was the first APBI technique to achieve clinical acceptance due to excellent disease control rate, reduced morbidity, and greater convenience, but technical complexities have limited its widespread adoption. More recent innovations include the development of single-entry intracavitary catheter-based devices (e.g., Mammosite®, Axxent®, Savi®, and Contoura®) and 3D-conformal external beam radiotherapy.

Intraoperative radiotherapy is the ultimate strategy in the effort to reduce radiotherapy treatment burden. Intraoperative radiotherapy (IORT) of the breast is the administration of a single fraction of radiation during surgery that allows intensification of the radiation dose to the tumor bed while shielding or displacing lower risk and uninvolved tissues (e.g., skin, lung, and heart) away from the path of radiation. IORT is administered under the guidance of a surgeon, radiation oncologist, and medical physicist following multidisciplinary review of the patient's risk factors and treatment options. The appeal of one-stop surgery and radiotherapy and the potential for reduced morbidity have promoted acceptance of IORT among patients and clinicians as an alternative to fractionated post-operative breast radiotherapy. The following discussion will review emerging data regarding the efficacy and safety of this emerging technology.

PRACTICAL AND THEORETICAL ADVANTAGES OF IORT

In addition to the obvious advantages of expediting and maximizing breast radiotherapy compliance, several additional practical and theoretical advantages of IORT have been recognized: (1) initiation of radiotherapy during surgery limits the opportunity for repopulation of residual tumor cells that may occur during the multiple-week to multiple-month interval between surgery and initiation of adjuvant chemotherapy and/or adjuvant radiotherapy [5]; (2) placement of the radiation applicator adjacent to the clinical target volume (CTV) under direct visualization eliminates the potential for a topographical miss that frequently results from variable patient set-up, patient movement, and imprecise identification of the tumor bed weeks or months after surgery. Topographical misses of the boost volume reportedly occurs in 24–88% of women receiving WB-EBRT [6,7]; (3) administration of radiation therapy to a richly vascularized and oxygenated tumor bed increases the tumoricidal effect of radiation; (4) irradiation of the surgical cavity from the inside out maximizes the parenchymal dose while minimizing radiation exposure of skin and adjacent organs; and (5) administration of radiotherapy at the time of surgery might alter the microenvironment of the surgical bed and reduce the production of cytokines that contribute to tumor cell proliferation, migration and chemotaxis, and ultimately, recurrence [8].

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IORT AS BOOST RADIOTHERAPY

In 2005, the Early Breast Cancer Trialists' Collaborative Group reported that WB-EBRT combined with adjunctive irradiation of the tumor bed substantially reduced local recurrences compared to WB-EBRT alone [1]. This finding was affirmed by the 2007 publication of the EORTC 22881-10882 "boost" versus "no boost" trial that demonstrated improved local control in pre- and postmenopausal women when a tumor bed boost was added to WB-EBRT [4]. Based on these studies, the current standard of care for all premenopausal and most postmenopausal women is the administration of a 10–16 Gy post-operative external beam tumor bed boost following the standard 5- to 6-week course of daily WB-EBRT.

The ability to escalate the tumor bed dose while protecting adjacent skin and underlying chest structures have led multiple centers to introduce IORT as an alternative to conventional post-operative external beam boost radiotherapy in the management of breast cancer. This strategy was pioneered by Dobelbower et al. [9] in 1989 as a means of delivering a tumor bed boost prior to planned post-operative WB-EBRT. In their initial publication, 21 women with invasive breast cancer were treated with breast conserving surgery and single fraction IORT (10–15 Gy) tumor bed boosts followed by a 5–6 week, 45–50 Gy course of post-operative WB-EBRT. Ten-year follow-up of this initial cohort yielded only one ipsilateral breast tumor recurrence and minimal acute and late toxicity (e.g., no Grade III fibrosis), providing early evidence of the safety and effectiveness of IORT [10]. Excellent outcomes were also reported in 1997 by Dubois et al. [11] who observed no local recurrences and excellent cosmesis among 51 women with stage I–II breast cancer treated with breast conserving surgery, a 10 Gy IORT tumor bed boost, and a 45 Gy course of post-operative WB-BERT. Comparison of these women with a matched cohort of 50 women treated with WB-EBRT without boost detected no wound healing differences [11].

