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A prospective phase I comparison of toxicity and cosmesis outcomes of single-fraction IORT and hypofractionated radiotherapy with IORT boost in early-stage breast cancer

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ABSTRACT

PURPOSE: Radiation therapy is proven to reduce local recurrence in patients with early-stage breast cancer. To reduce toxicity, treatment time, and improve accuracy, intraoperative radiation therapy was used as definitive treatment or as a boost. The study's objective was to compare the short-term toxicity and cosmesis of single-fraction (SF) IORT and hypofractionated radiotherapy with IORT boost (HfB) given as definitive treatment.

METHODS AND MATERIALS: Between March 2011 and December 2013, 57 patients aged 45–91 years and 24 patients aged 43–83 years (total $n = 81$) with Stage 0–II were treated with SF or HfB (Mobetron, IntraOp Medical, Sunnyvale, CA). For SF treatment, 21 Gy was delivered using 4.5–6 cm applicators with electron energies from 6 to 12 MeV. For HfB, an intraoperative boost of 10 Gy was delivered using 4–7 cm applicators with energies from 4 to 12 MeV followed by whole-breast radiation with 40.5 Gy over 15 fractions. Toxicity was assessed at 2 weeks, 6 months, and 12 months per Radiation Therapy Oncology Group acute skin toxicity criteria and cosmesis.

RESULTS: At 12 months, SF and HfB were well tolerated by all patients with no Grade 3+ toxicity. At 1 year, Grade-2 toxicity was resolved. Ninety-eight percent of SF patients and ninety percent of HfB patients had 0–1 grade toxicity. In the SF and HfB groups, 100% of patients had excellent or good cosmesis at 12-month followup interval. The SF exhibited a more favorable cosmesis with a higher percentage of excellent scores compared with HfB (80.4% vs. 45%; $p = 0.0033$).

CONCLUSIONS: After breast conservation surgery, SF or HfB may be an option for patients with early-stage breast cancer compared to conventional external beam radiotherapy.

Keywords: IORT; Cosmesis; Toxicity; Hypofractionation; Breast cancer

Introduction

The conventional treatment of early-stage invasive breast cancer is breast-conserving surgery (BCS) followed by 5–6 weeks of 45–50 Gy external whole-breast radiation therapy (WBRT). This may be followed by an additional 10–16 Gy external radiation boost dose to the tumor bed, which significantly reduces local recurrence rates. WBRT substantially decreases the risk of local recurrence; it is occasionally accompanied by acute and chronic toxicities, which result in change in the overall breast appearance and sensory morbidity. Side effects such as dermatitis, hyperpigmentation and volume loss in the treated breast contribute to breast cosmesis (1). The major sensory toxicity includes firmness, soreness, and intermittent pain.

In Canada and the United Kingdom, alternative schedules using adjuvant radiotherapy that offers more convenient, shorter schedules of external beam radiotherapy have been introduced. The 10-year results report that local tumor control and breast cosmesis were no worse with a 3-week hypofractionated regimen compared with conventional treatment (2–4).

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One example of a shorter method of delivering adjuvant radiotherapy is hypofractionated radiotherapy with a intraoperative boost (HfB). This is defined as hypofractionated WBRT (40.5 Gy in 2.7 Gy per fraction) given over a period of 3 weeks. This is preceded by an intraoperative boost to the tumor bed (10-Gy intraoperative radiation therapy [IORT]), given *in lieu* of the standard external radiation boost. HfB effectively decreases treatment time by 3 weeks compared to conventional treatment.

The outcomes of numerous clinical trials and observational studies have revealed that roughly 90% of local recurrences after BCS occur within the same quadrant of the breast where the primary tumor originated (index quadrant) (5, 6). This finding challenges the idea that WBRT is essential in the management of breast cancer patients and suggests that targeted radiotherapy to the index quadrant of the breast would be adequate for local control in selected patients (7).

