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CLINICAL INVESTIGATION

NOVEMBER, A Phase 2 Trial of a 9-Day Course of Whole Breast Radiation Therapy With a Simultaneous Lumpectomy Boost for Early-Stage Breast Cancer

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Purpose/Objectives: A phase 2 prospective noninferiority trial evaluating a novel 9 fraction course of whole breast radiation and simultaneous lumpectomy boost.

Materials and Methods: Tis and T1-3N0 patients enrolled to receive 3420 cGy radiation to the breast with 3960 cGy to the lumpectomy cavity. The primary endpoint was averaged photographic cosmetic scores at 24 months with a hypothesis of >70% good to excellent cosmetic breast scoring 24 months after completing radiation, assuming a baseline excellent/good cosmetic scoring of 80% with an 80% power, $\alpha = 0.1$.

Results: From 2018 to 2020, with institutional review board approval, 103 patients were enrolled. Patients had mostly invasive ductal carcinoma (75%), tumor size ≤ 2cm (88%), negative margins (92%), no lympho-vascular invasion (80%), and estrogen receptor positive (85%). Patients had a mean age of 59.5 years (33-82). With a mean follow-up of 51 months, there were no local recurrences and 1 patient with both regional (axilla) and distant (brain) recurrence. Twenty-four-month post-radiation therapy (RT) cosmetic photos were 68% excellent/good, and 32% fair/poor. The null hypothesis was not rejected with one-

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sided 95% exact binomial confidence interval of 59.1% (59.1%-100%). There were no reported late ≥grade 3 radiation toxicity events and only 4 patients with late grade 2 events. Patient-reported outcomes utilizing the Breast-Q survey revealed breast satisfaction in 85% of women.

Conclusions: We demonstrate an effective novel 9 fraction whole breast + lumpectomy boost radiation schedule. This trial uses one of the shortest published radiation schedules for a lumpectomy boost. Although we did not meet our prespecified cosmetic endpoint, no significant cosmetic change from baseline was seen in 80% of patients. We demonstrate excellent local control, and patient-reported satisfaction with low RT-related toxicity. We hope to move this concept forward in a randomized trial against the 5-day United Kingdom (UK) Fast Forward regimen, inclusive of a simultaneous lumpectomy cavity boost.

Introduction

Adjuvant radiation therapy (RT) plays an important role in the treatment of early-stage breast cancer as RT has been shown to significantly reduce the risk of breast cancer recurrence over surgery alone.[1-3] Adding breast radiation to breast cancer treatment following lumpectomy has enabled women the option of safely keeping their natural breast, as multiple randomized trials have demonstrated equivalent overall and disease free survival compared with mastectomy.[4-7] Meta-analyses have concluded that post-lumpectomy radiation improves breast cancer survival, with an estimated 1 life saved for every 4 recurrences prevented.[1] An important component of RT is the time-dose-fractionation schedule. Up until the last 10 to 15 years, the standard radiation schedule in North America involved 6 to 8 weeks of daily radiation. The addition of an extra dose of radiation to the lumpectomy cavity, called a boost, has been shown in 2 randomized trials to significantly reduce the risk of a local breast cancer recurrence in higher risk women compared with whole breast radiation alone.[8-13] Multiple randomized trials have demonstrated the ability to safely shorten the course of radiation, utilizing accelerated hypofractionation; however, the majority utilized a sequential lumpectomy boost, or no boost at all.[14-17] In 2020, the first publications of simultaneous lumpectomy cavity boost (SIB) trials demonstrated equivalent local control and toxicity for standard fractionation patients.[18] Several subsequent studies confirmed the safety of SIB breast radiation with hypofractionated schedules as short as 15 fractions.[19-23] Recent registry trials of ultra-hypofractionation inclusive of an SIB also appear to demonstrate safety and efficacy.[24,25]

