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Stereotactic image-guided neoadjuvant ablative single-dose radiation, then lumpectomy, for early breast cancer: the SIGNAL prospective single-arm trial of single-dose radiation therapy

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ABSTRACT

Background and Purpose   Adjuvant whole-breast irradiation after breast-conserving surgery, typically delivered over several weeks, is the traditional standard of care for low-risk breast cancer. More recently, hypofractionated, partial-breast irradiation has increasingly become established. Neoadjuvant single-fraction radiotherapy (RT) is an uncommon approach wherein the unresected lesion is irradiated preoperatively in a single fraction. We developed the SIGNAL (Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy) trial, a prospective single-arm trial to test our hypothesis that, for low-risk carcinoma of the breast, the preoperative single-fraction approach would be feasible and safe.

Methods   Patients presenting with early-stage (T < 3 cm), estrogen-positive, clinically node-negative invasive carcinoma of the breast with tumours at least 2 cm away from skin and chest wall were enrolled. All patients received prone breast magnetic resonance imaging (MRI) and prone computed tomography simulation. Treatable patients received a single 21 Gy fraction of external-beam RT (as volumetric-modulated arc therapy) to the primary lesion in the breast, followed by definitive surgery 1 week later. The primary endpoints at 3 weeks, 6 months, and 1 year were toxicity and cosmesis (that is, safety) and feasibility (defined as the proportion of MRI-appropriate patients receiving RT).

Results   Of 52 patients accrued, 27 were successfully treated. The initial dosimetric constraints resulted in a feasibility failure, because only 57% of eligible patients were successfully treated. Revised dosimetric constraints were developed, after which 100% of patients meeting MRI criteria were treated according to protocol. At 3 weeks, 6 months, and 1 year after the operation, toxicity, patient- and physician-rated cosmesis, and quality of life were not significantly different from baseline.

Conclusions   The SIGNAL trial presents a feasible method of implementing single-dose preoperative RT in early-stage breast cancer. This pilot study did not identify any significant toxicity and demonstrated excellent cosmetic and quality-of-life outcomes. Future randomized multi-arm studies are required to corroborate these findings.

Key Words   Radiation oncology, stereotactic body radiotherapy, SBRT

INTRODUCTION

The modern management of low-risk breast cancer involves the use of breast-conserving surgery plus radiotherapy (RT), which can be hypofractionated without sacrificing efficacy or safety compared with standard RT (that is, 50 Gy in 25 fractions)[1–7]. Recently, accelerated partial-breast irradiation was postulated to be a viable treatment option

for low-risk disease, given that most local recurrences are located in the lumpectomy cavity[8,9].

The most accelerated example of accelerated partial-breast irradiation is single-fraction radiation therapy (SFRT), which is well established in the literature and has been used to treat large cohorts of women with low-risk breast cancer, with acceptable clinical outcomes[10,11]. The technique is more convenient and might reduce health care costs by freeing space on radiation treatment units. Furthermore, SFRT might entice more women to undergo standard-of-care treatment (that is, breast-conserving surgery with RT), because the primary reasons for underuse of adjuvant RT after breast-conserving surgery are the time, travel, and effort required[12,13]. Despite such benefits, the risk of treatment-related toxicity is increased for SFRT compared with standard techniques, and the treatment planning and delivery platforms historically required for SFRT have not been widely available, which limit use of the technique in North America[14]. In Canada, intraoperative RT is cost-prohibitive because of the expense of disposable components, and it is currently used in very few centres. With the movement toward hypofractionation in the radiotherapeutic management of low-risk carcinoma of the breast in general, a discussion of how best to implement and to incorporate SFRT into routine clinical practice is very timely.

