NOVEMBER (Novem- (9), BrEast Radiation), A Phase II trial of a 9 day course of whole breast radiotherapy for early stage breast cancer.
Lead Trial ID: HCI103976/IRB# 103976
NCT03345420

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Investigational agent	External Beam Radiation Therapy (EBRT)
IND Number	*N/A*

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography

Abbreviation or Term[1]	Definition/Explanation
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
Hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio

Abbreviation or Term[1]	Definition/Explanation
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine

Abbreviation or Term[1]	Definition/Explanation
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

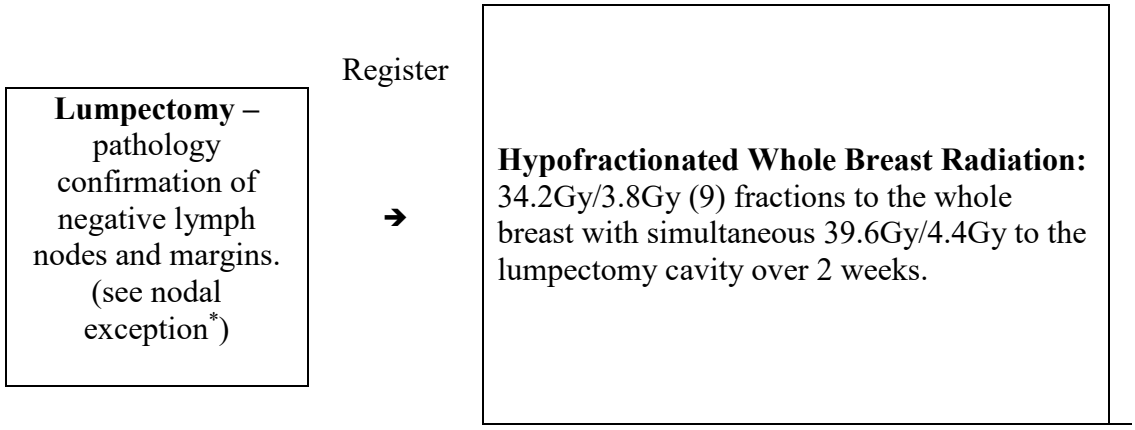
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	NOVEMBER (Novem- (9), BrEast Radiation), A Phase II trial of a 9 day course of whole breast radiotherapy for early stage breast cancer.
Short Title	NOVEMBER.
Protocol Number	IRB#103976
IND	N/A
Phase	Phase II
Design	Single arm non-inferiority trial
Study Duration	8 years (3 years enrollment, 5 years follow-up)
Study Center(s)	Single-center at Huntsman Cancer Institute
Objectives	Primary objective will be to evaluate 24 month breast photographic cosmetic scores with 9 fraction hypofractionated radiation compared to published hypofractionation radiation. Secondary objectives include evaluation of patient reported outcomes, radiation toxicities, disease recurrence, and cost effectiveness.
Number of Subjects	102 enrolled for at least 87 evaluable
Diagnosis and Main Eligibility Criteria	Stage 0-IIB breast cancer in the setting of breast conservation. Exclusion: Prior RT, Recurrent setting, Node positive, NO chemo before RT, No pregnancy
Study Product, Dose, Route, Regimen	External Beam Radiation Therapy (EBRT)
Duration of administration	9 days of Radiation (11-14 calendar days)
Reference therapy	Study therapy will be compared with published phase III data on 15 day, & 16 day hypofractionation breast RT studies from the UK and Canada.
Statistical Methodology	The primary analysis will be 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. The one sided alternative hypothesis is a good to excellent photographic breast cosmetic assessment in > 70% of patients. Assuming the true rate is 80% (e.g. exact equivalence), a sample of 87 evaluable subjects will provide 80% power at the alpha = 0.1 significance level.

STUDY SCHEMA



*Regional Nodes will not be specifically targeted, however some level I/II nodes may be incidentally covered. Nodal evaluation requirement waived for selected patients (Section 5.1).

Patients will be followed with clinical visits for 3 years or until death, whichever comes first. Data at 5 years will be by chart review only.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

1 OBJECTIVES

1.1 Primary Objectives and Endpoint

1.1.1 To evaluate 24 month breast photographic cosmetic scores with 9 fraction radiation compared to standard hypofractionation.

1.2 Secondary Objectives and Endpoint

1.2.1 To evaluate Breast-Q Patient Reported Outcomes (PROs) compared to historical control in breast conservation.

1.2.2 To evaluate the incidence of acute and late radiation complications, based on CTCAE 4.0 toxicity.

1.2.3 To evaluate the local and local regional recurrence rate.

1.2.4 To compare the direct and indirect patient costs for radiation therapy compared to historical controls as well as quality adjusted life years, utilizing the Breast-Q Patient Reported Outcomes (PROs) and the EQ-5D.

2 BACKGROUND

2.1 Rationale for the Study

Adjuvant radiation therapy (RT) plays an important role in successful breast conservation in early stage breast cancer, and has been shown to significantly reduce the risk of breast cancer recurrence over surgery alone[1-4]. Adding breast radiation to lumpectomy has allowed women to keep their natural breast, as multiple randomized trials have demonstrated equivalent overall and disease free survival compared to a 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.[8] An important component of radiation therapy is the time-dose-fractionation schedule. Up until the last decade, the standard radiation schedule in North America involved 6-8 weeks of daily radiation.