Given the importance of a lumpectomy cavity boost for many women, we designed a novel prospective phase 2 institutional trial in which patients receive 9 days of whole breast radiation, inclusive of a lumpectomy cavity boost delivered during the same treatment session, concurrent with the whole breast radiation. As the background of hypofractionation breast radiation data support equivalence in local control, we designed our trial for noninferiority to published cosmetic outcomes. We believe our proposed fractionation will provide a significant improvement in convenience and cost effectiveness, while delivering equivalent cancer control without additional toxicity. The rationale for our chosen fraction size is based on the linear quadratic model of fractionation sensitivity.[26] We assumed an α/β ratio of 4 Gy in determining bioequivalent dosing, based on in vitro experiments in human breast carcinoma cell lines and the multiple fractionation results of the United Kingdom (UK) Start trials.[27-29]

Methods and Materials

Trial design/patient eligibility

We conducted a prospective, single arm phase 2 trial (NCT3345420) entitled NOVEMBER. We enrolled women over 18 years of age with an Eastern Cooperative Oncology Group performance status ≤1 and an anatomic stage 0 to IIB breast cancer (pTis-T3, N0), based on final lumpectomy surgical pathology. Patients were required to have negative surgical margins, defined as no tumor on ink; however, a focal positive deep margin was considered negative if the surgeon reported a dissection to the pectoralis fascia. Nodal evaluation was required unless patients had pure ductal carcinoma in situ (DCIS) or were aged ≥70 years with invasive tumors that were estrogen receptor (ER) positive and ≤2.0 cm in size. Isolated tumor cells found in evaluated nodes were allowed and considered N0. There were no specific criteria for a lumpectomy boost, but patients had to be recommended for a lumpectomy cavity boost by their radiation oncology. Patients were excluded if they had prior RT to the chest, neck, and/or axilla, prior ipsilateral breast cancer (DCIS or invasive), active collagen vascular disease, poor performance status, limited life expectancy, or significant post-lumpectomy complications, such as infection requiring IV antibiotics, or unplanned reoperation before enrollment. Re-excision for margins, however, was permitted. Chemotherapy administered more than 10 days after radiation completion was allowed; however, patients were not allowed to receive neoadjuvant chemotherapy or adjuvant chemotherapy before RT administration. Hormonal and biological therapy could begin any time but routinely started after radiation, per standard of care.

RT planning and technique

We delivered 3-dimensional (3D) conformal or intensity modulated RT with megavoltage photons. All patients

underwent CT simulation, supine or prone, with left-sided supine patients treated with breath hold and/or heart blocking techniques where appropriate. We prescribed 34.2 Gy to the whole breast and 39.6 Gy to the lumpectomy cavity, all delivered in 9 consecutive daily treatments, excluding weekends and holidays. Volume delineation for breast and lumpectomy targets were based on the Radiation Therapy Oncology Group (RTOG) breast atlas, with a 1-cm lumpectomy cavity to clinical target volume (CTV) and 5 mm planning target volume (PTV) expansion.[30] Dosimetric goals were achieved in all patients, as shown in Table 1. As 2 patients experienced rib fractures in our first 20 patients enrolled, an institutional review board (IRB) amendment was placed for an additional dosimetric goal to keep the max rib dose for the entire plan sum less than 36 Gy, with a lumpectomy PTV reduced coverage of 90% dose to 90% volume allowable to achieve this goal. After adding this additional dose constraint, no additional rib fractures occurred, and no chest wall pain was reported by patients. We utilized daily kilovoltage-cone beam CT to verify that the breast and lumpectomy CTV were properly aligned.