Accelerated partial-breast irradiation (APBI) is the delivery of radiation therapy to the area of the breast where the tumor was initially plus a margin of 1–2 cm of tissue surrounding the lumpectomy cavity. One such example of an APBI technique is IORT. IORT during BCS is the ability to deliver a single high dose to the area at highest risk for subclinical tumor cell contamination with utmost precision due to direct visualization (8). In highly selected patients, single-fraction (SF) IORT may be considered as an alternative to conventional external beam radiotherapy. Such a treatment protocol offers the advantage to considerably decrease normal tissue toxicity by decreasing radiation to the skin and adjacent normal breast and surrounding tissue.

Limited prospective comparative data are available with regard to toxicity and cosmesis outcomes among these newer fractionation schedules for the management of breast cancer (9). In Europe, the International Society of Intraoperative Radiation Therapy European section (ISIORT-Europe) pooled analysis and TARGIT-A report late toxicity and fibrosis of 3.9% and 37.5%, respectively (10, 11).

In our Phase I study, the primary objective is the prospective assessment of the early toxicity and cosmetic outcome for patients with early-stage breast cancer who received adjuvant radiotherapy using either an SF or HfB treatment schedule. If favorable toxicity and cosmesis outcomes are observed, these SF and HfB schedules may be incorporated into practice while offering a more convenient and efficient treatment compared to conventional therapy.

Methods and materials

Patient selection

From March 2011 to December 2013, patients eligible for breast-conserving therapy were enrolled in a Phase I study in which adjuvant radiation therapy was given using SF or HfB (Table 1). There were 57 SF and 24 HfB consecutive patients included in this study.

Surgery and IORT procedure

For patient treated under SF protocol, partial mastectomy was performed with an incision centered over the tumor or periareolar region. On a selective basis, a pathologist performed a microscopic assessment of margins after excision based on preoperative imaging, tumor localization, and/or palpation. Specimen radiography was performed on all excised breast tissues. Sentinel axillary lymph node dissection was carried out in all patients with invasive disease. Patients with ductal carcinoma *in situ* did not undergo nodal evaluation. After tumor removal, the tissue surrounding the excision cavity was mobilized. A 1 cm copper shield was placed between the treatment volume and the chest wall. This tissue was temporarily approximated using sutures into the radiation's planned target volume (PTV). PTV is defined as a 3D volume of 1–2 cm beyond the former macroscopic tumor edge. For patients treated under the SF protocol, 21 Gy was applied to the 90% reference isodose, using a cone with diameters of 4–7 cm and electron energies in the range of 6–12 MeV. Intraoperative ultrasound or direct measurement was used to determine the depth to the chest wall and target volume. The appropriate radiation energy was selected based on these measurements.

For patients treated under the SF protocol, IORT was delivered using a mobile device (Mobetron, IntraOp Medical, Sunnyvale, CA). Nanodots (GP nanoDot Landauer, Inc., Glenwood, IL) were used to measure the dose at the superficial and deep tissue plane. After IORT, the sutures used to approximate the tissue were removed, and the surgeon completed the operative procedure. Tumor cavity remodeling was done with oncoplastic techniques per the surgeon's preference.

For patients treated with the hypofractionation protocol, IORT was delivered using a mobile device (Mobetron, IntraOp Medical) with variable electron energies in the range of 4–12 MeV. A dose of 10 Gy was specified as maximum, with a minimum target volume dose of 90% encompassing the PTV. After IORT, closure was performed in a similar manner as stated previously. The margins of the resected specimen must be histologically free of tumor per National Surgical Adjuvant Breast and Bowel Project (NSABP) definition (12).

After wound healing, WBRT was initiated within 14–56 days postoperatively (Weeks 2–8 post-op). This entailed giving 15 fractions over 3 weeks. Each fraction dose is 2.7 Gy. The total dose administered was 50.5 Gy (40.5 WBRT + 10-Gy IORT boost).

Followup examinations

Patients were evaluated for radiation toxicity at 2 weeks, 6 months, and 12 months after completion of their radiation therapy. The assessment of breast irradiation toxicity was made according to the Radiation Therapy Oncology Group (RTOG) acute (2 weeks) and late (6 and 12 months)

radiation morbidity scoring criteria for breast skin as shown in Appendix A1.

