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Clinical Investigation

A Novel Form of Breast Intraoperative Radiation Therapy With CT-Guided High-Dose-Rate Brachytherapy: Results of a Prospective Phase 1 Clinical Trial

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Summary

Intraoperative radiation therapy (IORT) is an emerging treatment method for breast cancer; however, existing IORT techniques lack image guided treatment planning and use low-energy photons, thus resulting in poor dosimetry and low radiation dose. We pioneered a novel method of IORT that incorporates customized computed tomography (CT)-based treatment planning and high-dose-rate (HDR) brachytherapy to overcome

Purpose: Existing intraoperative radiation therapy (IORT) techniques are criticized for the lack of image guided treatment planning and energy deposition with, at times, poor resultant dosimetry and low radiation dose. We pioneered a novel method of IORT that incorporates customized, computed tomography (CT)-based treatment planning and high-dose-rate (HDR) brachytherapy to overcome these drawbacks: CT-HDR-IORT.

Methods and Materials: A phase 1 study was conducted to demonstrate the feasibility and safety of CT-HDR-IORT. Eligibility criteria included age $\geq$50 years, invasive or in situ breast cancer, tumor size $<$3 cm, and N0 disease. Patients were eligible before or within 30 days of breast-conserving surgery (BCS). BCS was performed, and a multilumen balloon catheter was placed. CT images were obtained, a customized HDR brachytherapy plan was created, and a dose of 12.5 Gy was delivered to 1-cm depth from the balloon surface. The catheter was removed, and the skin was closed. The primary endpoints were feasibility and acute toxicity. Feasibility was defined as IORT treatment interval (time from CT acquisition until IORT completion) $\leq$90 minutes. The secondary endpoints included dosimetry, cosmetic outcome, quality of life, and late toxicity.

Results: Twenty-eight patients were enrolled. The 6-month follow-up assessments were completed by 93% of enrollees. The median IORT treatment interval was 67.2 minutes

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these drawbacks: CT-HDR-IORT. Our phase 2 study supports CT-HDR-IORT as a feasible and safe treatment for breast cancer.

(range, 50-108 minutes). The treatment met feasibility criteria in 26 women (93%). The dosimetric goals were met in 22 patients (79%). There were no Radiation Therapy Oncology Group grade 3+ toxicities; 6 patients (21%) experienced grade 2 events. Most patients (93%) had good/excellent cosmetic outcomes at the last follow-up visit.
Conclusions: CT-HDR-IORT is feasible and safe. This promising approach for a conformal, image-based, higher-dose breast IORT is being evaluated in a phase 2 trial.
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Introduction

Large randomized clinical trials have established that mastectomy and breast conserving therapy (BCT; lumpectomy and adjuvant radiation therapy) provide equivalent survival for the treatment of early-stage breast cancer (1-7). Lumpectomy without adjuvant radiation therapy is associated with an increased rate of recurrence and mortality (1, 8-10). Since the acceptance of BCT as the preferred management of breast cancer by the National Institutes of Health in 1990 (11), there have been a series of clinical advances aimed at reducing the volume of breast tissue irradiated (partial breast irradiation), the duration of radiation therapy (hypofractionated irradiation) (12), or both (accelerated partial breast irradiation; APBI) (13). The results of the National Surgical Breast and Bowel Project (NSABP) B-39, designed to assess the long-term efficacy of APBI, are forthcoming. However, APBI in appropriately selected patients is included in the most recent National Comprehensive Cancer Center Network guidelines (14).

High rates of good to excellent cosmetic outcomes—over 90%—have also been reported after breast conserving therapy with APBI (15).