Photographic cosmetic analysis

As has been documented in randomized boost versus no-boost radiation trials, the additional radiation received from a lumpectomy cavity boost is associated with a worse photographic cosmetic outcome.[9,13,31] We collected baseline and 24 months digital photographs to study in our trial as the primary endpoint. The European Organization for Research and Treatment of Cancer (EORTC) Breast Cosmetic Rating system is a blinded digital photographic method that has been utilized in prior radiation studies and shown to be reliable and valid in detecting effects of radiation morbidity.[9,17] This method compares the radiated breast with the contralateral untreated side and evaluates size, shape, location of the areola/nipple, appearance of the surgical scar, skin pigmentation changes, presence of telangiectasia, and provides a global cosmetic score. Characteristics are graded on a four-point scale: 0 = excellent or no difference between treated and untreated breasts; 1 = good or small difference; 2 = fair or moderate difference; and 3 = poor or large difference. The National Cancer Institute of Canada (NCIC) utilized this rating system in their phase 3 hypofractionated whole breast trial noting no significant difference in 50 Gy over 25 fraction versus 42.5 Gy in 16 fractions.[17,32] In their consensus of 3 reviewers at 3 years after radiation, patients had good/excellent scores in 77% of patients, with no patients receiving a lumpectomy boost. In the EORTC boost versus no-boost trial, the same EORTC photographic method was used with 5 reviewers scores averaged (not a consensus) with good/excellent at 3 years in 85.6% in no-boost arm (50 Gy in 25 fx) and 70.9% boost arm (additional 16 Gy in 8 fx). In the boost group, 63% of patients were unchanged, 27% worse and 10% improved at 3 years. The UK Start A, Start B, Fast, and Fast Forward trials used a slightly different 3-point scale and were mainly reported as a change in score of none, mild, or marked.[14,15,33-35] In the UK Start B analysis of more than 900 patients, one-third of patients had a mild to marked photographic (3-point scale) change by year 5, with 43% receiving a 10 Gy lumpectomy boost.[34] Similar to previously published hypofractionated trials, we anticipate that our experimental arm will have a noninferior cosmetic score at 24 months postradiation, compared with previously published hypofractionated whole breast radiation trials.

Table 1 Dosimetric planning objectives

	Goal
Mean heart	<1.5 Gy
Heart V18 (left)	<10%
Heart V18 (right)	<2%
Ipsilateral lung V14.5	<35%
Contralateral lung V4	<15%
Contralateral breast V4	<10%
Breast PTV_eval V32.5*	>95%
Breast PTV_eval V36.6*	<10 cc
Breast PTV_eval V38.3	<50%
Breast PTV_eval V39.6	<30%
Lump PTV_eval V37.6	>95%
Lump PTV_eval V43.5	<5%
Lump PTV_eval V45.5	<0.03 cc

Abbreviation: Vx = volume (V) receiving x Gy dose or greater dose, expressed as percentage of total volume.
* Evaluated on the breast only treatment plan before accounting for the boost dose.

Patient-reported outcomes

There is a growing recognition that patient-reported outcomes (PROs) are critical in oncology trials. Patient-reported adverse event collection has shown to be different than provider-generated assessments, with consistent under-reporting of side effects by providers, especially as it relates to pain and distress.[36-38] We used the Breast-Q survey tool to assess patient breast satisfaction and well-being following adjuvant RT for this study.[39,40] This tool has been validated for use in patients after mastectomy and breast conservation and is provided free of charge for academic research. A team from Heidelberg, Germany validated the Breast-Q against an EORTC validated tool and noted the Breast-Q assesses precisely those impacts of breast surgery that matter most to the patients.[41] Domains for the survey include satisfaction with breast, adverse effects of radiation, psychosocial well-being, physical well-being, and satisfaction with treatment. We use previously published data for comparison with our patient outcomes. Oemrawsingh et al[42] examined the Breast-Q 2.0 version

with 705 Dutch patients with a history of breast surgery. A team in Australia compared various surgical techniques in their population with the Breast-Q, including 104 breast conserving surgery patients, who were contacted retrospectively several years after treatment.[43] Mundy et al[44] recruited 1201 volunteers through an online community of women with no history of breast surgery or breast cancer to establish a Breast-Q normal reference. As a secondary tool, the EuroQol 5 Dimension (EQ-5D) was used to assess PROs. The EQ-5D was developed by the Dutch non-profit EuroQol group to show patients' true change in underlying health status over time.[45]