Beginning in 1998, Reitsamer et al. evaluated the efficacy of combining the IORT boost with WB-EBRT (an approach they called "the Salzburg concept") in a case-controlled study of 388 patients with T1–T2 invasive breast cancer. Half of the participants received WB-EBRT (51–56.1 Gy in 1.7 Gy fractions) followed by standard tumor bed boosts (9 Gy) and the other half received IORT boosts (12 Gy) using the Elekta (Phillips Medical Systems, Stockholm, Sweden) followed by WB-EBRT (51–56.1 Gy in 1.7 Gy fractions) [12]. Although median follow-up differed significantly between the two treatment groups, no local recurrences were detected in the IORT group (median follow-up 25.8 months) compared to a 4.3% local recurrence rate in the post-operative WB-EBRT boost group (median follow-up 53.3 months). Promising results were also reported by Lemanski et al. [13] who documented the long-term outcomes of 50 women with stage I–II breast cancer treated with 50 Gy WB-EBRT after receiving a 10 Gy IORT boost administered using a dedicated stationary linear accelerator (Saturne 20, Varian, Buc, France). After 9.1 years median follow-up (range 5–15 years), only two recurrences were reported within the tumor bed for a crude local recurrence rate (LRR) of 4%. Grade II fibrosis (defined as increased density and firmness) was observed in 14% of participants and no cases of Grade III fibrosis (marked density, retraction, fixation) were detected.

More recently, Wong et al. reported the 79-month median follow-up of 52 women with clinical stage I breast cancer treated with a 10 Gy IORT tumor bed boost administered using the Mobetron System followed by WB-EBRT (48 Gy) [14]. The crude local control rate was 96% despite two local recurrences in patients whose cancers were found to have an extensive intraductal component. Cosmesis was excellent or good in 87% of participants. Poor cosmesis due to fibrosis was observed in two patients: in one following seroma aspiration and in a second following revision of the lumpectomy bed.

Vaidya et al. [15] examined the efficacy of the TARGIT method for delivery of a tumor bed boost (20 Gy) prior to WB-EBRT (45–50 Gy) in a case controlled study of 299 high risk patients who were ineligible for IORT alone due to young age or unfavorable surgical pathology findings. At median follow-up of 60.5 months, the 5-year actuarial LRR of the TARGIT boost was 1.73%, which compared favorably with the 4.3% 5-year LRR reported among EORTC boost recipients and the 2.8% 5-year LRR reported by the U.K. *ST*Andardisation of breast *R*adio*T*herapy (START-B) hypofractionation study despite a higher proportion of node positive patients (29%) in the TARGIT boost study compared to the EORTC (21%) and U.K. START-B (24%) studies [16,17]. Long-term toxicity of the TARGIT IORT boost was reported by Blank et al. in 58 women with 5 years of follow-up, revealing telangiectasias in eight individuals and hyperpigmentation in one for a 13.8% overall rate of chronic skin toxicity. Grade III fibrosis was observed in three (5.1%) individuals, including one managed with mastectomy [18].

Acceptable morbidity and superior local control among TARGIT boost recipients inspired the 2013 launch of the TARGIT B Trial (NCT01792726), an international, randomized controlled trial of 1,796 women comparing TARGIT IORT boost (20 Gy) to standard post-operative external beam boost (16 Gy) after breast conserving surgery in women with a high risk of local recurrence schedule to receive 40–50 Gy WB-EBRT. TARGIT B inclusion criteria include age <46 years, extensive intraductal carcinoma, positive nodes, and lymphovascular invasion. Table I summarizes the findings of a selected list of publications employing the use of an IORT boost prior to planned WB-EBRT.

IORT AS DEFINITIVE RADIOTHERAPY

A new milestone in the evolution of IORT was reached in 2013 with the publication of two landmark journal articles describing the findings of two prospective, randomized controlled trials comparing single fraction IORT and standard WB-EBRT in the management of early-stage breast cancer treated with breast conserving surgery [18,19]. In the larger of the two studies, the TARGIT Trial, 3,451 women were randomized to receive either standard 25 or 35-fraction WB-EBRT administered after surgery or single-fraction partial breast targeted intraoperative radiotherapy delivered with low energy (50 kV) X-rays using the Intrabeam System (Carl Zeiss Meditec, Inc., Oberkochen, Germany). The second study, the ELOIT Trial, randomized 1,305 women to receive either standard 35-fraction WB-EBRT or single-fraction partial breast electron intraoperative radiotherapy (ELIOT) delivered with high-energy (6–9 MeV) electrons using NOVAC 7 (Hitesys, Aprilia, Italy) or Liac (Sordina SpA, Padova, Italy) systems. Both methods of IORT were performed collaboratively between the breast surgeon and radiation oncologist.