Intraoperative radiation therapy (IORT), which consists of a single fraction of radiation given intraoperatively to the lumpectomy bed and adjacent breast tissue, has developed as an extension of APBI with emphasis on reducing treatment time and sparing normal tissue. In recent years, 2 distinct techniques for IORT have been prospectively assessed in large randomized trials and have demonstrated acceptable recurrence rates when patients are selected appropriately, although follow-up times remain short (16, 17). The intraoperative radiation therapy with electrons (ELIOT) trial used electrons to deliver a dose of 21 Gy to the lumpectomy bed (including to the tissue 1 cm from the lumpectomy cavity). With a median follow-up time of 5.8 years, the 5-year recurrence rate was 4.4% for ELIOT versus 0.4% ($P<.0001$) for whole breast irradiation (WBI). A low-risk ELIOT subgroup was identified with a 5-year recurrence rate of 1.5% after IORT (17). The targeted intraoperative radiation therapy trial (TARGIT) used 50-kV X rays to deliver 20 Gy to the surface of the lumpectomy bed (5-7 Gy to 1 cm depth). With a median follow-up time of 29 months, the 5-year recurrence rates for the TARGIT versus WBI patients were 3.3% and 1.3%, respectively ($P=.042$) (18). Despite these relatively favorable clinical results, there are several well-recognized limitations to available forms of IORT. Most important are the lack of intraoperative imaging (which can be used for catheter placement confirmation, target delineation, and to simulate/optimize radiation therapy delivery) and the poor dosimetry resulting from the physical limitations of low-energy photons (19, 20). We sought to improve on these technical limitations by devising a novel form of IORT at our institution that incorporates 3-dimensional treatment planning, image guidance, and higher prescription dose.

We developed a novel form of breast IORT that is composed of high-dose-rate (HDR) brachytherapy delivered through a multicatheter brachytherapy balloon, with computed tomography (CT)-based treatment planning through an in-room CT-on-rails unit (CT-HDR-IORT). Intraoperative imaging of any modality is uncommon in breast IORT, and no other systems use CT-based imaging. The CT images provide the ability to evaluate applicator placement and facilitate customized treatment planning (21). Compared with other forms of IORT, HDR brachytherapy allows for superior target volume coverage and a higher prescription dose delivered to the adjacent breast tissue without excessive balloon surface dose (20). A multichannel brachytherapy balloon allows computerized optimization of the dose on the CT dataset so that the dose delivered to critical structures (skin, ribs, heart, and chest wall) is within tolerance while not sacrificing coverage of the target volume (20). To demonstrate the feasibility and safety of CT-HDR-IORT in partial breast irradiation, we conducted a phase 1 trial of this novel approach.

Methods and Materials

Eligibility criteria

Twenty-eight patients were enrolled in this single-arm pilot study. Eligible patients were at least 50 years old, had a new diagnosis of breast cancer, and had opted for breast conserving surgery (BCS). Patients were eligible before or within 30 days of their BCS. Patients receiving IORT after lumpectomy (but within 30 days) were part of a post-pathology cohort. To be eligible, patients were required to meet the suitable or cautionary APBI eligibility criteria proposed by the American Society of Radiation Oncology (ASTRO) (22). All patients with invasive cancer underwent sentinel node biopsy before the date of their IORT and had

pathologically confirmed benign nodes. This was done to exclude any patients ineligible for the trial before study enrollment. Exclusion criteria included patients with bilateral breast cancer or a history of ipsilateral breast cancer treated with radiation, lymph node involvement, BRCA gene mutation, and treatment with neoadjuvant therapy. The institutional review board at our center approved the design of the trial before it was initiated. The primary outcomes were safety, measured by acute toxicity, and feasibility, defined by IORT treatment interval (time from CT until end of IORT) of 90 minutes. The secondary endpoints included achievement of dosimetric goals, cosmetic outcome, late toxicity, and patient-reported quality of life (QOL).

Intraoperative radiation therapy

Figure 1 displays the trial schema. All components of the CT-HDR-IORT procedures were performed in our institution's brachytherapy suite. This is a dedicated, shielded suite with full anesthesia and HDR brachytherapy capabilities (23). Additionally, the suite contains an integrated CT-on-rails unit (Siemens Medical Solutions USA, Inc; Malvern, PA). Eligible patients were given general anesthesia. The breast surgeon performed initial BCS or re-excision of a positive margin, depending on the clinical indication. A multicatheter brachytherapy balloon was then placed into the lumpectomy bed (Contura multi-lumen, Hologic, Inc, Bedford, MA). A series of CT images was obtained using the CT-on-rails system. The images were reviewed by the breast surgeon, radiation oncologist, and medical physicist, and the balloon and breast tissue were adjusted as needed to improve tissue conformity (21). Patients participating in the trial in the postpathology cohort proceeded through the same process as above, but without BCS. Rather, the previous lumpectomy cavity was reopened, and the applicator was placed for imaging and treatment delivery as above (Fig. 1).