In 1986 Royal Marsden Hospital and the Gloucestershire Oncology Centre collaborated in a prospective trial evaluating 3 breast fractionations: 50Gy in 25 fractions, 39Gy in 13 fractions (3.0Gy/fx), or 42.9Gy in 13 fractions (3.3Gy/fx) all over 5 weeks [9]. In 1999, after over 1400 patients had been enrolled the trial design was expanded into a multi-institutional trial and patient data from the earlier study was rolled into what became START A, with the 13 fraction regimen changed to 3.2Gy/day for 41.6Gy. A total of 2236 women were randomized to one of three arms between 1986 and 1999, treating patients with 2D planning and Cobalt-60. The overall treatment time of 5 weeks was kept constant in all three arms. The primary endpoint was late breast change. Local control

was a secondary endpoint. Locoregional relapse was non-significantly different in the 3 arms at 10 years at 7.4%, 6.3% and 8.8%.[10] Fourteen percent of patients received CMF chemotherapy. Running in parallel to STARTA, the UK STARTB trial was an accelerated hypofractionation trial comparing 50Gy in 2Gy daily fractions for 5 weeks versus 40Gy delivered in 2.67Gy daily for 15 days.[11] This trial accrued 2215 stage I and II breast cancer patient between 1999 and 2001, treating patients with Cobalt-60, utilizing 2D planning. 23% of patients received chemotherapy +/- tamoxifen. In 1993, shortly after the RMH began their prospective trial, researchers with the National Cancer Institute of Canada (NCIC) and Ontario Clinical Oncology Group conducted a similar hypofractionated randomized trial comparing whole breast radiation of 50 Gy in 25 fractions versus a hypofractionated regimen 42.5 Gy in 16 fractions. 10 year data was published by Whelan et al in 2010 revealing equivalent outcomes in terms of cancer control and toxicity.[12,13] Cosmesis was identical with excellent or good scores at 3 and 5 years in 77% of patients in both groups. Toxicities were comparable. Grade 2 and 3 toxicities were negligible. At 5 years, 87% of women in the experimental arm had no skin toxicity, and 66% of women had no subcutaneous toxicity, compared with 82% and 60% in the control arm, respectively. A major limitation of the Canadian study is the lack of a lumpectomy boost. 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 further the risk of a local breast recurrence.[14,15] Women in the NCIC study were not allowed a breast lumpectomy boost, but the UK start trials allowed an optional boost of 14Gy in 5 daily fractions. This occurred in 61% of patients in STARTA and 43% in STARTB.

Adding a lumpectomy cavity boost in a sequential manner, adds an additional 5-8 treatment days of radiation, significantly increasing treatment burden. Several institutions have published results suggesting the safety of delivering the lumpectomy cavity boost concurrent with the whole breast radiation.[16-19] From 2011-2015, the Radiation Therapy Oncology Group (RTOG) moved this single institution data into the phase III randomized trial 1005, randomizing women with a sequential vs. concurrent lumpectomy cavity boost.[20] In this trial, the whole breast radiation could be administered in 15 vs. 25 fractions, at the discretion of the treating physician. In the concurrent arm, the breast received the UK START dose of 40Gy (2.66/day) while the lumpectomy cavity received an additional daily dose, resulting in a total of 48Gy delivered, 3.2Gy/day. In the conventional arm, the breast received the boost delivered over an additional 6-7 daily treatments as the treating physician discretion.

The UK has tried to advance the hypofractionation concept further with the UK Fast trial. This trial enrolled 915 patients from 2004 to 2007 into one of three treatment arms: 50Gy in 25 fractions, 28.5Gy in 5 fractions or 30Gy in 5 fractions, all delivered over 5 weeks. The primary endpoint for the trial is change in photographic breast appearance. Initial publication in 2011, with a mean follow up of 3 years, has shown all arms acceptable in regards to conventional toxicity. The 50Gy and 28.5Gy arms appear to be similar in 2 year photographic appearance, however the 30Gy arms appears to be inferior with a risk ratio of mild to marked change in appearance 1.7:1 (1.26-2.29, $p<0.001$).[21] There are two potential problems with this hypofractionation model. The radiobiology is not well understood when taking 6 days off between each treatment fractions, therefore the long term disease control outcomes will need to be carefully followed over the next 5-10 years

to ensure equivalent cancer control. Additionally, for women residing a long distance from the nearest treatment facility, this results in additional burden for housing and transportation.
With the publishing of the hypofractionated data from the UK and Canada, there has been an increasing adoption rate of short course radiation here in the US, despite some reluctance.[22-25] This is likely due to the difficulty some physicians have with changing 30+ years of tradition, as well as the decreased reimbursement rates that come with hypofractionation, given the current fee for service payment model.
We feel our proposed fractionation will provide a significant improvement in convenience and cost effectiveness, while delivering equivalent cancer control.