Cosmetic evaluations were made at 2 weeks, 6 months, and 12 months after completion of radiotherapy using the Harvard/NSABP/RTOG Breast Cosmesis Grading Scale derived for national trials. Cosmesis scores ranged from "poor" to "excellent" as described in Appendix A2. All comparisons (except 12 month cosmesis) used Fisher's exact test. At the 12 month follow up, *p*-value for cosmesis was obtained with the chi square test.

Theory/dose specification/calculation

The mobile Mobetron IORT unit makes use of the shallow penetration characteristics of electron beam radiation with a fast dose drop-off to protect the underlying normal tissue (such as muscle, heart, lung and ribs). Energies typically used include 6 MeV, 9 MeV, and 12 MeV. Applicator cones of various diameters (3–10 cm) and various angles (0°, 15°, or 30°) of beveling are used to confine the beam to the volume of interest within the surgical area. Additional beam modifiers such as bolus or shielding are used as needed either to reduce beam penetration or to shield critical structures. During commissioning of the mobile unit, full-beam characteristic profiles (depth dose, cross-plane, and leakage profiles) for each energy and applicator are acquired, as well as other essential dosimetry factors (applicator factors, air gap factors) and output calibration. These data are tabulated for use in determining the needed energy, cone, and beam modifiers to achieve the desired dose prescription once characterization of the treatment volume is determined.

Dose prescription is typically defined at the 90% isodose line that covers the target volume. The mobile IORT unit has favorable dose characteristics for delivery of a uniform dose within an operating field. As shown and discussed in the Task Group 72 report, the depth–dose curves of the mobile unit have a higher surface dose to that of a standard linear accelerator due to the greater number of energy-degraded, scattered electrons in the beam. In addition, beam flatness and symmetry profiles taken at dmax have smaller horns than typical linear accelerators due to the differences in the source-to-surface distance variation and the scattering foil design.

Results

Patient demographics

From March 2011 to December 2013, a total of 81 patients were enrolled. The demographics and clinical disease characteristics of the patient population are summarized in Table 2.

For analysis, there were a total of 59 breasts (57 patients) treated with SF IORT and 24 breasts treated with HfB. The mean age of the SF patients was significantly older than that of the HfB group ($p = 0.017$). The tumor types treated did not differ between the groups, whether looking at individual or grouped tumor types, $p = 0.73$ and $p = 0.59$, respectively. There was no difference in the number of breasts that underwent oncoplastic reconstruction ($p = 0.58$), nor the number of breasts with positive margins after surgery ($p = 1.00$). There was a higher percentage of breasts that received an MRI before surgery in SF vs. HfB treatments with a *p*-value approaching significance ($p = 0.064$). Average tumor size did not differ between the groups ($p = 0.17$). Finally, mean followup time differed between the groups. Mean HfB followup time was significantly longer than that of SF at 1082.9 vs. 683.7 days ($p < 0.0001$).

Of the 59 SF cases, eight were ultimately lost to follow-up by 12 months.

Table 1
Inclusion criteria

Single-fraction inclusion criteria	Hypofractionation inclusion criteria
• Histological-proven invasive breast carcinoma ductal, lobular, and/or DCIS	• Histological-proven invasive breast carcinoma (ductal and lobular)
• Age >40 years	• Age >40 years
• Karnofsky performance status >70%	• Karnofsky performance status >70%
• Tumor: single discrete tumor or focal microcalcifications that can be imaged on a specimen radiograph or multifocal disease within the same quadrant with a maximum dimension of equal to or less than 2.5 cm	• Tumor: single discrete tumor or focal microcalcifications that can be imaged on a specimen radiograph or multifocal disease within the same quadrant with a maximum dimension of 4 cm (invasive foci)
• Nodal status: preoperative N0	• Nodal status: N0–1
• Clear surgical margins: R0	• Clear surgical margins: R0. Reexcision after IORT is permitted but not required to achieve (–) margin
• All grades: G1–G3	• All grades: G1–G3
• Any hormonal receptor and HER2 status	• Any hormonal receptor and HER2 (HER2/neu) status
• Informed consent	• Informed consent

DCIS = ductal carcinoma *in situ*;
IORT = intraoperative radiation therapy.