After image acquisition and confirmation of applicator placement, a computerized treatment plan was created and

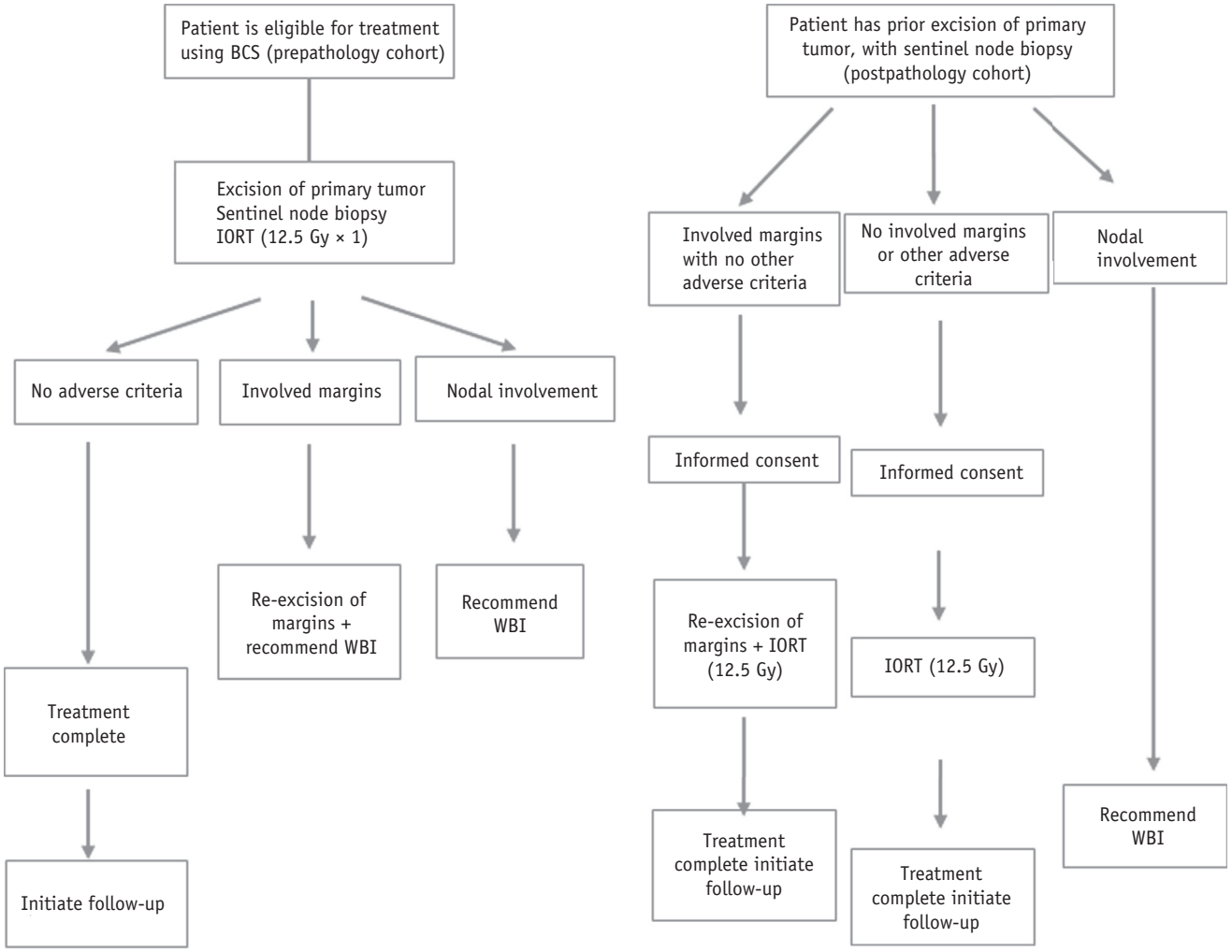

Fig. 1. Trial schema. *Abbreviations:* BCS = breast-conserving surgery; IORT = intraoperative radiation therapy; WBI = whole breast irradiation.