2.2 Baseline Toxicity from whole breast radiation

In reviewing toxicity data from previous hypofractionation trials, the UK STARTB 40Gy in 15 fraction treatment arm (majority received an optional 10Gy boost) reported a 5 and 10 year local recurrence rate of 2% and 3.8% (respectively), and 10 year 4.3% local-regional relapse (3.2-5.2%, CI). Reported toxicities are shown in the table below. Cosmetic results overall were better in the 3 week 40Gy hypofractionation arm compared to the 5 week 50Gy standard arm.[10,11]

Symptomatic rib fracture	2.2%
Lung fibrosis	1.7%
Ischemic heart disease	1.5%
Breast edema	5%
Telangiectasia	4.2%
Breast shrinkage	26%
Breast induration	14%

In the NCIC hypofractionation randomized study the local recurrence rate (invasive only) at 5 and 10 years was 2.8% and 6.2%. Grade 3 RT associated morbidity was 4%. 30% of women had less than an excellent or good cosmetic result (grade 2 or 3 on the EORTC photographic assessment).[12,13] This slight higher recurrence rate compared to the UK start data may reflect a higher risk group or the fact the NCIC patients did not receive a lumpectomy cavity boost.

Based on this information, we feel that a reasonable expected combined radiation grade 2 or greater non-acute toxicity rate (non-cosmetic) would be 7-10%, a conservative estimate from several prospective trials.

Also based on this information, we feel that a reasonable expected local recurrence rate would be 5-6%, with an upper limit of 10% acceptable.

2.3 Altered Fractionation in Breast Cancer

In standard breast irradiation, daily fraction sizes of 180 cGy or 200 cGy are commonly used and are described as conventional or standard. The rationale for conventional fractionation and the relationship between fraction size and tissue response is well described by the α/β ratio in the linear quadratic model of fractionation sensitivity.[26] In this empiric model, "late-reacting" normal tissues such as fibroblasts and neurons have a low α/β ratio (2-5 Gy) and are very responsive to increases in fraction size, while "acutely-reacting" normal tissues such as intestinal epithelium have a high α/β ratio (>7 Gy) and are less responsive to changes in fraction size. The biological effect of a given fractionation scheme size is related to the α/β ratio by the equation:

$$\text{Biological Effective Dose} = \text{BED} = nd\ (1 + \frac{n}{\frac{\alpha}{\beta}}) \text{ where}$$

d = dose/fraction

n = # of fractions

Although relatively high cumulative doses of radiation are needed for tumor control, the daily fraction size has to be respectful of the fraction sensitivity of normal tissues in the treated volume. Accounting for these assumptions, increases in fraction size have to be compensated for by reductions in cumulative radiation dose, which typically are insufficient for tumor control. As a result, daily fractions of 1.8 to 2 Gy are delivered over 4-6 weeks to reach a cumulative dose of 45-60 Gy. In vitro experiments in human breast carcinoma cell lines have suggested an α/β ratio of about 4 Gy.[27,28]

This 9 day radiation treatment design is supported in its safety and efficacy through similar randomized trials in early stage breast conservation, confirming the BED modeling.

Table of Biological Effective doses from different radiation fractionations

		Biological Effective Dose	
	Total dose/fx size	α/β=2 (normal tissue)	α/β =4 (breast cancer)
Whole Breast			
NSABP-B06	50Gy/2	100	75
NCIC	42.56Gy/2.66	100	71.2
UK Start B	40Gy/2.66	93	66.4
UK FAST	30Gy/6 (5 wks)	120	75
UK FAST	30Gy/5.8 (5 wks)	110	69
November	34.2Gy/3.8	99.2	66.7
With Lump Boost			
Lyon Boost	60Gy/2	120	90
EORTC Boost	66Gy/2	132	99
UK Start w/Boost	40Gy/2.66 + 10Gy/2	113	81.4
RTOG 1005 SIB	48Gy/3.2	125	86
November	39.6Gy/4.4	126.7	83.2

Hopefully, this short treatment schedule will reduce cost while likely improving patient satisfaction for women. The promise of short-course radiation lies in the added

convenience it may offer to patients who otherwise may not be able to receive radiation, and 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. In this trial, we will require adjuvant chemotherapy to be delivered after radiation. Given the excellent cure rates and low morbidity with current adjuvant radiation therapy technique and fractionation, it is only natural that subsequent improvements in the field take convenience and economic impact into account.

2.4 Photographic Cosmetic Assessment

The 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.[10,15,21,36,37] 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 a global cosmetic score based on all of the factors. Characteristics are graded on a four-point scale: 0, excellent or no difference; 1, good or small difference; 2, fair or moderate difference; and 3, poor or large difference. In the UK Start B analysis of more than 900 patients, the rate of good/excellent photographic cosmetic assessment was 80% at 2 years.[2] In the NCIC analysis of over 1200 patients the 3 year rate of good/excellent cosmetic assessment was 77% (no 2 yr rate given).[4] Based on the NCIC and UK start photographic assessment, we anticipate that our patients will have an overall good-excellent cosmetic score in ≥ 70% of patients, when compared to their baseline.

2.5 Patient Satisfaction and Well-being as Patient Reported Outcomes (PROs)

The assessment of patient-reported outcomes (PROs) in clinical research provides important insight into how therapies impact the daily lives of patients. There is a growing recognition that patient-reported endpoints are critical in oncology trials, particularly when cosmesis and toxicity are likely to be different in the treatment arms. Patient-reported adverse event collection has been shown to be more thorough than collection by provider-report, with consistent underreporting of side effects by providers.[29] Patient-reporting of health-related quality of life has become the gold standard in part because providers have been found to underestimate the pain and distress their patients are experiencing.[30,31]

In a trial of different radiation schedules, in which cosmesis may be substantially different in the two arms of the study, patient-reported satisfaction and well-being are particularly important. Although short-term differences between the treatment arms may be momentarily relevant to patients, the long-term cosmetic outcomes are most critical, so we have chosen to collect this data at 24 months (and compare to historical controls). In order to avoid burdening patients, we will only administer the Breast-Q survey to patients at baseline, 6, and 24 months. The EQ-5D-3L will be administered at baseline and 2-8 weeks post radiation therapy.