Table 2
Demographics and descriptive statistics

	Single fraction	Hypofractionation	
	$N \pm$ SD (range)		p-value
Total patients	57	24	
Total treatments given	59[a]	24	
Patient age at date of surgery/IORT	67.1 ± 10.9 (45–91)	60.8 ± 10.1 (43–83)	0.017
Total tumors by dominant histology			0.59[b]
Invasive ductal carcinoma	42	21	
Invasive lobular carcinoma	3	0	
DCIS	13	3	
Other	1	0	
Total breasts that received MRI before surgery	50	17	0.064
Operation			
Partial mastectomy	14	3	
Partial mastectomy with sentinel lymph node biopsy	45	20	
Partial mastectomy with axillary node dissection	0	1	
Total breasts that had oncoplastic reconstruction	31	11	0.58
Final tumor size (mm)	13.8 ± 9.8 (1.5–70)	16.9 ± 8.2 (1–38)	0.17
Total SLN biopsies			
Negative	40	16	
Positive	4	4	
Total breasts with positive margins after surgery	3	1	1.00[b]
Total breasts that underwent additional surgeries			
Yes	4	1	
No	55	23	
Followup time (d)	683.7 ± 195.7 (391–1020)	1082.9 ± 269.9 (484–1392)	<0.0001

IORT = intraoperative radiation therapy; DCIS = ductal carcinoma *in situ*.
[a] Two patients with bilateral lesions.
[b] Fisher's exact test used to obtain p-value.

For the SF group, 51.7%, 41.4%, and 6.9% had an acute toxicity score of 0, 1, and 2, respectively, at 2 weeks' postradiation treatment. Toxicity and cosmesis was recorded by the treating radiation oncologist. At 6 months' postradiation treatment, 70.4%, 29.6%, and 0% had a late toxicity score of 0, 1, and 2, respectively. At 12 months' postradiation treatment, 68.6%, 29.4%, and 2.0% had a late toxicity score of 0, 1, and 2, respectively (see Table 3).

At 2 weeks' postradiation treatment, 69.0%, 29.3%, and 1.7% of patients had a cosmetic appearance of excellent, good, and fair, respectively. At 6 months' postradiation treatment, 85.2%, 14.8%, and 0% had a cosmetic appearance of excellent, good, and fair, respectively. At 12 months' postradiation treatment, 80.4%, 19.6%, and 0% had a cosmetic appearance of excellent, good, and fair, respectively (see Table 3).

Of the 24 hypofractionation cases, four were ultimately lost to followup by 12 months.

Of the patients with followup, 47.8%, 47.8%, and 4.4% of patients had a toxicity score of 0, 1, and 2, respectively, at 2 weeks' postradiation treatment. At 6 months' postradiation treatment, 40%, 50%, and 10% had a toxicity score of 0, 1, and 2, respectively. At 12 months' postradiation treatment, 50%, 40%, and 10% had a toxicity score of 0, 1, and 2, respectively (see Table 3).

Table 3
Single fraction vs. hypofraction toxicity and cosmesis outcomes

	Two weeks: N (%)		Six months: N (%)		Twelve months: N (%)	
	SF	HfB	SF	HfB	SF	HfB
Toxicity grade						
0	30 (51.7)	11 (47.8)	38 (70.4)	8 (40)	35 (68.6)	10 (50)
1	24 (41.1)	11 (47.8)	16 (29.6)	10 (50)	15 (29.4)	8 (40)
2	4 (6.9)	1 (4.4)	0 (0)	2 (10)	1 (2.0)	2 (10)
Cosmesis						
Excellent	40 (69.0)	15 (65.2)	46 (85.2)	12 (60)	41 (80.4)	9 (45)
Good	17 (29.3)	8 (34.8)	8 (14.8)	7 (35)	10 (19.6)	11 (55)
Fair	1 (1.7)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)

SF = single fraction; HfB = hypofractionated radiotherapy with IORT boost.