optimized to deliver 12.5 Gy in a single fraction to the planning target volume (PTV) with an iridium 192 HDR brachytherapy source. This dose was selected to replicate the dose delivered to the surface of the applicator using low-energy photons and, 1 cm from the surface, corresponds to an equivalent dose in 2-Gy fractions of 28.1 Gy (assuming $\alpha/\beta = 10$ for acute effects) (20). The prescribed dose was calculated in an attempt to increase the dose at a depth of 1 cm compared with the alternative low-energy kV IORT technique (16) while maintaining an acceptable dose at the applicator surface (20). The investigators chose this dose selection strategy empirically because of concerns regarding the risk of fat necrosis from high-dose volumes in breast tissue. The PTV was a volume defined as a rind of breast tissue 1 cm around the balloon surface. For dosimetric evaluation, a structure was created (PTV_eval), which was defined as the PTV structure modified to avoid overlap with ribs and air outside the patient. These definitions were modeled after the methods of the NSABP B-39 clinical trial (24). If the dose to the skin or chest wall exceeded prespecified constraints, the optimization parameters were adjusted, and the dose was recalculated to limit doses to skin and chest wall. A representative CT-HDR-IORT treatment plan is shown in Figure 2. After quality assurance checks, HDR brachytherapy was delivered according to plan. All parts of the treatment were performed without transferring or repositioning the patient from the time of CT image acquisition. After radiation therapy delivery, the applicator was removed, and the breast surgeon completed skin closure.

If, on final histopathologic evaluation, patients were found to have pathologically involved surgical margins, a re-excision lumpectomy was performed to obtain negative margins. In this situation, the protocol recommended additional WBI to a dose of 45 Gy in 25 daily fractions (Fig. 1).

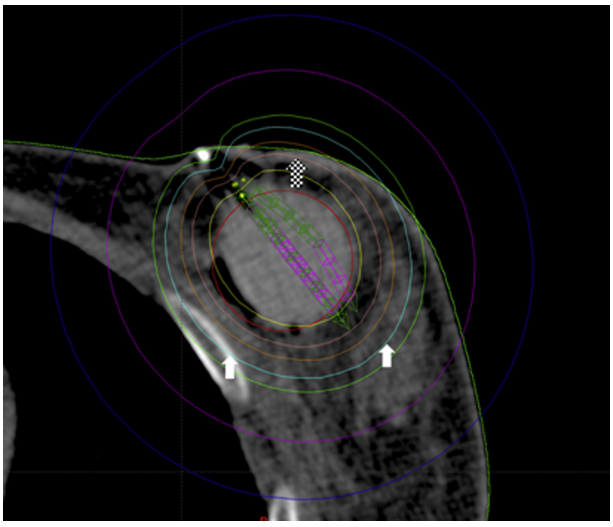

Fig. 2. Representative axial computed tomographic image of the planned high-dose-rate brachytherapy dose in a patient with left-sided breast cancer. Note that the prescription isodose line was adjusted to limit skin exposure by reducing the brachytherapy source dwell time in the channel closest to the skin surface, demonstrating the technical advantage of 3-dimensional treatment planning with a multichannel applicator. Checkered arrow: 150% isodose line. Solid white arrow: 100% (prescription) isodose line.

Data collection and endpoints

The patient- and disease-specific clinical characteristics were recorded. The primary feasibility endpoint was the IORT treatment interval, defined as the time from acquisition of the initial CT series until IORT treatment completion. For each patient, CT-HDR-IORT was deemed feasible if the IORT treatment time interval was $\leq$90 minutes. Planning time (time from CT to start of treatment delivery), radiation therapy delivery time, and total IORT procedure time were also collected. Dosimetric endpoints were collected, including the dose received by 90% of the target volume (D90), maximum skin dose, maximum heart dose, and maximum rib dose.

Patient assessments were performed at baseline, 2 to 4 weeks, 3 months, and 6 months after IORT. This included patient-reported QOL assessment using the European Organisation for Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-BR23), physician-reported toxicity, and cosmetic outcome scoring based on digital photographs compared with preoperative images (25). For each patient, a major toxicity was defined as the occurrence of skin breakdown or delayed wound healing, hematoma requiring surgical evacuation, seroma requiring more than 3 aspirations, or wound infection requiring intravenous antibiotics or surgical intervention, or any National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or 4 toxicity (26).

Statistical considerations

The trial was designed to differentiate between an acceptable major toxicity null rate of 4% compared with an unacceptable alternative rate of 8% with approximate type I and II errors of 10%, and to differentiate between an unacceptable feasibility rate of 70% versus an alternative rate of 90% with approximate type I and II errors of 10%. Safety was monitored continuously to determine whether the safety bound was crossed. A 2-stage design was used to assess feasibility after the accrual of 15 patients, with a total target accrual of 28 patients if the study did not stop early. At final analysis 23 (82%) or more study participants were required to have acceptable IORT treatment interval to have the IORT delivery system deemed feasible. Point estimates and 90% confidence intervals (CI) were used to summarize overall toxicity and feasibility rates. Medians

and range were used to describe continuous measures. Cosmetic outcome at last follow-up visits were tabulated, and where feasible, repeated measure models were used to assess changes over time for the QLQ-BR23 subscales. Graphic methods were used to display changes over time.