We will be using the Breast Q survey tool to assess patient satisfaction and well-being.[32,33] This tool has been validated for use in patients after breast conserving therapy to assess well-being and patient satisfaction with results, and is provided free of charge for academic research.[34] Domains for the survey include: satisfaction with breast, adverse effects of

radiation, psychosocial well-being, physical well-being and satisfaction with information. Cronbach's alphas for the scale range from 0.81 to 0.98, and the BREAST-Q has test-retest reliability, demonstrated by an intra-class correlation coefficient ranging from 0.85 to 0.987.[35] The electronic 2.0 version we will be using was given retrospectively to 3497 women who had undergone a lumpectomy (1622 with adjuvant radiation) and determined to be a reliable and validated survey tool, with median score for Satisfaction with Breast to be 62 (44-77), and no significant difference in the radiated cohort.

We will be using the EQ-5D-3L survey tool. The 3-level version of EQ-5D (EQ-5D-3L) was introduced in 1990 by the EuroQol Group. The EQ-5D-3L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).
The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

2.6 Cost Effectiveness

We hypothesize that a 9 fraction course will be more cost effective. Costs will be compared to 45 de-identified patients that were treated with a standard hypofractionated regimen of 19 treatments. Direct costs of medical care to each patient will be estimated using utilization information from HCI financial/claims data. Generalized linear models will then be used to model these costs as a function of treatment, time on study, and all available baseline patient characteristics to assess the extent to which estimated direct cost is impacted by the type of radiation dosing. Given the well-known fact that healthcare costs are typically highly skewed, regression models will employ the appropriate distribution and transformation link.

3 STUDY DESIGN

3.1 Description

This will be a phase II single arm non-inferiority trial. Trial patients will receive 9 fractions hypofractionated radiation. Patients will be evaluated for breast photographic cosmetic scores with hypofractionated radiation compared to standard fractionation 24 months after radiation. Secondary objectives include evaluation of toxicities, recurrence, patient reported outcomes and cost effectiveness.

3.2 Number of Patients

87 Analyzable patients. Plan for 15% drop out rate, therefore plan to enroll 102 patients

3.3 Number of Study Centers

At this time, Huntsman Cancer Hospital is the only planned enrolling institution.

3.4 Study Duration

We anticipate enrolling 30 patients per year on this trial with 3 years of clinical follow up. We plan to do a chart review at 5 years for any long-term toxicities or evidence of late breast cancer recurrences.

4 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with enrolling investigators signature in the patient research chart.

Patient No. _____
Patient's Initials: (L, F, M) _____

4.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

4.1.1 _____ Histologically confirmed invasive carcinoma and/or Ductal Carcinoma In Situ (DCIS) of the breast.

4.1.2 _____ Final pathologic Tis, T1-T3, all must be N0 and M0 status).

4.1.3 _____ Negative inked histologic margins from lumpectomy, with the exception of a focus of positive margin at the pectoralis fascia.

4.1.4 _____ Radiation oncologist does not plan to treat regional lymph nodes beyond standard whole breast tangent fields.

4.1.5 _____ Lumpectomy with negative lymph node on surgical evaluation (Isolated tumor cells in lymph nodes will be permitted). Patients with invasive carcinoma ≥ 70 yrs and with ER+ positive tumor ≤ 2.0cm may enroll without surgical lymph node evaluation, per section 5.1. Patients with Ductal Carcinoma In Situ (DCIS) of the breast only may enroll without surgical lymph node evaluation.

4.1.6 _____ Negative serum or urine β-HCG in women of child-bearing potential ≤ 7 days prior to registration.

A female of childbearing potential is a sexually mature female who has not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 12 consecutive months.

4.1.7 _____ Women of child-bearing potential must agree to utilize a form of birth control or agree to undergo sexual abstinence during radiation therapy.

4.1.8 _____ ECOG (Zubrod) Performance Status 0-1.

4.1.9 _____ Patient ≥ 18 years of age.

4.1.10 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

4.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

4.2.1 _____ Prior radiation therapy to the chest, neck or axilla.

4.2.2 _____ Prior history of ipsilateral breast cancer (invasive disease or DCIS). LCIS and benign breast disease is allowed.

4.2.3 _____ History of prior or concurrent contralateral invasive breast cancer. Benign breast disease, LCIS or DCIS of contralateral breast is allowed.

4.2.4 _____ Active collagen vascular diseases, such as: systemic lupus erythematous, scleroderma, or dermatomyositis.

4.2.5 _____ Significant post lumpectomy complications requiring an unplanned re-operation or admission for IV antibiotics. Re-operation for margins evaluation or nodal evaluation is acceptable.

4.2.6 _____ Co-existing medical conditions with life expectancy < 5 years.

4.2.7 _____ Other malignancy within 5 years of registration with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the cervix.

4.2.8 _____ Neoadjuvant chemotherapy or adjuvant chemotherapy delivered before radiation.