Table 4
Single fraction vs. hypofraction outcomes

	Two weeks (%)			Six months (%)			Twelve months (%)		
	SF	HfB	*p*-value[a]	SF	HfB	*p*-value[a]	SF	HfB	*p*-value[a]
Toxicity grade									
0	51.7	47.8	0.92[a]	70.4	40	0.013[a]	68.6	50	0.16[a]
1	41.4	47.8		29.6	50		29.4	40	
2	6.9	4.4		0.0	10		2.0	10	
Cosmesis									
Excellent	69.0	65.2	0.85[a]	85.2	60.0	0.029[a]	80.4	45.0	0.0033[b]
Good	29.3	34.8		14.8	35.0		19.6	55.0	
Fair	1.7	0.0		0.0	5.0		0.0	0.0	

SF = single fraction; HfB = hypofractionated radiotherapy with IORT boost.
[a] *p*-values obtained using Fisher's exact test due to low cell counts.
[b] *p*-value obtained with χ^2 test.

At 2 weeks' postradiation treatment, 65.2%, 34.8%, and 0% of patients had a cosmetic appearance of excellent, good, and fair, respectively. At 6 months' postradiation treatment, 60%, 35%, and 5% had a cosmetic appearance of excellent, good, and fair, respectively. At 12 months' postradiation treatment, 45%, 55%, and 0% had a cosmetic appearance of excellent, good, and fair, respectively (see Table 3).

The data show that there is no difference in the toxicity grades for the SF and HfB groups at the 2-week followup period ($p = 0.92$), but there is a significant difference at the 6-month followup period ($p = 0.013$). At 6 months, there are a greater proportion of lower toxicity grades in the SF group than in the HfB group. This difference disappears at the 1-year followup. Cosmesis grades at 2 weeks show no difference between groups ($p = 0.85$), but they differ significantly at the 6- and 12-month followup time points ($p = 0.029$ and $p = 0.0033$, respectively), with the SF group having more favorable cosmesis findings than the HfB group (Table 4).

Discussion

To gain experience with the technique of breast IORT using electrons in the initial stages, the protocol was designed with an IORT boost and followed by adjuvant whole-breast radiation using a standard fractionation scheme over 5.5 weeks. Subsequently, the HfB and SF protocols were developed and activated after an approval by an institutional review board. The inclusion criteria for these studies were derived from the APBI experience in regard to patient eligibility and recruitment. An IORT boost was included in the HfB protocol based on several clinical trials demonstrating improvement in local recurrence rates (5, 10, 12). Finally, IORT was offered in the SF format in selected patients. Toxicity and cosmesis were evaluated and reported using the RTOG radiation morbidity scoring criteria and NSABP protocol B-39 cosmesis evaluation scale (12). This allowed for consistency in review and scoring and comparisons to other studies with similar end points.

It was anticipated that the HfB group would have a greater skin toxicity compared to the SF treatment group. The radiation delivered in the HfB group included a total dose of 50.5 Gy (40.5 WBRT + 10-Gy IORT boost) while the SF group received 21 Gy. At 2 weeks, there was no difference in the toxicity grades of the SF and HfB groups ($p = 0.92$); however, there was a significant difference at 6 months ($p = 0.013$) favoring the SF group. At 6 months' postradiation treatment, the SF toxicity scores were Grade 0 (70.4%), Grade 1 (29.6%), and Grade 2 (0%). In comparison, the HfB group had toxicity scores of Grade 0 (40%), Grade 1 (50%), and Grade 2 (10%). This difference disappeared at 1 year of followup ($p = 0.16$). Of the 83 total breasts treated, no patient had an acute or late toxicity grade of 3 or 4. These minimal rates of high-grade toxicity are consistent with those reported in similar hypofractionation trials (13, 14). Despite the higher toxicity seen at the 6-month mark for the HfB group, this difference disappears at 12 months suggesting resolution from the acute side effects. It is anticipated after radiation treatment that patients receiving both intraoperative and external radiation (HfB) may experience increased long-term toxicity compared to those receiving the SF treatment.