The TARGIT and ELIOT trials represent an international effort to evaluate the efficacy and safety of IORT in the treatment of breast cancer in geographically diverse populations. The TARGIT Trial was conducted at 33 institutions in 11 countries, while the ELIOT Trial was concurrently conducted at a single institution, the European Institute of Oncology, in Milan, Italy.

The TARGIT A and ELIOT trials share several key features that reinforced the significance of their respective findings. The vast majority of trial participants were women age 50 and older with low or intermediate nuclear grade (85%), hormone receptor positive (91–93%), invasive ductal carcinomas measuring 2 cm or less (81–85%), consistent with international guidelines for APBI. Both trials also sought to determine if the LRR after IORT would be within 2.5% (TARGIT) or 4.5% (ELIOT) of the expected LRR after lumpectomy and standard WB-EBRT.

The TARGIT A and ELIOT trials also had two (2) important differences. First, the TARGIT A Trial utilized a broad risk-adaptive policy that allowed recipients of IORT to receive additional therapy if high-risk factors (e.g., surgical margins <1 mm, extensive DCIS,

TABLE I. Selected Publications of Trials Employing the Use of IORT Boost Prior to Planned WB-EBRT

Study	N	Age	Size	Nodes	Histology	Dose (Gy)	Device	Median F/u	LRR	OS	DFS
MCO/CRLC [10]	72	33–81		N0-1		10–15		2–17 years	1.39%		
Salzburg [12]	378 (190 IORT)	57	≤5	N0-1	IDC/ ILC/DCIS	9	Phillips Electra	81	5 years: 4.2%		95.8%
Montpellier [13]	50	54.4	≤3	N0-1	IDC/ILC	10	Saturne 20	109	4%	10 years: 94%	10 years: 83%
Mannheim [17]	197	61.8	≤5	N0-3		20	Intrabeam	37	3%	91.3%	81.0%
UCL [15]	299	57	≤5	N0-1	IDC/ILC	20	Intrabeam	60.5	5 years: 1.73%	NR	NR
Mayo AZ [14]	52	98% >50	≤5	N0		10	Mobetron	79	7 years: 2%	6 years: 89%	6 years: 96%
ISIORT [42]	2,395	60.8	≤5	N0-1	Tis, IDC, ILC	8–12	Various	4.4			88%

infiltrating lobular carcinoma, positive lymph nodes) were detected in the surgical specimen. Additional therapy for targeted IORT recipients typically involved the addition of WB-EBRT (50 Gy in 25 daily fractions) to the single fraction of IORT already received. As predicted by the study organizers, approximately 15% of targeted IORT recipients required additional therapy due to unfavorable surgical pathology findings. The ELIOT Trial was less broadly risk-adaptive and prescribed 25-fractions of standard radiotherapy only to ELIOT recipients with ≥ 4 positive nodes. ELIOT recipients with margins <1 mm, extensive DCIS, infiltrating lobular carcinoma, or 1–3 positive nodes were not routinely prescribed additional radiotherapy, which had a direct bearing on ELIOT Trial results.

A second key difference between the TARGIT A and ELIOT trials relates to the timing of IORT delivery. All ELIOT Trial participants received IORT at the time of breast conserving surgery, whereas one-third of TARGIT A Trial participants received IORT at a second operation "post-pathology" following initial breast conserving surgery —a requirement of the Australian and Denmark study sites.

The key outcome measures presented in the TARGIT A and ELIOT publications were the rates of local recurrence, regional (axillary) lymph node recurrence, and overall survival. Breast cancer and non-breast cancer survival rates were addressed in the TARGIT A publication, but omitted from the ELIOT publication. Neither the TARGIT A Trial nor the ELIOT Trial evaluated the use of IORT delivered using the Axxent or Mobetron Systems. Although the Mobetron System mirrors the Liac and Novac 7 systems from a radiobiological perspective, difference in dose rate and depth dose curves between the Intrabeam and Axxent systems undermines the view that the TARGIT A Trial's outcome data are validative of the Axxent approach.