Results

Patient characteristics

The basic patient demographic and tumor characteristics are summarized in Table 1. For all patients, all final surgical margins were negative. Twenty-three (82%) of the patients were in the prepathology cohort, and 5 (18%) were treated in the postpathology arm. Two patients did not return for their 6-month follow-up assessment.

Feasibility

Each step in the CT-HDR-IORT was successfully performed in all patients. Feasible IORT delivery times (≤90 minutes) were obtained in 26 of the 28 patients (93%; 90% CI 79, 99%). The median IORT treatment interval was 67.2 minutes, the median planning time was 38.5 minutes, the median total radiation delivery time was 26.1 minutes, and the median total procedure time was 140.5 minutes (range, 82-214 minutes).

The CT-HDR-IORT technique was considered unfeasible by predefined timing criteria in 2 patients (7%): 1 patient in either arm of the trial. In the 2 cases that failed time feasibility criteria, IORT treatment intervals were 98 and 108 minutes. Delays were attributable to CT-identified need for applicator repositioning that required additional CT scans and planning time.

Safety

At 6 months after IORT, grade 1 and 2 toxicities had occurred in 14 (50%) and 6 (21%) of patients, respectively. No grade 3 to 5 toxicities were reported. Table 2 outlines the most severe toxicities reported in all study patients. To date, no patients have met protocol-specified criteria for, or received, WBI.

Dosimetry

Prespecified brachytherapy planning goals were achieved in 22 patients overall (79% with a 90% CI [62, 90%]). Table 3 provides these dosimetric goals and data on the treatment volumes of the patients studied. The prespecified limit for maximum dose to rib was met in 23 patients (82%), and the prespecified limit for maximum dose to heart was met in all patients. The PTV_eval was modified from the PTV based on imaging in 23 (82%) patients. The PTV_eval was affected by selective trimming off of the ribs and skin in 17 (61%) and 22 (79%) patients, respectively, from the uniform 1-cm expansion of the balloon applicator.

Cosmetic outcomes and quality of life

As measured by the Harvard breast cosmesis grading scale, the majority of patients (93%) had excellent (68%) or good

Table 1 Demographic and clinical characteristics of the 28 patients enrolled

Characteristic	Overall	Range or %
n	28	-
Median age, y	63.8	51.6-77.1
Histology		
DCIS	10	36%
IDC	16	57%
ILC	1	4%
Tubular carcinoma	1	4%
Laterality		
Right	11	39%
Left	17	61%
cT median, mm	9.0	4.0-24.0
pT median, mm	7.5	0.0-15.0
Closest margin median, mm	8.0	1.0-14.0
Grade		
Low	10	36%
Intermediate	14	50%
High	4	14%
Receptor status		
ER+	26	93%
PR+	21	75%
HER2+	0	0%

Abbreviations: cT = clinical T stage; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; PR = progesterone receptor; pT = pathologic T stage.

Table 2 Most severe toxicity among enrolled study participants to date (n=28)

Characteristic	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Pain	1 (4)	1 (4)	-	-
Dermatitis	6 (21)	1 (4)	-	-
Seroma	4 (14)	4 (14)	-	-
Deep fibrosis	1 (4)	-	-	-
Superficial fibrosis	12 (43)	-	-	-
Pruritus	2 (7)	-	-	-
Hyperpigmentation	4 (14)	-	-	-
Lymphedema	1 (4)	-	-	-
Overall	14 (50)	6 (21)	-	-

Toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (26).