We therefore developed SIGNAL (Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy), a single-arm, single-institution clinical trial in which a cohort of women with early-stage low-risk carcinoma of the breast would be treated with neoadjuvant RT delivered 1 week before lumpectomy[15]. Based on a dose-escalation trial and another single-arm trial, and radiobiologic calculations described previously[15–17], we selected 21 Gy in 1 fraction, delivered prone, by external-beam volumetric modulated arc therapy, with dosimetry planning based on computed tomography (CT) simulation images co-registered with magnetic resonance imaging (MRI) images. Our objectives were to evaluate the feasibility and safety of this approach in a pilot design as a guide for future randomized controlled studies. Our hypothesis was that, for selected patients with low-risk breast carcinoma, neoadjuvant partial-breast hypofractionated stereotactic body RT (SBRT) would be technically feasible, with acceptable toxicity and cosmesis. Here, we report the toxicity and cosmesis outcomes observed in a cohort of patients treated using that regimen.

METHODS

The SIGNAL protocol was previously published, and Figure 1 shows the study schema[15]. Two primary endpoints were considered in SIGNAL: radiation toxicity and feasibility. Radiation toxicity was defined as grade 2 or greater toxicity (such as fibrosis), measured using the *Common Terminology Criteria for Adverse Events*[18]. Feasibility was defined as the ability to deliver treatment in accordance with the study-defined dosimetry constraints in 90% or more of the patients. Secondary endpoints were cosmesis (scored by the patient and the radiation oncologist or surgeon using the Modified Harvard–Harris Cosmetic Scale[19]) and quality
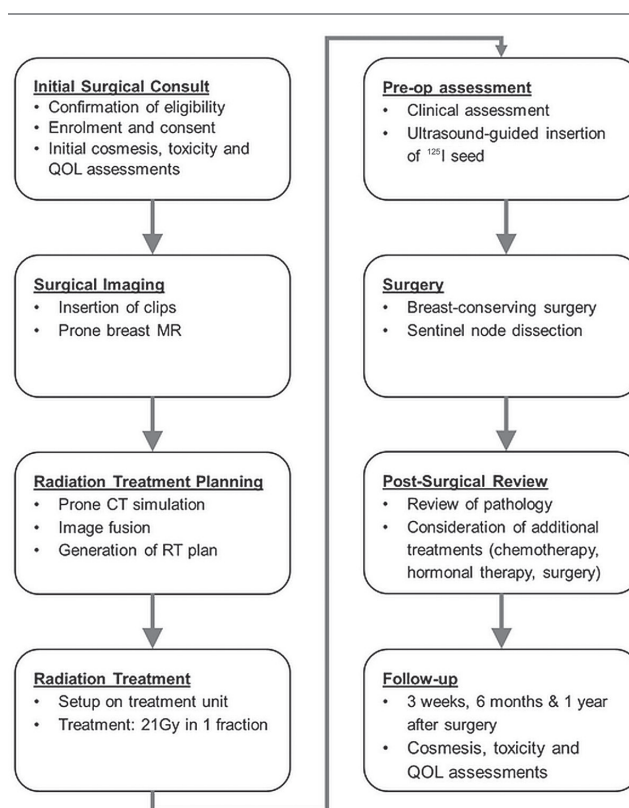
FIGURE 1 Study schema showing the entire course of the experimental protocol undergone by the patients. QOL = quality of life; MR = magnetic resonance; CT = computed tomography; RT = radiotherapy.

of life (QOL) measured using the Functional Assessment of Cancer Therapy–Breast tool[20]. Postoperative complications were also collected, analyzed, and reported. Approval for SIGNAL was given by Western University's Health Sciences Research Ethics Board (no. 105643), and the trial was registered with http://ClinicalTrials.gov/ (NCT02212860).

All postmenopausal women presenting for surgical consultation between 2014 and 2016 with a new diagnosis of early-stage (<3 cm in size, node-negative), estrogen receptor–positive, unifocal breast cancer were approached for participation. If initial ultrasonography suggested sufficient distance (that is, ≥2 cm) both between the lesion and the skin and between the lesion and chest wall, patients were enrolled.