LOCAL RECURRENCE RATE

The most important finding of the TARGIT A and ELIOT trials is that all methods of radiotherapy delivery were associated with relatively low local recurrence rates. The unexpected finding of both trials is that the 5-year LRR (1.3% and 0.4%, respectively) following WB-EBRT fell considerably below expected historical benchmarks of 6.0–7.5%, pointing to the high quality of comprehensive breast cancer care among participating centers [20,21]. Nevertheless, the key endpoint of both trials was to determine if the LRR after IORT was within an "acceptable" pre-specified range of standard radiotherapy. In that regard, both trials met their expressed goals. In the TARGIT A Trial, the 5-year LRR for IORT was 3.3% compared to the 1.3% for standard radiotherapy—within the 2.5% absolute difference considered "acceptable." Furthermore, when TARGIT A data was analyzed by "time of IORT delivery", the 5-year LRR for the subgroup receiving IORT at the time of initial breast conserving surgery was only 2.1% versus 1.1% for standard radiotherapy, an absolute difference of only 1%. Unexpectedly, the 5-year LRR in the post-pathology group was 5.4% for IORT versus 1.7% for EBRT, a 3.7% difference that exceeded the 2.5% "acceptable" threshold. The higher LRR among post-pathology IORT recipients was likely attributed to delays between breast conserving surgery and IORT delivery during which the wound may have partially healed or contracted, making it more difficult to identify and precisely target IORT to the original surgical margins. Interval tumor cell repopulation might have also contributed to the high LRR in the post-pathology cohort.

In the ELIOT Trial, the 5-year LRR for IORT was 4.4% versus 0.4% for WB-EBRT, but within the 4.5% margin considered "acceptable" by trial planners. Though it would be unscientific to directly compare the 5-year LRR for ELIOT (4.4%) and the targeted IORT pre-pathology group (2.1%), the higher LRR seen after ELIOT was likely greatly influenced by the failure to administer WB-EBRT to women found to have unfavorable findings in their surgical specimen (e.g., <1 mm margins, extensive DCIS, 1–3 positive lymph nodes, or infiltrating lobular carcinoma). Had WB-EBRT been administered to ELIOT recipients possessing high-risk features, a lower overall LRR would have likely been observed. Indeed, when stratified by ASTRO and ESTRO "suitable" criteria, the 5-year LRR for ELIOT recipients was only 1.5% (ASTRO) and 1.9% (ESTRO) [22,23].

Node Recurrences

Both the TARGIT A and ELIOT trials reported low rates of axillary nodal recurrences among IORT and WB-EBRT recipients. The key difference between the two studies is that the ELIOT Trial reported a significantly higher axillary recurrence rate among ELIOT recipients compared to WB-EBRT (1.0% vs. 0.3%, $P = 0.03$). A plausible explanation for the higher axillary recurrence rate for ELIOT was the omission of WB-EBRT for patients with 1–3 positive lymph nodes, a group comprising 21% of ELIOT recipients. That the axillary recurrence rate was not even higher among ELIOT recipients speaks to the indolent nature of many nodal metastases as well as the ability of systemic therapy to control axillary disease. Nonetheless, the prescription of WB-EBRT for all node-positive TARGIT A Trial participants likely accounted for equivalent axillary recurrence rates observed in the two study arms (IORT 1.1% vs. WB-EBRT 0.9%, NS).

Survival Outcomes

Neither the TARGIT A nor ELIOT trials demonstrated a difference in the overall survival of IORT and WB-EBRT recipients. However, the TARGIT A Trial did reveal an improved overall survival trend in favor of IORT (96.1% vs. 94.7% $P = 0.069$) due to fewer cardiovascular and non-breast cancer-related deaths seen after IORT compared to WB-EBRT (1.4% vs. 3.5%, $P = 0.0086$). Cardiovascular deaths and deaths from other cancers were not specifically reported in the ELIOT publication. The cardiovascular survival difference was an unexpectedly early finding in the TARGIT A Trial due to the expectation that longer follow-up would be needed to discern the cardiovascular impact of breast radiotherapy. However, a recent publication confirmed that radiotherapy-related cardiovascular events following standard WB-EBRT could be detected as early as 4 years after radiotherapy [24].