Table 3 Target volumes and dosimetric goals among all patients (n=28)

Volume	Goal	Median	Range	Goal achieved in
Balloon volume, cc	-	40	30.3-78.0	-
PTV volume, cc	-	87.8	44.8-117.4	-
D90, % of 12.5 Gy	-	100.7	94.3-103.3	-
V100, %	≥90	91	81.8-94.1	21 of 28 (75%)
Max skin (% of 12.5 Gy)	<145	107.3	31.6-200.0	26 of 28 (93%)
Max heart (% of 12.5 Gy)*	ALARA	6.9	2.4-11.0	17 of 17 (100%)
Max rib (% of 12.5 Gy)	<145	99.4	20.1-158.0	23 of 28 (82%)

Abbreviations: ALARA = as low as reasonably achievable; D90 = dose received by 90% of the PTV; Max = maximum; PTV = planning target volume; V100 = percentage of volume of the PTV receiving 100% of the prescription dose of 12.5 Gy.

* For left sided-tumors. Heart dose for right-sided tumors was 0.0 Gy.

(25%) cosmetic outcomes at the time of their last assessment; the remaining 2 patients had fair outcomes. The 2 patients who did not return for their 6-month follow-up visits had excellent outcomes at 3 months. The cosmetic outcomes are summarized in Table 4.

Where model assumptions were satisfied, repeated measure models were used to describe changes over time for QOL subscales of body image, arm, and breast symptoms. No significant changes over time were detected for body image scores. Arm symptom scores decreased by 7 points at 6 months compared with the baseline. Patterns of change for breast symptom scores are displayed in Figure E1 (available online at www.redjournal.org) and indicate an increase of 11 points at 1 month ($P<.001$), with a return to baseline at 6 months ($P=.7$). No changes in the other subscales were noted.

Discussion

Our results demonstrate that CT-HDR-IORT is a safe and feasible method of providing adjuvant radiation therapy to women with early-stage breast cancer. This technique was successfully performed in all patients and within prespecified time constraints in 93% of patients. No major toxicities were observed, and there was a 21% rate of grade 2 acute toxicities. These clinical results compare favorably with other forms of IORT (16, 27). Inasmuch as CT-HDR-IORT also has the technical advantages of image-guided treatment planning and a higher prescription dose, this novel IORT method warrants additional study in an ongoing phase 2 trial.

The approach tested in the current trial delivers a prescription dose of 12.5 Gy to the PTV_eval, which is substantially higher than the 5 to 7 Gy delivered to 1 cm from the applicator in the TARGIT trial (16, 20). The TARGIT and ELIOT trials provide evidence that suggests IORT may be an acceptable option in the treatment of early-stage breast cancer, but there are drawbacks to those radiation therapy delivery techniques. The photon technique used in the TARGIT trial limits dose delivery to 1 cm beyond the lumpectomy cavity because of a high superficial dose (at the applicator surface) (19, 20). However, there is some evidence that the relative biological effectiveness of

Table 4 Cosmetic outcome summary for various scales (n=28)

Score* at (1 month, 6 months)	Harvard n (%)	Score† at (1 month, 6 months)	Pigmentation n (%)	Size n (%)	Shape n (%)
(E, E)	10 (36)	(N, N)	8 (29)	10 (36)	10 (36)
(G, E)	9 (32)	(L, N)	4 (14)	8 (29)	5 (18)
(F, E)	0 (0)	(S, N)	3 (11)	1 (4)	0 (0)
(E, G)	2 (7)	(N, L)	1 (4)	3 (11)	2 (7)
(G, G)	4 (14)	(L, L)	8 (29)	4 (14)	4 (14)
(F, G)	1 (4)	(S, L)	3 (11)	0 (0)	3 (11)
(E, F)	1 (4)	(N, G)	0 (0)	0 (0)	2 (7)
(G, F)	1 (4)	(L, G)	1 (4)	1 (4)	1 (4)
(F, F)	0 (0)	(S, G)	0 (0)	1 (4)	1 (4)
Last score‡	% (90% CI)	Last score‡	% (90% CI)	% (90% CI)	% (90% CI)
E or G	93 (79%, 99%)	N or L	96 (84%, 100%)	93 (79%, 99%)	86 (70%, 95%)

Abbreviation: CI = confidence interval.

Images obtained at follow-up visits were compared with preoperative images and were given an overall cosmetic score (excellent, good, fair) and a separate score to assess the change in the pigmentation, size, and shape (none, a little, a lot) in the treated breast. This table represents a summary view of the patients' scores at 1 month and 6 months of follow-up.

* E = excellent; G = good; F = fair.

† N = none; L = a little; S = some.