Once enrolled, patients underwent ultrasound-guided insertion of a surgical clip as a fiducial marker. They were then immobilized on a prone breast board and were imaged by contrast-enhanced prone breast MRI. If MRI confirmed unifocal disease less than 3 cm that was sufficiently distant from the skin and the chest wall, patients proceeded to radiation treatment planning. All patients reaching planning were again positioned and immobilized on a prone breast board for CT simulation. Using rigid body registration, the prone breast MRI was fused onto the prone CT simulation images. The gross tumour volume (GTV) was defined as the primary breast lesion seen on MRI. The clinical target volume was defined as the GTV plus a 5 mm margin. The planning target volume (PTV) was defined as the clinical

target volume plus a 5 mm margin. Radiation treatment plans were devised to deliver a prescription dose of 21 Gy to the PTV in a single fraction.

With the patient in prone position, 21 Gy was delivered by SBRT, using cone-beam CT imaging to confirm patient positioning and the accuracy of delivery by using the surgical clip to localize the tumour. Real-time image acquisition monitored patient positioning and allowed the beam to be disabled if the patient moved significantly. Relevant as-treated dosimetric constraints were based on a thorough review of the relevant published literature, published SBRT-based clinical trials, and general radiobiologic principles (Table I). After induction RT, radiolocalizing ^{125}I seeds were placed adjacent to the surgical clip to facilitate localization and guided excision. All patients underwent breast-conserving surgery and sentinel lymph node biopsy (where clinically indicated), ideally within 1 week of RT. Older patients could opt out of sentinel lymph node biopsy in accordance with clinical guidelines. Toxicity, cosmesis (patient- and physician-assessed), and QOL measures were collected at baseline and at 3 weeks, 6 months, and 1 year postoperatively. Toxicity was reported as the number of patients who experienced any grade 2 or greater toxicity at each time point, with comparison to baseline by the Fisher exact test. To allow for comparisons to other publications using the Modified Harvard–Harris Cosmetic Scale in breast irradiation trials, the cosmesis score (excellent, good, fair, poor) was collapsed into the proportion of patients or physicians rating the cosmesis as excellent or good or as fair or poor. The proportion of patients or physicians reporting a good or excellent cosmetic score at each time point was compared with baseline using the Fisher exact test. The QOL total score at each time point was compared with baseline using the Student *t*-test.

RESULTS

Between February 2014 and September 2016, 53 patients were approached for participation, and 52 patients were initially enrolled (Figure 2). Of those 52 patients, 13 were excluded at the time of MRI (2 were upstaged by MRI, 5 did not fit in the MRI bore or were unable to remain still, and 6 did not meet the study criteria because of proximity of the tumour to skin or chest wall as measured on MRI). Of the remaining 39 patients who met the criteria for breast MRI and who went on to radiation treatment planning, the study-specified dosimetric constraints could not be met in 12 (in every case, either the chest wall or the skin constraint, or both, could not be met). Those patients were taken off the study protocol and instead went on to surgery and standard whole-breast adjuvant RT.

The remaining patients fell into one of two distinct cohorts depending on when they were treated (Figure 2). The first of those cohorts consisted of the first 36 patients

TABLE I   Normal tissue dosimetric limits,[a] original and revised

Structure	Cohort			
	Original (*n*=16)		Revised (*n*=11)	
	Dose (Gy)	Specification	Dose (Gy)	Specification
Breast				
Uninvolved ipsilateral	10	≤50%	10.5	≤50%
	18	≤20%	20	≤47%
	21	≤47 cm³	21	Point dose
Contralateral	0.6	Point dose	1	Point dose
Lung				
Total	—	—	11	≤35%
Ipsilateral	6	≤15%	7.5	≤15%
	10	≤10%		
Contralateral	3	≤5%	1.7	≤15%
Heart	3	≤5%	22	Point dose
	1	≤40%	3	<5 cm³
			16	≤15%
Thyroid	1.8	Point dose	1.1	Point dose
Skin	16	Point dose	18.3	<5 cm³
	10	≤10 cm³		
Chest wall	10	≤10 cm³	10	<10 cm³
	15	Any point	16	<2 cm³