Side Effects

Adverse event reporting was incomplete in both trial publications, but each trial revealed safety outcomes in favor of IORT. The TARGIT A Trial demonstrated no difference in the overall major wound complication rate assessed 6 months after randomization, but did not report the 5-year surgical site complication rates. Nonetheless, at 6 months, moderate to severe skin side effects were less common in IORT recipients. Five-year wound complication rates were reported for the ELIOT Trial, but data were available for only 71% of IORT recipients and 62% of WB-EBRT recipients. ELIOT reported significantly lower rates of skin redness, dryness, darkening, and itching among IORT recipients. A separate analysis of 119 randomly selected participants in the ELIOT off-trial study identified grade II fibrosis in 31.9% of subjects and grade III fibrosis in 5.9% at 71 months median (28–115 months) follow-up [25].

ELIOT also reported a higher incidence of fat necrosis among IORT recipients, a side effect previously reported for TARGIT A [26,27]. The overall low, but comparatively higher, rate of fat necrosis observed among IORT recipients is as much the consequence of extensive tissue mobilization as a direct effect of radiation. Wound fluid collections requiring needle aspiration were infrequent overall but reportedly more common in IORT recipients, yet showed no association with patient age [28,29]. In the analysis of long-term toxicities in the TARGIT A Trial, targeted IORT recipients were observed to have significantly less telangiectasias ($P = 0.015$), skin retractions ($P = 0.006$), and pain ($P = 0.044$) compared to the WB-EBT group at 3 years of follow-up [30].

Additional data regarding the safety of ELIOT may be obtained from an analysis of 1,822 participants in the ELIOT off-trial study in which Veronesi et al. [31] reported a 1.8% incidence of mild fibrosis and 0.1% incidence of severe fibrosis with median follow-up of 36.1 months. Fibrosis generally peaked at 6–12 months following IORT, stabilized over the next 6–12 months, then gradually resolved [32]. By comparison, higher rates of severe (4.4%) and moderate (5–11%) fibrosis have been reported following WB-EBRT + boost [4,33,34]. Researchers observed symptomatic fat necrosis in 4.2% of patients treated with ELIOT, which was sometimes mistaken for a breast abscesses when presenting as erythematous, painful masses that yielded sterile brown fluid on needle aspiration [32]. This phenomenon reportedly occurred more commonly in elderly patients. Telangiectasia, desquamation, and other skin complications were relatively uncommon among ELIOT recipients [34]. Although specific fibrosis data remain unreported for the Mammosite or similar intracavitary devices, anecdotal evidence finds fibrosis to be a relatively common occurrence among recipients of intracavitary brachytherapy.

Multiple single institution series of single-fraction IORT have been published over the last decade employing various approaches to delivering IORT following tumor resection (Table II). The one notable exception to this approach is a study by VanderWalde et al. [35] in which the Mobetron System was used to administer IORT to the tumor bed prior to breast conserving surgery. This pre-excision treatment strategy was based on the hypothesis that radiation of the tumor in situ would allow better tumor localization and better dose distribution. In addition, since pre-excision treatment eliminates the opportunity to insert a radiation barrier into the retromammary space, the study selected a lower single fraction dose (15 Gy) to minimize pulmonary morbidity. Among 53 patients receiving pre-excision IORT in this study, local recurrences were detected in eight individuals yielding an unexpectedly high crude 6-year LRR of 15.1%—more than four times the 3.5% LRR expected in similar cohorts treated with WB-EBRT. The authors hypothesized that their high rate of local failures might result from mammographic and ultrasound underestimation of lesion dimensions (MRI was not routinely used), off-center placement of the applicator which was positioned using tumor palpation alone, and suboptimal radiation dosing (15 Gy). While study design modifications might improve the efficacy of pre-excision treatment, current evidence shows clear advantages to administering IORT immediately following tumor resection when margin assessment, CTV definition, internal shielding, and dose escalation can be optimized to enhance local control.

SEQUENCING OF THERAPY

Several concerns exist regarding the relative timing of IORT, WB-EBRT, and chemotherapy. Consideration must be given to avoiding prolonged delays in initiation of WB-EBRT that might have a negative impact on local or systemic control. There is also concern that delaying chemotherapy for completion of radiotherapy might adversely effect overall survival. Prospective randomized trials of conventional radiotherapy show no survival advantage to administering radiotherapy prior to chemotherapy, nor has an overall survival advantage been shown for simultaneous administration of radiotherapy and chemotherapy [36,37]. Nonetheless, the optimal timing of IORT, WB-EBRT, and chemotherapy remain to be elucidated. Fortunately, the local recurrence and morbidity implication of WB-EBRT timing will be addressed in the TARGIT B randomized controlled trial that stratifies patients by timing of WB-EBRT delivery relative to chemotherapy. Prior to enrollment, each institution must specify its chemotherapy sequence (e.g., pre- or post-WB-EBRT), which should provide a body of data regarding the outcome of various approaches.