‡ At last follow-up visit.

superficial photons is higher than in other radiation modalities (28), which may mitigate this point somewhat. The electron technique used in the ELIOT trial has superior dose homogeneity but requires increased shielding, including a plate under the target to prevent irradiation of the underlying chest wall and lungs. Our IORT program, which leverages multichannel HDR brachytherapy and CT-on-rails-based treatment planning, was designed to deliver a higher radiation dose than in the TARGIT trial and still minimize dose to normal structures. Whether the higher prescription dose reduces recurrence rates constitutes a goal of our ongoing phase 2 trial.

In the current study, intraoperative CT imaging was used to evaluate applicator placement and permit 3-dimensional treatment planning, which differs from other methods for breast IORT, although it is very similar to many methods of postoperative brachytherapy-based APBI. The TARGIT and ELIOT trials each relied solely on visual placement of the applicator into the surgical cavity without confirmation with radiography (16, 27). Since the publication of these 2 trials, 2 early reports have incorporated intraoperative ultrasonography and megavoltage portal imaging into the TARGIT and ELIOT workflows, respectively (29, 30). Whereas these techniques are likely beneficial compared with no image guidance, they do not provide the same 3-dimensional analysis afforded by CT imaging. In our experience, the use of CT leads to changes in applicator positioning in nearly a quarter of breast IORT cases (21), and in this study the PTV_eval was modified based off of CT imaging in a majority of patients. For the 2 patients in this trial whose treatment time exceeded the predefined feasibility criteria, it is noteworthy that this was related to the need for the adjustment of the brachytherapy applicator. Both of these patients were able to complete the IORT procedure without event. Because the currently available IORT techniques do not provide a means to reliably identify malposition applicator placement (outside of direct visualization of the open cavity and in some cases intraoperative ultrasonography), such positioning errors may have been missed in alternative IORT methods. Additionally, CT imaging is a necessary component of calculation of the doses to the target and organs at risk as customization of the brachytherapy dose distributions before therapy initiation as performed in this trial.

High rates of good to excellent cosmetic outcomes, 70% to 90%, are obtained after breast conserving therapy, and these outcomes are similar between WBI and external beam partial breast irradiation (31). There remains a potential for improvement with brachytherapy delivery techniques (32-34). In this pilot study, 93% of patients had good or excellent cosmetic outcomes at the end of their last assessment. In terms of QOL, several small series suggest superior QOL in patients undergoing partial breast irradiation, particularly when treated with brachytherapy (35, 36). In this study, only breast symptom scores increased during the follow-up period with a return to baseline at 6 months.

This phase 2 trial was not designed to evaluate efficacy. An ongoing phase 2 clinical trial is being conducted to define recurrence rates, cosmetic outcomes, and QOL after treatment with CT-HDR-IORT. The clinical impact of the increased time to prepare and deliver HDR-based radiation therapy (compared with low-energy photon therapy) during IORT is unknown. Moreover, there are more physical limitations with any balloon-based technique than with electron-based techniques, and our study was not designed to compare these.

There are several potential drawbacks to the IORT technique proposed in the current trial that limit the ability for wider clinical implementation for more patients. The most practical concern is that many centers do not have HDR brachytherapy suites with in-room imaging, and implementation of such an integrated image guided brachytherapy suite requires significant financial and personnel resources. Whereas the intense resource requirements limit the dissemination of CT-HDR-IORT to other centers, it is worth noting that the delivery of IORT in a single day does make it reasonable for a small number of centers to serve a broad geographic region if patients are willing to travel for treatment. Additionally, we are working with collaborators to assess the feasibility of CT-HDR-IORT in centers without integrated HDR brachytherapy suites. Although our method of image guided IORT with HDR brachytherapy addresses recognized the technological and dose limitations of IORT (20, 21, 37, 38), inherent limitations of IORT remain, such as the lack of final pathology results for surgical margins and nodal status. Although we attempted to improve on the latter through a pre-IORT sentinel lymph node evaluation, this results in 2 separate surgical procedures for the patient. Last, the appropriate selection criteria for APBI have not been prospectively validated (22, 39), leaving some uncertainty regarding which patients should be treated with IORT and other APBI approaches.

It is concluded that CT-HDR-IORT, a method of image guided IORT with HDR brachytherapy, demonstrates a favorable feasibility and safety profile in this study population and has the potential to maximize a patient-centric multidisciplinary approach to treating women with early-stage breast cancer. A phase 2 trial is under way to evaluate the long-term safety and efficacy of this novel technique.

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