[a]   The initial study cohort (*n*=16, 2014) was treated according to the original limits. After an interim review and quality assurance assessment, a new set of limits was adopted (*n*=11 completed treatment, 2016).
x cm³ = dose delivered to a volume of *x* cm³.
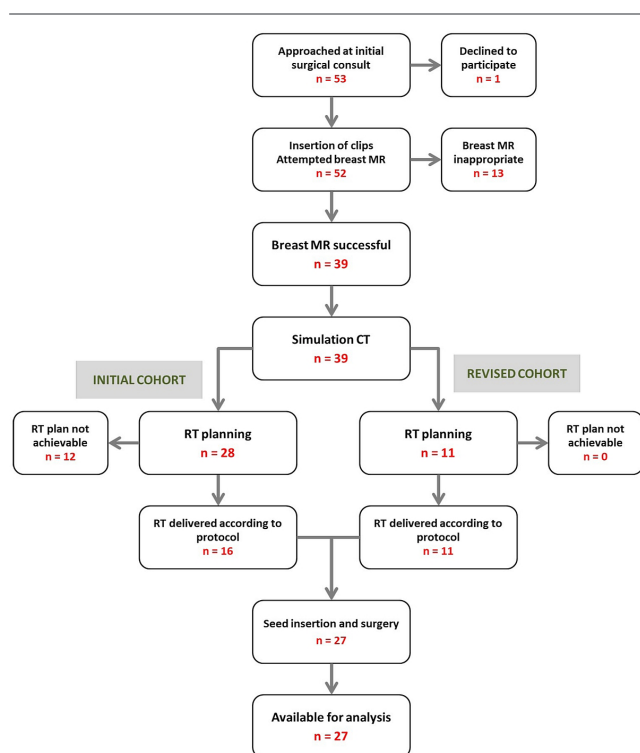
FIGURE 2 Patient flow diagram. MR = magnetic resonance; CT = computed tomography; RT = radiotherapy.

approached (the "initial cohort"). Of those 36 patients, 8 were excluded at the time of MRI (2 were upstaged by MRI, 2 did not fit in the MRI bore, and 4 did not meet the study criteria because of proximity of the tumour to skin or chest wall). The study-defined dosimetric constraints could not be met in 12 of the remaining 28 patients (the same 12 already mentioned).

Therefore, in the initial cohort, only 16 of 28 patients meeting the study criteria by breast MRI went on to receive the study-defined treatment, representing a cohort-specific success rate of 57%. That result was deemed a failure of the approach, triggering an interim review as required by the protocol. During the interim review, we concluded that our dosimetric constraints were too restrictive, especially with respect to dose to skin. We similarly concluded that our original definition of skin (external contour less 5 mm) was too restrictive and more conservative than had been used in similar published clinical trials of SFRT[21]. Revised dosimetric constraints were therefore developed (Table I) and implemented to treat the next 16 patients who were accrued (the "revised cohort"). Of those 16 patients, 5 were excluded at the time of MRI (3 did not fit in the MRI bore; 2 did not meet the criteria for proximity of the tumour to skin or chest wall). Of the remaining 11 patients, all went on to receive the study-defined treatment, representing a cohort-specific success rate of 100%. The actual mean dose delivered in both patient cohorts was similar whether the cohort underwent treatment at the initial dosimetric constraints or at the revised constraints (Table II).

All treated patients underwent local excision of the primary tumour to negative margins within 7 days of ra-

diation, without any delay or complication. No patients showed signs of erythema at the time of surgery, none described any pain, and every patient expressed pleasure with the entire process. No surgery was made more complicated as a result of the preoperative radiation, and in fact the tissues appeared healthy and normal. No postoperative complications were encountered. No patients required *in situ* drains, and none had prolonged seroma, wound dehiscence, skin necrosis, or infection in the postoperative period.