In both the U.K. START A and START B trials, a 10-Gy tumor bed boost delivered in five fractions was used in 61% and 43%, respectively. Moderate or marked breast shrinkage, induration, telangiectasia, and breast edema were significantly lower in the hypofractionated regimen compared to standard fractionated group (15). Our short-term toxicity and cosmetic results in the HfB group seem to parallel those seen in respect to change in breast appearance in other reported hypofractionated trials.

In the recent 5-year update comparing IORT to conventional external beam radiotherapy in TARGIT-A and ELIOT trials, the skin side effects including erythema, dryness, and hyperpigmentation were less in the IORT group. There were few Grades 3 and 4 radiotherapy–related skin complication reported (16, 17). At 12 months, no Grade 3 or 4 toxicity was identified.

ISIORT-Europe published a pooled analysis including 1109 patients among seven centers that received intraoperative electron radiotherapy 10-Gy boost preceded by whole-breast irradiation (WBI) with 50–54 Gy. Sixteen in-breast recurrences were found, yielding an in-breast tumor control rate of 92.2% at 73.3 months. Their reported frequency of any complications and major toxicity was similar to that of the TARGIT trial (3.3% TARGIT vs. 3.9% WBI) (10).

Valente *et al*. reported the TARGIT-R (retrospective) North American experience with IORT using low-kilovoltage X-rays in which 14% received a planned boost followed by WBI. The complication rates were similar to that of the TARGIT-A trial (18).

Recently, The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology published the 5-year results of APBI using sole interstitial multicatheter brachytherapy vs. WBI with boost after BCS. There was no significant difference in the incidence of local recurrence; it was 1.44% vs. 0.92% with APBI vs. WBI, respectively. No Grade 4 late side effects were reported. The 5-year risk of Grades 2–3 late side effects to the skin was 3.2% with APBI vs. 5.7% with WBI ($p = 0{\cdot}08$), and 5-year risk of Grades 2–3 subcutaneous tissue late side effects was 7.6% vs. 6.3% ($p = 0{\cdot}53$). The risk of severe (Grade 3) fibrosis at 5 years was 0.2% with WBI and 0% with APBI ($p = 0{\cdot}46$). Our results appear to parallel other shortened courses of breast radiotherapy for early-stage breast cancer; however, continued longer followup is necessary (19).

Ongoing trials including the prospective, randomized TARGIT-B (Boost) comparing TARGIT IORT Boost to an external beam boost have been initiated. More than 20 centers have already started recruiting, and 1800 young or high-risk patients will be included (https://clinicaltrils.gov/ct2/show/NCT01792726) (20).

In addition, in an attempt to further reduce overall treatment, the hypofractionated whole-breast irradiation preceded by intraoperative radiotherapy with electrons as anticipated boost trial was initiated by the ISIORT. In this trial, 10-Gy intraoperative electron radiotherapy boost is combined with hypofractionated WBI 15 × 2.7 Gy for Stage I/II breast cancer (http://www.clinicaltrials.gov/ct2showNCT01343459?term=hiob&rank=1). (21).

Surgical techniques and the delivery of radiation are likely to have effects on the cosmetic outcome. At 2 weeks' postradiation treatment, there was no difference in cosmesis grades between each group ($p = 0.85$); however, they differ significantly at the 6- and 12-month followup time points ($p = 0.029$ and $p = 0.0033$, respectively), with the SF group yielding a more favorable cosmesis than the HfB group. At 6 months' postradiation treatment, SF cosmesis scores were excellent (85.2%), good (14.8%), and fair (0%) and HfB scores were excellent (60%), good (35%), and fair (5%). At 12 months' postradiation treatment, the SF cosmesis scores were excellent (80.4%), good (19.6%), and fair (0%), whereas HfB cosmesis scores were excellent (45%), good (55%), and fair (0%). When cosmesis was analyzed, tumor size although numerically different did not hold statistical significance ($p = 0.17$). Therefore, a cosmetic difference in one group cannot be attributed to a larger surgical incision, which can result in greater thickening and scar tissue formation. Furthermore, the difference in cosmetic outcome cannot be due to a larger amount of breast tissue removal, which would result in a greater difference in the shape or size between the treated and untreated breast. The number of breasts that underwent oncoplastic reconstruction was balanced in both groups (SF-52.5%; HfB-45.8%). If this number was unbalanced favoring either group, a concern would be raised that oncoplastic reconstruction not the radiation approach contributed to the more favorable cosmetic outcome in the SF group at the 6- and 12-month followup intervals.