4.2.9 _____ Neuroendocrine carcinoma or sarcoma histology.

4.2.10 ____ Concurrent radiation sensitizing medications concurrent with radiation, per treatment physician.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5 TREATMENT PLAN

Initial surgery is defined as lumpectomy and any subsequent surgeries related to the initial lumpectomy, including additional margin resection, or lymph node removal.

Radiation treatment may begin no later than 84 days after initial surgery. Chemotherapy must be delivered after (NOT BEFORE) radiation.

Chemotherapy is defined as cytotoxic chemotherapy, not biological therapy, such as trastuzumab, pertuzumab, etc.

5.1 Surgical Management

Lumpectomy

Margins should be negative, defined as no tumor on ink. A focally positive deep margin will be considered a negative margin if the deep margin is the pectoralis fascia. This is provided there is no evidence of pectoralis fascia invasion by imaging or pathological evaluation.

Lymph nodes must be evaluated by sentinel node biopsy or axillary dissection. The exception, per the CALGB 9343 criteria is patients who are ≥ age 70 and have ER positive tumors ≤ 2.0cm.[38] These patients will not require lymph node evaluation. This protocol does not stipulate sentinel node versus axillary dissection, but does require lymph node management per standard of care. Patients will be recorded as having undergone a sentinel node only procedure or an axillary dissection. A sentinel node procedure will be considered an axillary dissection if more than 5 lymph nodes are removed.

5.2 Systemic Therapy

Any **adjuvant hormonal therapy** is allowed. It may begin any time relative to the radiation, at the discretion of the treating physician.

Chemotherapy is allowed, but must be delivered after radiation therapy. Neoadjuvant chemotherapy is not allowed. Patients may be co-enrolled on systemic therapy trials, if there is no contraindication on the other trial.

Cytotoxic systemic therapy may not be used concurrently with radiation; however, trastuzumab, pertuzumab or other biological therapy may be given concurrently per standard of care.

If cytotoxic chemotherapy is started after radiation, a minimum of 10 days must pass after the last fraction of radiation before beginning chemotherapy. If a patient is experiencing a CTCAE Grade 2 or higher skin reaction, it is recommended that this be extended to 21 days, or until the skin reaction has resolved.

5.3 Radiotherapy

Radiation therapy treatment planning should begin after consultation with the radiation oncologist and prior to radiation treatment.

5.3.1 Technical Factors

3-dimentional CT based treatment planning is required. Megavoltage photon beam energies with energies ≥ 4 MV are required. Electron beams require megavoltage energies, if utilized. Proton beams are not allowed on this trial.

Localization, simulation and immobilization

Simulation and treatment must be performed with the patient in the supine or prone position. Patients should be optimally positioned with alpha cradle casts, vac fix, breast boards, wing boards and/or other methods of immobilization at the discretion of the treating physician.

Methods to minimize the cardiac exposure to RT such as a heart block, gating or breath-hold are allowed at the discretion of the treating physician.

A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV), planning target volumes (PTV), and Organs at Risk (OAR).

Radio-opaque markers are to be placed on the patient's skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set.

The CT scan should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of < 0.5 cm should be employed.

External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

Use of IMRT is allowed. Please see the section below for IMRT guidelines.

Calculations shall take into account the effect of tissue heterogeneities.

Each of the following volumes and normal structures must be delineated on each slice of the planning CT:

Post Lumpectomy Volumes: Ipsilateral and Contralateral Breast and Lumpectomy Cavity.

Normal tissue: Right and left lung, contralateral breast, heart, thyroid.

Normal tissues should be delineated as follows:

Breast: Breast CTV. Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation, the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the RTOG breast cancer atlas. The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratus anterior muscle excluding

chest wall, boney thorax and lung. In general, the pectoralis and/or serratus anterior muscles are excluded from the breast CTV unless clinically warranted by the patient's pathology. The breast CT should generally follow consensus guidelines

Contralateral breast: Includes the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas.

In general the borders are:

- *Posterior border:* At the anterior surface of the pectoralis, serratus anterior muscles excluding Breast, ribs, boney thorax, and lung/heart.
- *Medial border:* The sternal-costal junction.
- *Lateral border:* Varies based on the size of the breast, but typically is at the mid-axillary line and excludes the ipsilateral lattismus dorsi muscle.
- *Cephalad border:* Should be similar to that of the ipsilateral breast CTV.
- *Anterior border:* Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface.

Ipsilateral and contralateral lung: These may be contoured with auto-segmentation with manual verification.

Heart: This is to be contoured on all cases – not just the left sided cases. The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (pa). Above the pa, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

Thyroid: The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured. For patients who have undergone total thyroidectomy, there may be no thyroid tissue to contour.

IMRT

The following definitions and conditions are applied concerning IMRT in this protocol:

1) The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints.

2) A plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose-volume constraints are met and at least 3 apertures for each beam direction are used.

3) If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam, as described in number 1) above, should deliver > 50% of the total number of monitor units for the beam orientation.

4) If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the composite dose distribution and DVHs should be generated.

5) All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and shoot, VMAT, tomotherapy) are allowed and classified as IMRT as long as target and critical structure dose-volume constraints are met.

6) IMRT planning and delivery systems using physical beam-intensity compensators designed by an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.