Table III presents patient demographics and tumour details. Toxicity, cosmesis (patient- and physician-assessed), and QOL measures (all assessed at baseline and at 3 weeks, 6 months, and 1 year postoperatively) are presented in Table IV. No patients experienced toxicity of grade 2 or higher at baseline or at 3 weeks or 1 year postoperatively, and 1 of 27 evaluable patients had a grade 2 delayed wound infection at the 6-month postoperative visit, which was not significantly different from baseline (p = 1.0). Physician-rated cosmesis (Harvard–Harris score) was slightly worse than baseline (100% judged good or excellent) at 3 weeks (93% judged good or excellent, p = 0.16), 6 months (96% judged good or excellent, p = 0.29), and 1 year (92% judged good or excellent, p = 0.13) postoperatively, but none of the differences were statistically significant. Physician-rated cosmetic outcomes for the patients was judged 96% good or excellent at baseline and 93% at 3 weeks (p = 0.60), 92% at 6 months (p = 0.53), and 96% at 1 year (p = 0.98) postoperatively. Again, none of those changes were statistically significant. Compared with baseline, QOL was significantly improved at 3 weeks (p = 0.01) and at 1 year postoperatively (p = 0.001) and was elevated, although not significantly so, at 6 months postoperatively (p = 0.09).

DISCUSSION

The SIGNAL study represents a novel approach to the radiotherapeutic management of early-stage low-risk carcinoma of the breast. The classic approach for such patients, established over many decades, is surgery followed by RT. The benefit of adjuvant RT in such a setting is well known and so too are its toxicities. In principle, neoadjuvant RT holds several advantages over adjuvant RT, including improved tumour oxygenation, reduced dose to the surrounding normal tissues because of a smaller target volume, and of course the ability to recognize and to delineate the disease *in situ.* That latter benefit was of particular interest to us, given the availability of MRI for radiation treatment planning with image co-registration. Hypofractionation is now established in the treatment of multiple malignancies. As SFRT, SBRT, and other hypofractionated techniques likewise become more established in the management of breast cancer, it is incumbent upon us to understand as fully as possible the potential benefits and toxicities of that approach.

The unique aspects of the SIGNAL trial include the use of volumetric arc therapy with strict dosimetry constraints to skin and normal tissues, avoiding any early skin erythema or dermatitis, and any delayed fibrosis or telangiectasias by latest follow-up at 1 year. The co-registration of prone breast imaging allowed for high-fidelity treatment delivery,

TABLE II   As-treated target dosimetry doses, averaged over the study cohorts

Dosimetry	Value by study cohort		
	Original (*n*=16)	Revised (*n*=11)	Overall (*n*=27)
Prescription dose (Gy)	21.0	21.0	21.0
Mean[a] prescription isodose (%)	95.7±0.4	96.5±0.30	95.9±0.3
Mean[a] delivered dose at isocentre (Gy)	22.0±0.09	22.2±0.36	22.0±0.11
Mean[a] minimum dose to 100% PTV (Gy)	19.5±0.2	19.1±0.45	19.3±0.22
Mean[a] minimum dose to 95% PTV (Gy)	21.0±0.1	21.0±0.06	21.0±0.05

[a]   With standard error.
PTV = planning target volume.