Statistical analysis

Our primary goal was to achieve an overall good to excellent photographic cosmetic result based on an observer rating of the treated compared with the untreated breast, 24 months after radiation, with our primary endpoint deemed noninferior if true in >70% of patients, assuming the true rate is ≥80%. This is conservatively based on the NCIC hypofractionated randomized breast trial by Whelan et al,[32] recognizing that none of those patients received a lumpectomy boost. We utilized 3 blinded reviewers (nurse, surgeon, and radiation oncologist) who independently assigned categorical variables of excellent, good, fair, and poor to each photograph. Reviewers completed the EORTC photographic training module with examples of each scoring category; however, the scoring was ultimately a subjective measure by each reviewer. Scores were graded from the EORTC scoring system and converted to numerical values (0, 1, 2, and 3) for averaged statistical analysis. To account for the possibility of preradiation photographic assessments with fair/poor scores before radiation, average scores of 1.5 or greater, these patients were considered to have a good outcome if their average blinded review scoring from pre- to postradiation did not increase by more than 1.0 point. The primary analysis is a one sample t test. The null hypothesis will be that the true rate is good to excellent photographic breast cosmetic assessment in ≥70% of patients. Assuming the true rate is 80% (eg, exact equivalence), a sample of 87 evaluable subjects was planned for 80% power at the $\alpha = 0.1$ significance level. Our hypothesis will be tested using "binom.test" in R version 4.3.2.

After 45 patients had been enrolled and followed for 6 months, a preplanned interim analysis was performed of all patients for RT toxicity and recurrence rates. Early stopping rules were not met, thus the study continued enrollment. The cumulative incidence of local and local regional recurrence was estimated using the cumulative incidence function treating death as the competing risk and summarized using the Kaplan−Meier estimators. Incidence of acute and late radiation complications are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 toxicity. Any event longer than 6 months after completion of radiation was considered a late effect. PRO scores at 24 months postradiation were summarized and compared with prior published data, utilizing a two-sample t test with a 2-sided alternative.

Economic analysis

A cost effectiveness analysis is planned in a later publication as we are collecting an economic impact survey of study patients, which will be compared with a cohort of patients treated with standard hypofractionation and sequential lumpectomy boost.

Results

A total of 102 patients were prospectively enrolled from 2018 to 2020, under IRB approval. With a mean follow-up of 51 months, there were no local only recurrences and only 1 patient with a local and simultaneous distant recurrence (brain and axilla). This compares favorably with the 5 year local recurrence rate of 3.5% (95% CI, 1.8%-7.1%) and 4.3% (95% CI, 3.8%-4.7%) of the randomized Lyon and EORTC boost trials.[8,13] With a yearly recurrence rate of 0.0071, as in the Lyon study, one would expect 3.09 recurrences in 435 person years (n = 435*0.0071). The probability of zero recurrences as in November would be exp(−3.09) = 0.045. Similarly, if the yearly rate is 0.0088, as in the EORTC trial, one would expect 3.8 recurrences, and the probability of no recurrences is 0.022.

Patient characteristics

Patient characteristics are shown in Table 2. The median age at enrollment was 59 years with 25% of patients being younger than age 50 and 14% of patients being over the age of 70. Most tumors were invasive ductal cancer with ER positive histology, measuring 5 mm to 2 cm in size. Twenty-four of patients had grade 3 cancers (evenly split grades 1 and 2) and 13% with triple negative receptors. Eighty-two (86%) patients had ≥1 of the following risk factors: age < 50, grade 3 histology, LVI, margins < 2 mm, or ER negative. Table 3 demonstrates the breakdown of adjuvant systemic therapy that was administered to the 18% of patients with a diagnosis of invasive carcinoma receiving chemotherapy after radiation, with no patient receiving neoadjuvant chemotherapy. Additionally, all 6 patients with Her2 positive receptor status received anti-Her2-based therapy with cytotoxic chemotherapy. Of the estrogen positive patients, 92% received anti-estrogen therapy with a selective ER modulator or aromatase inhibitor (AI).