In the meantime, the integration of IORT as definitive therapy or boost into the multidisciplinary management of breast cancer will continue to raise several key questions: (1) how soon should WB-EBRT be administered after an IORT Boost in a patient for whom chemotherapy is not planned; (2) how soon should chemotherapy begin after IORT definitive therapy in a patient for whom chemotherapy is planned; (3) how soon should WB-EBRT begin after completing IORT boost and chemotherapy; and (4) how soon should chemotherapy begin after completing IORT boost and WB-EBRT (e.g., utilizing hypofractionation)?

Wenz et al. [30] provided some insights into the optimal timing of WB-EBRT after an IORT boost. In their analysis of 48 women receiving 20 Gy targeted IORT followed by 46–50 Gy WB-EBRT, higher rates of grade fibrosis, telangiectasia, retraction, and hyperpigmentation were

TABLE II. Selected Publications of Trials Employing Use of Single Fraction IORT as Definitive Therapy

Study	N	Age	Size	Nodes	Histology	Dose (Gy)	FX	Median F/u	LRR	OS	DFS
MSKCC [43]	52	76.2	≤2	N0	IDC	20, 18	H.A.M.	31.4	0%		
Milan [30]	1,822	58	<2.5	N1-3	IDC/ILC	21	Liac, Novac 7	36.1	5 years: 2.3%	5 years: 97.4%, 10 years: 89.7%	5 years: 98.3%, 10 years: 94.6%
Montpellier [44]	42	72	≤2.0	N0	IDC	21	Saturne 43	72	5 years: 9.5%	100%	5 years: 92.7%
Verona [45]	226	63	≤5.0	N0-1	IDC	16.8	Mobetron	46	0.2%	100%	99.6%
UNC [35]	53	63	≤3.0	N0	IDC	15	Mobetron	69	6 years: 15.1%	94.4%	100% BCSS

TABLE III. Comparison of Four Consensus Guidelines for Patients Considered "Suitable" for APBI

	ASTRO [46]	ESTRO [47]	ASBS [48]	ABS [49]
Patient factors				
Age	≥60	≥50	≥45	≥50
BRCA 1/2 mutation	Negative			
Pathological factors				
Tumor size	≤2 cm	≤3 cm	≤3 cm	≤3 cm
T Stage	T1	T1–2		
Margins	≥2 mm	≥2 mm	Negative	Negative
Grade	Any			
LVSI	Absent	Absent		Absent
ER status	ER+			ER+/−
Multicentricity	Unicentric	Unicentric	Unicentric	
Multifocality	Unifocal	Unifocal		
Histology	IDC or other favorable subsets	IDC	IDC, DCIS	All invasive subtypes and DCIS
EIC	Absent	Absent		
Associated LCIS	Absent			
Nodal factors				
N Stage	pN0	pN0	pN0	pN0

Each guideline assumes that all criteria are present.

observed among women receiving WB-EBRT within 36 days (median 29.5 days) of IORT compared to those receiving WB-EBRT after 36 days (median 39.5 days, $P = 0.023$). Although the authors did not distinguish between surgical induration and radiation fibrosis, 42% of women receiving WB-EBRT within 36 days experienced grade II/III fibrosis compared to 17% of women treated after 36 days, suggesting that WB-EBRT should be withheld until at least 5 weeks after IORT.

For patients requiring chemotherapy after IORT, analysis of the Mammosite Registry showed significantly worse cosmesis when chemotherapy was initiated ≤3 weeks after APBI as opposed to >3 weeks after completing APBI, in addition to a statistically non-significant trend toward greater radiation recall when chemotherapy was initiated ≤3 weeks after APBI, a principal that might also apply to IORT [38].

Regarding the timing of chemotherapy, Vaidya et al. [15] reported that 45% of 299 patients in the TARGIT Boost cohort study received WB-EBRT after chemotherapy and the remaining patients received WB-EBRT before chemotherapy. An analysis of "after" versus "before" patients showed no impact on LRR, overall survival, or morbidity. However, the non-randomized nature of the trial and the low overall event rate make the findings more hypothesis generating than conclusive. For patient requiring WB-EBRT and chemotherapy, the current convention is to initiate radiotherapy 4 weeks after completing chemotherapy to allow sufficient time for wound healing. There is no indication that the convention should be altered in the setting of IORT or IORT boost.