The American Society of Radiation Oncology has recently published an update to its consensus statement on APBI and confirmed the use of electron beam IORT as an effective modality for the treatment of suitable patients with invasive breast cancer (22) (see Appendix A3).

This new milestone allows IORT with electron beam treatment to replace 6 weeks of conventional, postoperative external beam X-ray radiation of the entire breast. For qualified patients with breast cancer, this means potentially a shorter treatment and recovery, fewer side effects, and improved quality of life. Patients meeting criteria for treatment with IORT generally have a low absolute risk of ipsilateral breast tumor recurrence, yet this risk persists over a long period, likely at least 10 years. These biologic considerations coupled with the current followup reported from the ELIOT and TARGIT trials; it is recommended that patients treated with IORT undergo routine long-term followup for at least 10 years to screen for ipsilateral breast tumor recurrence (22).

Conclusion

Patients with breast cancer have many options for treatment, each option with associated benefits and risks. These newer techniques and alternative schedules using adjuvant radiotherapy to selected breast cancer patients offer a number of key advantages over conventional external beam radiotherapy. Shorter treatment times, patient convenience, and favorable cosmetic and toxicity outcomes are important considerations when individualizing breast cancer treatment in women. The findings of this study demonstrate that there is a more favorable cosmetic outcome at 6 and 12 months' postradiation treatment in those treated with SF compared to HfB. Grade 3 and Grade 4 toxicities were not observed in the present study. These findings support that these newer techniques are safe.

Compared to a 5- to 6-week course of conventional radiotherapy, it has been reported that a shorter course of

APBI will improve patient satisfaction and overall quality of life, potentially minimizing psychological and physical strain associated with radiation treatment (23).

Finally, IORT allows for smaller treatment volumes and complete skin sparing, both having positive impact on late tissue toxicity and hence overall cosmesis. Further analysis with long-term followup will assist with individualizing radiation therapy for patients with early-stage breast cancer.

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References

[1] Van de Steene J, Vinh-Hung V, Cutuli B, *et al*. Adjuvant radiotherapy for breast cancer: Effects of longer follow-up. *Radiother Oncol* 2004; 72:35–43.

[2] The START Trialists' GroupBentzen SM, Agrawal RK, Arid EG, *et al*. The UK standardisation of breast radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet Oncol* 2008;9:331–341.

[3] The START Trialists' GroupBentzen SM, Agrawal RK, Arid EG, *et al*. The UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet* 2008;371:1098–1107.

[4] Whelan T, Pignol JP, Levine MN, *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513–520.

[5] Holland R, Veling SH, Mravunac M, *et al*. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56:979–990.

[6] van Limbergen E, van den Bogaert W, van der Schueren E, *et al*. Tumor excision and radiotherapy as primary treatment of breast cancer. Analysis of patient and treatment parameters and local control. *Radiother Oncol* 1987;8:1–9.

[7] Keshtgar M, Wenz F. *Targeted intraoperative radiotherapy in oncology*. 1st ed. New York: Springer; 2014. p. 1–2. Targeted intraoperative radiotherapy: concept and review of evidence in breast c.

[8] Sedlmayer F, Reitsamer R, Wenz F, *et al*. Intraoperative radiotherapy (IORT) as boost in breast cancer. *Radiat Oncol* 2017;12:23.

[9] Raza S, Lymberis SC, Ciervide R, *et al*. Comparison of acute and late toxicity of two regimens of 3- and 5-week concomitant boost prone IMRT to standard 6-week breast radiotherapy. *Front Oncol* 2012;2:44.

[10] Fastner G, Sedlmayer F, Merz F, *et al*. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis. *Radiother Oncol* 2013;108:279–286.