All plans that are not fit into the above definitions and conditions are classified as 3DCRT plans. Specifically:

- The plans generated using forward-planning methods or segmental techniques such as “field-in-field” to meet dose-volume constraints are considered as 3DCRT plans. These forward-planned or segmental treatment techniques are those intended mainly to improve the uniformity of the dose distribution, but not to produce steep dose gradients to protect critical structures (e.g. heart or lung).

- The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms.

5.3.2 Treatment Planning

The goals of treatment planning in this study in both arms are to encompass the breast and minimize inclusion of the heart and lung.

Field arrangements for 3D conformal and IMRT of the breast are defined below with some discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the target volumes and normal tissues outlined below. This trial is specifically evaluating toxicity and cosmesis; therefore we have set tight constraints on maximum doses.

Treatment plans must meet Dose Volume Constraints for the contoured targets and normal structures. Various treatment approaches may be used to develop treatment plans.

Ipsilateral Breast CTV to PTV expansion is a range of 5-7mm, based on practice and technical capabilities.

The following volumes are to be delineated:

Lumpectomy GTV: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended). Patients without a clearly identifiable lumpectomy bed are not eligible for protocol participation.

Lumpectomy CTV: Lumpectomy GTV + 1 cm 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient's pathology. The Lumpectomy CTV should not extend outside of the Breast CTV and should be trimmed if necessary to accomplish this.

Lumpectomy PTV: Lumpectomy CTV + 5 mm 3D expansion (excludes heart).

Lumpectomy PTV Eval: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval which is edited. This Lumpectomy PTV EvaL is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (Breast, pectoralis muscles and lung) when pertinent. The lumpectomy PTV should not cross midline. This Lumpectomy PTV Eval is the structure used for DVH constraints and analysis. This Lumpectomy PTV Eval cannot be use for beam aperture generation.

Breast CTV: Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see section 5.3.1), the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the breast cancer atlas (section 5.3.1). The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chest wall, boney thorax and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the breast CTV unless clinically warranted by the patient's pathology. The breast CT should generally follow consensus guidelines

Breast PTV: Breast CTV + 5-7 mm 3D expansion (exclude heart and do not cross midline).

Breast PTV Eval: As a part of the Breast PTV often extends outside the patient, the Breast PTV is then copied to a Breast PTV Eval, which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. This Breast PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

Ribs: The ribs within the Breast PTV need to be contoured as a structure.

5.3.3 Dose-Volume Histogram (DVH) Analysis.

Breast:

** These are calculated by evaluating the whole breast plan before the summation of the lumpectomy cavity boost.

Preferred: ≥ 95% of the Breast PTV Eval contour that falls within the tangential treatment fields will receive 32.5Gy, 95% of the Breast prescribed dose of 34.2Gy. *Acceptable*: ≥ 90% of the Breast PTV Eval contour that falls within the tangential treatment fields will receive > 30.8Gy Gy which is ≥ 90% of the whole breast prescribed dose of 34.2 Gy.

Maximum Dose to Breast: Less than 10cc of PTV Eval will receive > 107% dose or 36.6 Gy for a prescribed breast/Breast dose of 34.2 Gy. Less than 0.03cc can receive > 115% of dose, 39.3Gy.

** These are calculated by evaluating the entire plan sum, inclusive of the lumpectomy cavity integrated boost.

Preferred: ≤ 30% of the breast PTV Eval will receive > 100% of the boost prescribed dose of 39.6Gy. *Acceptable* ≤ 35% of the breast PTV Eval will receive > 100% of the boost prescribed dose of 39.6Gy.

Preferred: ≤ 50% of the breast PTV Eval will receive > 37Gy. *Acceptable*: ≤ 50% of the breast PTV Eval will receive > 38.3Gy.

Lumpectomy:

** These are calculated by evaluating the entire plan sum, inclusive of the lumpectomy cavity integrated boost.

Preferred: ≥ 95% of the Lumpectomy PTV Eval contour will receive 37.6Gy, 95% of the Lumpectomy prescribed dose of 39.6Gy. *Acceptable*: ≥ 90% of the Lumpectomy or Lumpectomy PTV Eval contour that falls within the tangential treatment fields will receive > 35.6Gy Gy which is ≥ 90% of the whole Lumpectomy prescribed dose of 39.6 Gy.

Preferred: ≤ 5% of the Lumpectomy PTV Eval will receive > 43.5Gy, 110% of the boost prescribed dose of 39.6Gy. *Acceptable* ≤ 10% of the Lumpectomy PTV Eval will receive > 43.5Gy

Preferred: Maximal dose to greater than 0.03 cc will be 45.5 Gy. *Acceptable* is maximal dose no greater than 47.5 Gy.

Contralateral Breast:

Preferred: Less than 10% of the contralateral Breast or breast receives > 2 Gy.

Acceptable: Less than 10% of the contralateral Breast or breast receives 4 Gy or more.

Ipsilateral Lung:

Preferred: ≤ 35% of the ipsilateral lung should receive ≥ 14.5 Gy.

Acceptable: ≤ 40 % of the ipsilateral lung should receive ≥ 14.5 Gy.

Contralateral Lung:

Preferred: ≤ 10% of the contralateral lung should receive 4 Gy or more.

Acceptable is ≤ 15% of the contralateral lung should receive 4 Gy or more.

Heart:

Preferred ≤ 10% of the whole heart should receive ≥ 18 Gy for left-sided breast cancers, and < 2% of the heart should receive ≥ 18 Gy for right-sided breast cancers.