TABLE III   Baseline demographics and tumour characteristics for 27 study patients

Characteristic	Value
Mean age (years)	68.7±6.5
Laterality [*n* (%)]	
Left	14 (60.9)
Right	9 (39.1)
Mean tumour size (cm)	
Ultrasonography[a]	1.2±0.63
Pathology[b]	1.17±0.63
Pathologic nodal stage [*n* (%)]	
N0	21 (91.4)
N1mic	1 (4.3)
N1	1 (4.3)
Grade [*n* (%)]	
1	10 (43.5)
2	12 (52.2)
3	1 (4.3)
Receptor positivity [*n* (%)]	
Estrogen	23 (100)
Progesterone	18 (78.3)
HER2	2 (8.7)

[a]   Represents the best pretreatment estimate of baseline tumour size.
[b]   Represents the best estimate of post-treatment tumour size.

minimizing the dose to skin which, if these low-risk patients had requested mastectomy, would not require radiation at all, but when radiated, contributes to worsened cosmetic outcome and patient satisfaction. High-fidelity treatment might explain why our cosmetic outcomes were better than those reported by Pinnaro *et al.*[22] in their SFRT trial using intensity-modulated RT (59% of patients reporting a good or excellent cosmetic outcome), and similar or better than outcomes in other larger trials looking at cosmesis with more standard radiation regimens (in the range of 81%–95% reporting good or excellent cosmesis)[17,20,23].

As a pilot study, SIGNAL's primary endpoints were feasibility and safety. Our results suggested that SFRT, when delivered in the manner specified by SIGNAL, was certainly tolerable and well-liked by the patients. Our approach with the initial dosimetry constraints was not feasible, but it became feasible after revision of the conservative constraints, with successful treatment of all eligible patients in the revised cohort compared with only a proportion of the patients in the initial cohort. In the initial cohort, acceptable radiation treatment plans could not be generated for 12 patients who appeared eligible by breast MRI. For those 12 patients, the primary reason for ineligibility was proximity of the GTV to the skin (8 patients) or chest wall (4 patients), thereby rendering it impossible to meet the study-defined dosimetry limits. We therefore realized that our limits were simply too restrictive and would limit generalizability of the trial to a breast cancer population commonly seen in practice. This difficulty was most obvious for skin. We initially defined skin as the external contour contracted isotropically by 5 mm; we likewise required that the PTV could not extend into the skin. In addition, we imposed a maximum point dose of 16 Gy to the skin. Such definitions severely limited our ability to devise an acceptable treatment plan for patients whose disease was located more than 2 cm away from the skin surface. The situation was even less tenable when the PTV was situated in areas in which the external breast contour was changing rapidly in three dimensions, such as in the retroareolar region, where the PTV was surrounded by "skin" on every side except posteriorly. In addition, for lesions located very medially, buildup of dose was less, necessitating delivery of a somewhat higher dose both superficially and also through the chest wall if the prescription dose were to be attained.

When we devised the original normal-tissue dosimetric limits for SIGNAL, we reviewed multiple published studies of SFRT[11,17,21,24,25] and accelerated partial-breast irradiation[26,27], delivered using a variety of techniques in both the preoperative and postoperative settings. Most of those studies did not state specific skin constraints, even though the primary toxicity in most cases appeared to be skin toxicity. Our original dosimetric limits were therefore chosen to be conservative, recognizing that the available clinical data at that dose–fractionation were limited. Our revised dosimetric criteria were based on re-review of the published literature and on our limited clinical experience gained up to that point. Once the dosimetric limits were revised, 100% of MRI-eligible patients accrued to the study were successfully treated, which met our *a priori* feasibility threshold of 90%. We therefore feel that SIGNAL using the revised dosimetric constraints could be considered a feasible method of delivering single-dose neoadjuvant RT.

TABLE IV Outcomes for 27 study patients after treatment

Outcome	Baseline	Follow-up					
		3 Weeks	*p* Value[a]	6 Months[b]	*p* Value[a]	1 Year[b]	*p* Value[a]
Toxicity[c] (≥grade 2)	0	0	1.0	1	1.0	0	1.0
Cosmesis (%)							
Physician-rated[d]	100	93	0.16	96	0.29	92	0.13
Patient-rated[e]	96	93	0.60	92	0.53	96	0.98
Quality-of-life score[f]	118.68±16.8	123.56±16.9	**0.01**	122.48±15.7	0.09	127.15±15.4	**0.001**