Photographic cosmesis

Eighty-nine patients had valid preradiation photographs, and 90 patients had 24-month photographs. However, 3 of

Table 2 Patient characteristics

	Total (%)
Age (y)	Median 59
40	5 (5%)
41-50	20 (20%)
51-60	29 (28%)
61-70	34 (33%)
>70	14 (14%)
Laterality	
Right	47 (46%)
Left	55 (54%)
Invasive size	
≤5 mm	9 (10%)
5.1-10 mm	30 (34%)
10.1-20 mm	39 (44%)
>20 mm	11 (12%)
Histology	
IDC	77 (75%)
ILC	7 (7%)
Mixed invasive	5 (5%)
DCIS	13 (13%)
Grade (invasive only)	
1	34 (38%)
2	34 (38%)
3	21 (24%)
Margins	
Positive	8 (8%)
<2 mm	4 (4%)
≥2 mm	90 (88%)
LVSI (invasive only)	
No	71 (80%)
Yes	16 (18%)
Indeterminate	2 (2%)
Receptors (Her2, invasive only)	
ER Pos	87 (85%)
PR Pos	74 (73%)
ER−/Her2+	2 (2%)
ER+/Her2+	4 (4%)
ER−/PR−/Her2−	13 (13%)

Abbreviation: DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LVI = lympho vascular invasion.

the 24-month photos did not include the contralateral breast and thus could not be officially scored. This left a total of 87 evaluable photographs. Without comparison with baseline cosmesis, the 24-month post-RT cosmetic photos averaged

Table 3 Use of systemic therapy

	Total (%)
Adjuvant chemotherapy (% invasive)	**16 (18)**
Anthracycline and taxol	1 (1)
Taxol and carboplatin	7 (6)
Cyclophosphamide, methotrexate, and fluorouracil (CMF)	2 (3)
Herceptin	6 (7)
Pembrolizumab	1 (1)
No chemotherapy	73 (82)
Adjuvant anti-estrogen (% ER+)	**80 (92)**
Adj tamoxifen alone	33 (37)
Adj aromatase inhibitor (AI) alone	32 (36)
Adj tamoxifen followed by AI	15 (17)
CDK 4/6 inhibitor (abemaciclib)	1 (1)
No endocrine therapy	9 (10)

Bold text to highlight overall category.

scores of 57% excellent/good, and 43% fair/poor, noting that 17% of patients had fair/poor cosmesis at baseline. Our preplanned analysis declared patients who had fair/poor cosmesis before RT would be considered to have an excellent/good cosmetic result if those patients had less than a 1.0 increase (worse cosmesis) in their average pre- versus postradiation score. With that adjustment made, 68% of patients were considered to have an excellent/good result. Changes from baseline are shown in Table 4. Measured as a change from preradiation baseline, 80% of all patients had either an improvement or no noticeable change, defined as a change in score of ±0.7 points on average. Five percent improved by more than 1.5 points, and 17% improved 0.6 to 1.5 points. Eighteen percent of patients experience a worse cosmetic score after radiation of 0.7 to 1.5 points (one category) and 2% of patients had a score that declined by ≥1.5 points. As we had designed our trial to demonstrate noninferiority to published cosmetic data if >70 % of patients had good to excellent cosmetic results at 24 months, as opposed to a change from baseline, we did not prove

Table 4 Change in average photographic scoring

Average change (negative = improved)	Number of patients (%)
≤−1.5	4 (5)
−1.4 to −0.6	14 (17)
−0.5 to +0.7	48 (58)
0.8-1.5	16 (18)
≥1.5	2 (2)

Eighty percent patients were improved or unchanged. A negative value is an improved cosmetic score and a positive value is worse cosmetic score.

noninferiority. A 1-sided 95% exact binomial confidence interval has a lower bound of 59.1% (59.1%-100%), whereas the 2-sided 95% exact binomial confidence interval ranges from 57.4% to 77.7%.