Acceptable: ≤ 10% of the whole heart should receive ≥ 22 Gy for left-sided breast cancers, and < 2% of the heart should receive ≥ 22 Gy for right-sided breast cancers.

Preferred: Mean heart dose should be ≤ 1.5 Gy.

Acceptable is a mean heart dose ≤ 2.5 Gy.

Every attempt should be made to make the cardiac exposure to radiation as low as possible.

Ribs:

The max rib dose for the entire plan sum is 36Gy. Blocking the ribs from the boost field will likely be necessary. If the lump PTV_eval cannot be adequately covered by a minimum dose (90% volume to 90% dose), consider taking the patient off protocol.

5.4 Prohibited Concomitant Medications

No potential radio-sensitizers may be used concurrent with radiation therapy.

5.5 Duration of Therapy

Subjects must be withdrawn from the study treatment for the following reasons:

- Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- The development of a second cancer or recurrent disease.
- Death.

Subjects may be withdrawn from the study for the following reasons:

- The subject is non-compliant with radiation treatments, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.

6 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting. Dose Modifications

Radiation doses should not be modified and compliance with the protocol will be determined as defined above, by the ideal and acceptable dose constraint criteria. Dose deviations outside of the acceptable range will be considered major protocol violations. Patients may occasionally require treatment breaks, which should be kept to a minimum. Treatment breaks of up to 2 days will be considered acceptable. Treatment breaks of greater than 2 days are strongly discouraged.

6.1 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

7 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Tests & Observations	Prior to Registration	Before RT	Weekly during RT	2 to 8 weeks post RT	6 months post RT*	12 months post RT*	2 years post RT*	3 years post RT**	5 years Post RT**
Obtain Informed Consent[13]	X								
H&P	X[3,11]								
Symptom Directed Physical[11]			X	X	X	X	X	X	
ECOG Performance Score	X		X	X	X	X	X	X	
Recurrence Assessment[10]					X	X	X	X	X[5,10]
Adverse Events Assessment[1]			X	X	X	X	X	X	X[1,5]
Photographic Cosmetic Assessment[6]		X					X		
Serum or Urine HCG	X[2]								
Breast-Q Survey[7]		X			X		X		
Health Care Expense *Diary*			X[4]						
Health Care Expense Survey				X[8,12]					
EQ-5D Survey[9]		X		X					

* +/- 6 weeks

** +/- 3 months

1. Assessment of side effects related to radiation therapy should be assessed according to the history and physical examination.
2. For women of childbearing potential. Must be done within 7 days prior to registration.
3. All screening procedures should be performed within 28 days prior to registration except as otherwise noted.
4. Health Care Expense Diary should be provided to the patient each week during RT to assist in recall for the Health Care Expense Survey after radiation completion. (Appendix III)
5. Post hoc chart review only for 5 years.
6. Photographic assessment collection will be done as described in section 8.1.
7. Breast Q Survey should be completed by the patient prior to radiation therapy and at 6 months post radiation therapy. (Appendix I)
8. Health Care Expense Survey should be completed using the Health Care Expense Diary worksheet (Appendix III) during the 2-8 week window and is found in Appendix II.
9. EQ-5D Survey should be completed by the patient prior to radiation therapy and during the post radiation therapy 2-8 week window. (Appendix IV)
10. Disease recurrence will be determined by standard of care assessments as described in section 8.3.
11. Clinical assessments above are a minimum for trial purposes only and do not represent the entirety of necessary medical care. Weekly treatment visits occur once every 5 treatment fractions during radiation. Follow up visits should be scheduled per standard of care and physician discretion. Per NCCN guidelines, clinical follow up visit should occur 1-4 times per year with continued annual mammograms.
12. Identified patients who voluntarily agree to complete the Health Care Expense Survey should be provided this survey at 2-8 weeks post standard of care hypofractionated radiation. (See section 8.4 Economic Analysis for further instruction)
13. Patients who volunteer to complete the Health Care Expense Survey must be provided with the Informed Consent Letter prior to completing the questionnaire.

8 CRITERIA FOR EVALUATION AND ENDPOINT

8.1 Photographic Assessment

The primary outcome of this study is the overall photographic cosmetic outcome of 9 fraction radiation in NOVEMBER versus published hypofractionation radiation. Cosmetic effects of radiation can include telangiectasia, breast fibrosis, scar retraction and skin pigmentation changes. As this is not a blinded study, cosmetic assessment will be blinded with digital photography reviewed by a 3 unbiased reviewers. Reviewers will include a radiation oncologist, surgeon and nurse.

Confidential bilateral digital photographs (excluding the face) will be taken with a digital camera:

Photo #1) Bilateral, standing, anterior photo to show both breasts with the arms at 45° from the body and

Photo #2) Unilateral, close up of treated area to show the surgical scar at 24 months post radiation.

Photographs will be captured of both breasts at the following time points:

- Before radiation (Post Lumpectomy and before Radiation)
- 24 months after the completion of radiation

Photographs of both breasts will be collected as above and reviewed by a blinded Central Adjudication Committee according to the modified EORTC Cosmetic Rating System. An on-line training module is available.