[a] Compared with baseline by Fisher exact test (cosmesis and toxicity) or paired Student *t*-test (quality of life). Statistically significant values (α = 0.05) shown in boldface type.
[b] Cohort reduced to 24 patients (excludes 1 diagnosed with advanced renal cell carcinoma, 1 diagnosed with glioblastoma, 1 diagnosed with metastatic breast cancer from a prior remote contralateral breast cancer).
[c] Graded from 0 to 5 based on the *Common Terminology Criteria for Adverse Events* (ver. 4.03, 2010). Only 1 patient experienced a grade 2 toxicity event (delayed wound infection), felt to be treatment-related.
[d] Rated 1–4 on the Modified Harvard–Harris Cosmetic Scale[19].
[e] Percentage rated "good" or "excellent."
[f] Rated out of a total 148 possible points on the Functional Assessment of Cancer Therapy–Breast (FACIT.org, Elmhurst, IL, U.S.A.), each item scored on a scale of 0–4.

Our second primary endpoint was radiation toxicity, which is related to the secondary endpoints of cosmesis and QOL, because changes to the skin and underlying soft tissue of the breast can be immediately visible as discolorations. The mean toxicity score was not significantly different from baseline at 3 weeks, 6 months, or 1 year postoperatively (Table IV). A few grade 1 postsurgical toxicities were reported (such as transient postsurgical thickening at the scar), and 1 patient experienced a grade 2 toxicity (delayed wound infection at 6 months postoperatively), representing an expected breast wound infection rate from surgery alone. Neither patient- nor physician-rated cosmesis changed significantly from baseline at 3 weeks or 6 months postoperatively (Table IV). Finally, patients reported significantly improved QOL at 3 weeks compared with baseline, although QOL returned to baseline by 6 months.

The main limitation of this single-arm study is the small sample size and relatively short follow-up. The SIGNAL trial was designed to inform the design of future prospective randomized clinical trials by determining overall feasibility, identifying any early concerns about toxicity and safety, and assessing patient interest. The study was certainly well received by our patients (only 1 of 53 patients declined participation). Once we identified workable dosimetry constraints, we were successful in treating patients in a very timely manner, something that was highly popular with our local patient population, given that many lived several hours away. Although acute toxicity and cosmesis were certainly acceptable, it is not possible to comment about late radiation toxicity; we simply have not followed our patients for a sufficiently long time to permit such an assessment. The determination of late radiation toxicity is especially relevant with SFRT, given that the estimation of equivalent radiobiologic effects at a higher dose per fraction is notoriously difficult. Nonetheless, we are satisfied with our selected dose (21 Gy in a single fraction) for several reasons. It was selected based on both the standard linear-quadratic formulation as well as on newer approaches such as the "universal survival curve" which models effects at high doses per fraction more accurately[28].

In addition, our selected dose is consistent with doses delivered in several similar studies[11,17]. Finally, the use of MRI permitted very accurate definition of the GTV, and confinement of the prescription dose to the area targeted for excision likely reduced any significant effect on acute and delayed toxicity[29]. To ensure safety, we used very stringent criteria, including a requirement that lesions be at least 2 cm from the skin. To ensure accurate localization, we fused a breast MRI for each patient. Furthermore, we moved to a prone setup to minimize the effect of respiratory motion and day-to-day setup of the breast. Those three components of our treatment are not readily available in all institutions and would limit generalizability. However, to maximize safety, to provide a sufficient dose, and to ensure reliability for this new technique, they were included. In most centres, those components could easily be adopted, and an assessment of the need for each one (especially MRI) will be published separately.

CONCLUSIONS

Neoadjuvant single-fraction (21 Gy) partial-breast SBRT followed by breast-conserving surgery appears to be a feasible, safe, and well-tolerated method for delivering radiation in the prone position using external-beam RT and equipment available at standard RT facilities. The findings of the present study have to be confirmed in a prospective randomized clinical trial.

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