Patient-reported outcomes

PROs utilizing the Breast-Q survey are shown in Figure 1a. Eighty-eight patients had PRO survey values with results revealing breast satisfaction in 85% of women at 24 months after radiation, with a breakdown of very satisfied (42%), somewhat satisfied (43%), somewhat dissatisfied (14%), and very dissatisfied (1%). Converted to a 100-point scale to allow comparison with previously published Breast-Q outcomes, the average pre and post-RT breast satisfaction scores decreased by an average of 4.00, SD 21.59 (95% CI, −8.6 to +0.60). This compares favorably with previously published data (Fig. 1b).

The EQ-5D-3L HealthScale survey revealed an average score of 80.5 (SD 14.4; 95% CI, ±2.9) before RT and 83.1 (SD 13.4; 95% CI, ±2.7) at the first follow-up visit after

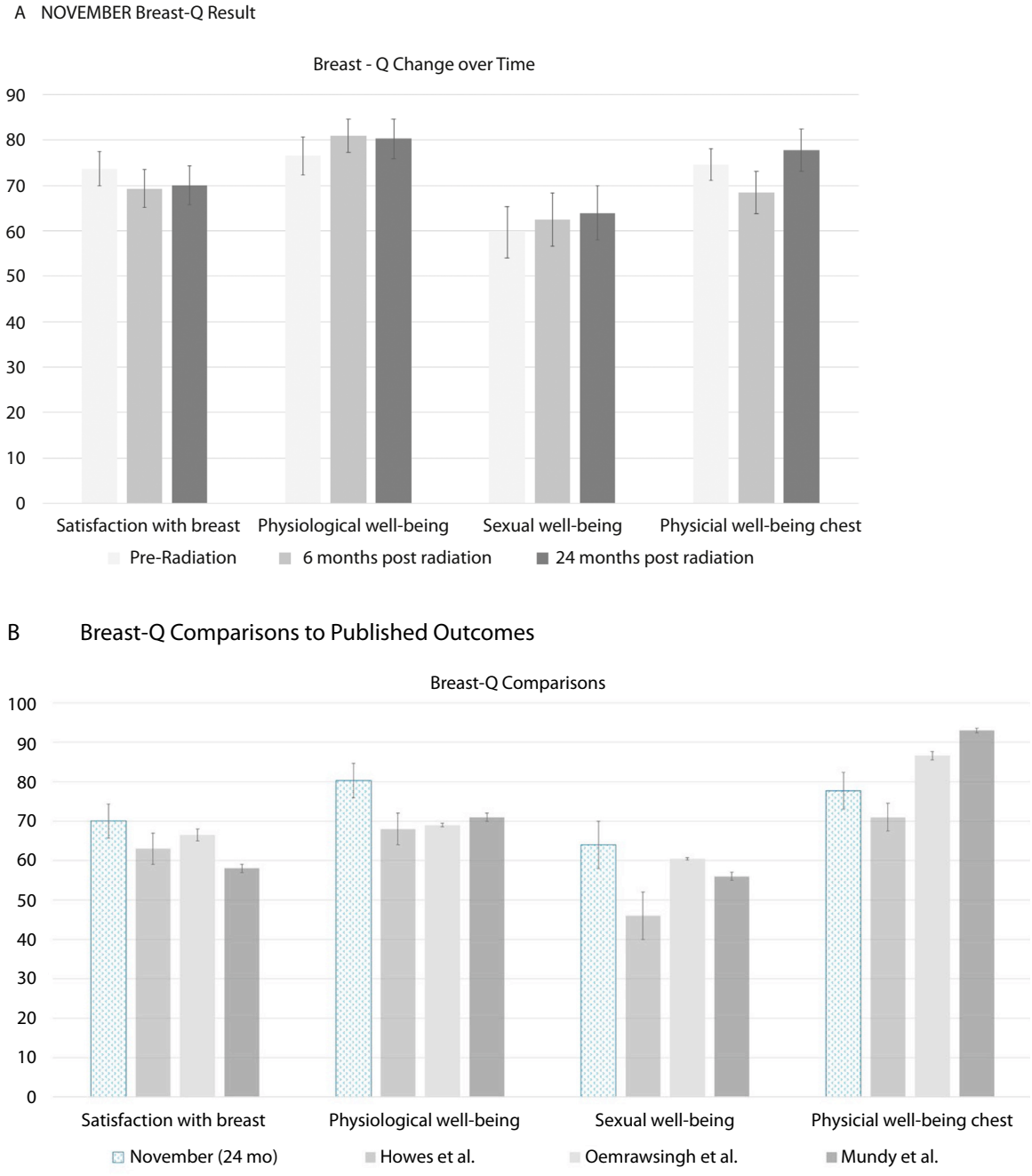

Fig. 1. (a) NOVEMBER Breast-Q results. (b) Breast-Q comparisons to published outcomes. Figures have been shown with 95% confidence intervals. Howes et al[43] lumpectomy patients, Oemrawsingh et al[42] breast surgery only patients, Mundy et al[44] nonbreast cancer "normal," population.

Table 5 Treatment-related toxicities

	Acute		Late*	
	Grade 2	Grade 3	Grade 1	Grade 2
Atrophy	0	1	0	0
Breast edema	3	0	0	0
Breast infection	4	1	0	0
Breast pain	7	0	5	1
Chest wall pain	3	0	3	1
Dermatitis	21	2	3	0
Fatigue	1	0	1	1
Fibrosis	2	1	2	1
Hyperpigmentation	0	0	4	0
Radiation recall	0	1	0	0
Rib fracture	2	0	0	0

* Late toxicities are defined as those occurring greater than 6 months after completion of radiation.

radiation completion. These scores are comparable with scores reported in other publications with breast cancer outcomes.[46,47] We did not collect EQ-5D-3L survey results at subsequent follow-up visits.

Radiation-associated toxicities