Several institutions have begun utilizing hypofractionated radiotherapy administered in 15 days as a strategy to expedite completion of the entire course of breast radiotherapy without significantly delaying initiation of chemotherapy [39]. This approach was evaluated in a pilot study of premenopausal women receiving 12 Gy ELIOT at the time of quadrantectomy followed 4 weeks later by 37.05 Gy hypofractionated external beam radiotherapy in 13 daily fractions. High rates of acute toxicity [Grade I (3.8%), Grade II (67.6%), Grade III (28.6%), and Grade IV (0%)] were observed at 1 month, post-radiotherapy follow-up similar to the findings reported by Wenz et al. [30]. Late toxicity assessed at 6 and 12 months post WB-EBRT was evaluable in 108 patients, revealing Grade II or less toxicity in 106 (98.2%) of patients. The long-term efficacy of the IORT followed by hypofractionation has yet to be reported, but marked improvement of breast symptoms suggests that hypofractionation might be a safe approach for completing radiotherapy prior to chemotherapy.

CONCLUSION

Intraoperative radiotherapy is a novel intervention capable of significantly reducing the inconvenience, morbidity, and cost of breast radiotherapy. The TARGIT A and ELIOT trials show IORT to be as safe and effective as standard radiotherapy for post-menopausal women with low to intermediate grade, lymph node negative invasive ductal carcinoma lacking high-risk features. This assessment aligns with the partial breast radiotherapy patient selection guidelines already established by American Society of Therapeutic Radiation Oncology, the American Society of Breast Surgeons, European Society of Therapeutic Radiation Oncology and American Brachytherapy Society (Table III). As the proportion of early-stage breast cancers continue to rise, the population of women meeting criteria for IORT and other forms of partial breast radiotherapy will grow steadily in coming years. For patients not meeting criteria for IORT as definitive therapy, emerging data support the use of IORT as a tumor bed boost prior to WB-EBRT.

The TARGIT A Trial emphasizes the importance of pre- and post-operative patient selection based on core biopsy and surgical pathology findings. The TARGIT A Trial's pragmatic approach mirrored community practice standards by permitting the radiotherapy treatment plan to be modified for the minority of women found to have high-risk findings in their surgical specimens. The delivery of IORT at the time of initial lumpectomy did not eliminate the option of additional radiotherapy if deemed necessary.

Much has been made of the higher local recurrence seen in unsuitable or unsuitably-timed IORT recipients. To the contrary, clinical trials not only enable assessment of efficacy and safety of specific therapies, they also provide guidance for future application of a given therapy. For example, following NSABP B24, Tamoxifen was not abandoned as a therapy for estrogen receptor positive DCIS once it was learned that it lacked efficacy against estrogen receptor negative DCIS [40]. Accordingly, a "real world" application of the TARGIT A and ELIOT trial results should restrict the use of definitive IORT to suitable patients while contraindicating its use in high risk or otherwise unsuitable women. For such patients, WB-EBRT (with or without IORT boost) remains the mainstay of therapy.

The lack of longer-term (e.g., 10-years) outcome data for the TARGIT A and ELIOT trials is a limitation that can only be overcome with the passage of time and continued close follow-up. Future breast and axillary node recurrences will undoubtedly occur among both IORT

and standard radiotherapy recipients, but there is little evidence to suggest that the rate of breast and/or axillary recurrences should differ dramatically between properly selected groups of women receiving standard breast radiotherapy or IORT at the time of initial lumpectomy. If a greater difference were to emerge in favor of standard radiotherapy, the well-informed patient would be empowered to balance the potential risk of higher breast cancer recurrence with the potential benefits of convenience, fewer side effects, and reduced cardiovascular mortality—already the leading cause of death in women. A recent patient preference study showed that most breast cancer patients would choose IORT over WB-EBRT even if it were associated with a 10-year 2.3% higher absolute risk of local recurrence [41]. Medical oncologists routinely offer women similar choices when they empower their patients to choose between endocrine therapy alone or endocrine therapy combined with chemotherapy, a decision that has not only impacts local recurrence risk but also affects overall survival. Given this precedent, physician should feel empowered to extend to well-informed patients the option of intraoperative radiotherapy for the management of well-selected invasive breast cancers.

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