[11] Sperk E, Welzel G, Keller A, *et al*. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: Results from the randomized phase III trial TARGIT A. *Breast Cancer Res Treat* 2012;135:253–260.

[12] NSABP Protocol B39-RTOG Protocol 0413. A randomized Phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with Stage 0, I, or II breast cancer. Available at: www.clinicaltrials.gov. Accessed August 30, 2017.

[13] Ivaldi GB, Leonardi MC, Orecchia R, *et al*. Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. *Int J Radiat Oncol Biol Phys* 2008;72:485–493.

[14] Sawaki M, Sato S, Noda S, *et al*. Phase I/II study of intraoperative radiotherapy for early breast cancer in Japan. *Breast Cancer* 2011; 19:353–359.

[15] Haviland J, Owen J, Dewar J, *et al*. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–1094.

[16] Vaidya J, Wenz F, Bulsara M, *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomized trial. *Lancet Oncol* 2014;383:603–613.

[17] Veronesi U, Orecchia R, Maisonneuve P, *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomized controlled equivalence trial. *Lancet Oncol* 2013;14:1269–1277.

[18] Valente SA, Tendulkar RD, Cherian S, *et al*. SR. TARGIT-R (retrospective): North American experience with intraoperative radiation using low-kilovoltage x-rays for breast cancer. *Ann Surg Oncol* 2016;23:2809–2815.

[19] Strnad V, Ott OJ, Hildebrandt G, *et al*., Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016;387:229–238.

[20] TARGIT-B no study results posted yet. Available at: https://clinicaltrials.gov/ct2/show/NCT01792726. Few articles that mention this trial but not presenting results. Accessed August 30, 2017.

[21] HIOB no study results posted yet. Available at: https://clinicaltrials.gov/ct2/show/NCT01343459. Few articles that mention this trial but not presenting results. Accessed August 30, 2017.

[22] Correa C, Harris E, Leonardi M, *et al*. Accelerated partial breast irradiation executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017;7:73–79.

[23] Kawase E, Karasawa K, Shimotsu S, *et al*. Estimation of anxiety and depression in patients with early stage breast cancer before and after radiation therapy. *Breast Cancer* 2012;19:147–152.

Appendix 1
Radiation Therapy Oncology Group (RTOG) acute (2 weeks) and late (6 and 12 months) radiation morbidity scoring criteria

RTOG acute radiation morbidity scoring criteria				
0	1	2	3	4
No change over baseline	Follicular, faint, or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
RTOG/EORTC late radiation morbidity scoring schema				
0	Grade 1	Grade 2	Grade 3	Grade 4
None	Slight atrophy pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration

Appendix 2
Harvard/NSABP/RTOG Breast Cosmesis Grading Scale

Cosmesis grade	Description
Excellent	Compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast but not enough to change the appearance.
Good	There is a slight difference in the size or shape of the treated breast compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
Fair	Obvious difference in the size and shape of the treated breast. This changes a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
Poor	Marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

Accelerated partial-breast irradiation: executive summary for the update of an American Society of Radiation Oncology evidence based consensus statement

"Electron beam IORT should be restricted to women with invasive cancer considered 'suitable' for partial-breast irradiation (Appendix A3) based on the results of a multivariate analysis with median followup of 5.8 years" (Moderate quality of evidence [MQE] recommendation rated as 'Strong', 100% agreement).

Appendix 3
Comparison of patients in the original and updated consensus statement

Patient group	Risk factor	Original	Update
Suitable	Age	≥60 years	≥50 years
	Margins	Negative by ≥2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50–59 years	• 40–49 years if all other criteria for "suitable" are met • ≥50 years if the patient has at least one of the following pathologic factors and does not have any "unsuitable" factors Pathologic factors: • Size 2.1–3.0 cm • T2 • Close margins (<2 mm) • Limited/focal lymph-vascular space invasion • Estrogen receptor negative • Clinically unifocal with total size 2.1–3.0 cm • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" are not fully met • Extensive intraductal component ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 years • 40–49 years and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

DCIS = ductal carcinoma *in situ*.