Toxicities associated with radiation were counted based on attributions of possible, probably, or likely related to treatment from RT, and are shown in Table 5. Late toxicities were scored if present ≥6 months after the completion of radiation. No patient reported late ≥grade 3 toxicities and only 4 patients noted a late grade 2 toxicity (chest wall pain, breast pain, skin tightness/fibrosis, and fatigue). Acute toxicities were more common but resolved soon after RT, as was evident by the low rate of late events. Acute grade 3 toxicity occurred in 6 patients [breast infection (2), dermatitis, fibrosis, atrophy, and radiation recall]. Acute grade 2 toxicity events occurred in 43 patients and were mainly radiation dermatitis or breast/chest wall pain. There were 4 total cases of breast infection discovered during or after finishing radiation.

Discussion

Given our unique position as the NCCN comprehensive cancer center with the largest geographic catchment area, we have a strong interest in offering patients shorter, more convenient RT schedules. As many of our patients live greater than 60 miles from our center, our goal was to design a breast radiation schedule in which all radiation (breast and boost), as well as the dry run (virtual simulation) could be completed in 2 calendar weeks, minimizing patient time away from home. An additional benefit of short-course radiation, besides the added convenience, it may offer to patients who otherwise may not be able to receive radiation, is that it may also allow earlier sequencing of radiation with systemic chemotherapy. Although sequencing seems to be unimportant in the context of breast preservation, it may be important in women at higher risk for locoregional recurrence. Given the excellent cure rates and low morbidity with current adjuvant RT techniques and fractionation, it is fitting that subsequent improvements in the field take convenience and economic impact into account.

This novel treatment schedule has been well received by patients and appears safe and effective, despite not achieving our noninferiority photographic cosmetic endpoint. In retrospect, we were overly ambitious in attempting to meet noninferiority with an assumption of good/excellent cosmesis of 80%, based on the NCIC hypofractionation trial without a lumpectomy cavity boost.[17] As the EORTC boost versus no-boost trial reported, only 71% good/excellent photographic outcomes, which would have been a more achievable endpoint for noninferiority.[9] Another alternative would have been in selecting a change in photographic score from baseline, as the UK trials reported,[15,33-35] or utilizing a patient-reported endpoint, such as the Breast-Q satisfaction with breast. NOVEMBER is currently the shortest whole breast SIB radiation schedule to be published from a prospective clinical trial. The UK Fast Forward trial reported results after enrollment was completed on NOVEMBER.[33] In that prospective randomized 3-arm clinical trial, they reported noninferiority in locoregional control and toxicity for a 1-week course of ultra-hypofractionated breast radiation with 26 Gy in 5 daily fractions, compared with a 15-fraction course of hypofractionated whole breast radiation.[33] Interestingly, a third ultra-hypofractionated arm in UK Fast Forward of 27 Gy in 5 fractions was reported to be inferior to the 15-fraction regimen with worse breast toxicity: breast

distortion, shrinkage, induration, telangiectasia, breast edema, change in photographic appearance and patient-reported breast firmness. Of the 4110 patients enrolled on UK Fast Forward, 25% received a sequential lumpectomy boost requiring an additional 5 to 8 days of radiation (10-13 total treatment days total). Toxicity analysis from the UK Fast Forward trial was reported without account of lumpectomy boost doses. NOVEMBER completed enrollment in 2020 as the shorted SIB whole breast radiation schedule; however, in 2023 to 2024, 2 prospective registry studies published 5-fraction schedules, also inclusive of an SIB to the lumpectomy cavity.[24,25] Both series from Spain, breast only and breast plus regional nodes, appear to show a 5-fraction SIB schedule to be safe and effective. The breast only series included 383 patients treated with 26 Gy in 5 fractions to the whole breast and 29 Gy to the lumpectomy cavity, 20% of patients with close or positive margins received an SIB of 30 to 31 Gy. All patients on this analysis received the SIB with 95% utilizing 3D techniques and only 1% with breath hold. With a follow-up of 18 month, there were no local recurrences and low rates of toxicity.[24] Our follow-on trial at HCI will be a phase 2 randomized trial evaluating a similar 5-fractionation schedule. This trial will randomize patients to our 9-day NOVEMBER schedule versus a 5-day Fast Forward schedule, both inclusive of an SIB. Although other centers are prospectively enrolling patients to a 5-day UK Fast Forward schedule, inclusive of a lumpectomy boost, none are randomized against another published SIB schedule. Given the finding in the UK Fast Forward trial demonstrating the increased breast toxicity seen in going from 26 to 27 Gy of radiation, we our randomization is necessary. The hypothesis of our phase 2 randomized trial is that a 9-fraction schedule will demonstrate superior patient satisfaction to a 5-day schedule. It is very possible that a 5-day schedule of radiation (inclusive of a boost), may be just too fast, and result in worse cosmetic results and PROs. From the appendix of UK Fast Forward, we see that 32% of patients described a moderate/marked change in the appearance of their breast, 24% note moderate/marked breast atrophy, and 12.3% report moderate/marked breast pain at 5 years. These PROs scores do not incorporate the effect of a sequential lumpectomy cavity boost. Although different PROs tools were utilized in our study, NOVEMBER appears to provide a better patient experience based on our phase 2 data.

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