8.2 Patient Reported Outcomes

We will be using the Breast Q survey tool to assess patient-reported satisfaction with breast, well-being, and overall satisfaction. This tool has been validated for use in patients before and after mastectomy as well as breast conservation, and is provided free of charge for academic research. We will be using the Breast Q Breast Conserving Therapy Module at baseline, 6 months and 24 months after radiation finishes. There are 119 questions with the conceptual framework of the BREAST-Q modules comprised of two overarching themes, which are health-related quality of life (QOL) and patient satisfaction.

Within QOL, there are two scales: Physical, Psychosocial and Sexual Well-being. Within the Psychosocial Well-being scale for patients, there are items that ask about body and a woman's confidence in social settings. Other items cover emotional health and self-esteem. Within the Sexual Well-being scale, there are items that ask about feelings of sexual attractiveness when clothed and unclothed and sexual confidence as it relates to one's breasts, as well as how comfortable or at ease a woman feels during sexual activity. Within the Physical Well-being scales here are questions asking about pain, activity limitations, and sleep problems due to discomfort.

Within patient satisfaction, there are three other scales: Satisfaction with Breasts, and Satisfaction with Care. “Satisfaction with Breasts,” measures body image in terms of a woman’s satisfaction with her breasts and asks questions regarding how comfortably bras fit, and how satisfied a woman is with her breast area both clothed and unclothed. Postoperative items ask about breast appearance (e.g., size, symmetry, softness) and clothing issues (e.g., how bras fit; being able to wear fitted clothes). The preoperative modules and the Satisfaction with Care scale will not be included in this study.

Each scale can be used independently and scored separately. The BREAST-Q scoring software, QScore, transforms patient-reported data into summary scores ranging from 0-100 with a higher number meaning better quality of life or higher satisfaction on the various scales.

BREAST Q questionnaires can be collected with pencil/paper or done electronically.

8.3 Local and local regional recurrence

Recurrence data will be collected at 6, 12, 24, and 36 months of follow up and will include a 5 year chart review.

8.3.1 Criteria for Local and regional recurrence

8.3.2 Local Recurrence

Local recurrence is defined as histologic evidence of ductal carcinoma in situ or invasive breast cancer in the same quadrant as the lumpectomy of ipsilateral reconstructed breast or breast. A recurrence elsewhere in the breast is considered a local-regional recurrence.

8.3.3 Regional Recurrence

Regional recurrence is defined as the cytologic or histologic evidence of disease in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of the ipsilateral axilla. A recurrence in a separate quadrant from the initial lumpectomy will also be scored as a regional recurrence.

8.3.4 Distant Recurrence

Distant recurrence is defined as the cytologic, histologic and/or radiographic evidence of disease in the skin, subcutaneous tissue, lymph nodes (other than local or regional metastasis), lung, bone marrow, central nervous system or histologic and/or radiographic evidence of skeletal or liver metastasis.

8.3.5 Second Primary Breast Cancer

Second primary breast cancer is defined histologic evidence of ductal carcinoma in situ or invasive breast cancer in the contralateral breast.

8.3.6 Second Primary Cancer (Non-breast)

Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the cervix is to be reported and should

be confirmed histologically whenever possible. If this occurs in the breast radiation field, it will be scored as a radiation induced secondary malignancy.

8.3.7 Death

Underlying cause of death is to be reported.

8.4 Economic Analysis

A reduction in number of radiation treatments and thereby number of visits to the radiation therapy department will benefit patients directly, both in terms of reduced direct and indirect healthcare costs. Direct healthcare costs are expected to go down because of an expected reduction in health care utilizations services (e.g., office visits, emergency room visits, inpatient admissions). With short-course treatment patients may be able to take less time off from work and/or return to work faster. Potential improvements in cosmetic-outcomes and side effects of radiation therapy with short-course therapy could also translate into a reduction in utilization of health care services, further enhancing the economic impact of hypofractionation. Indirect costs are also expected to be lower for the intervention arm because patients in this arm are expected to resume normal activities sooner. This in turn would help save family caregiver time as well as the cost of dependent care, which will further add to the saving in indirect costs. Therefore, robust measurement of the patient resources used to receive radiation therapy and utilization of health services is a critical component of this trial.

Patients will be given a diary with question domains to be filled out weekly during radiation therapy in order to help improve recall (Appendix II, III and IV).

We will utilize available CPT code charges generated from the time of registration to 2-8 weeks after the completion of radiation therapy. We will utilize the HCI financial data to estimate reimbursable charges.

Questions are adapted from the Medical Expenditure Panel Survey-Household Component (MEPS-HC) created by

AHRQ (https://meps.ahrq.gov/survey_comp/hc_survey/2014/DD111214.pdf).

For comparison assessment, this survey will be administered to an additional 45 patients undergoing standard of care hypofractionated radiation who are otherwise not eligible or interested in enrollment on this protocol. The Health Care Expense Survey should be provided to the patient and completed by the patient 2-8 weeks post standard of care hypofractionated radiation. The comparison group will either receive a $20 meal card or be reimbursed for a meal up to $20, with provision of a receipt from the date of the study visit, after completion of the Health Care Expense Survey. This comparison cohort will be case-matched for distance to treatment facility and employment status.

Collected 2-8 weeks after the completion of radiation:

- Work status prior to breast cancer diagnosis (job for pay or business owner, not including work around the house; including work in a family farm or business even if unpaid).

- If working number of days working per week.
- If working, number of hours working per day.
- Profession and the job title.
- Total number of hours spent for each radiation treatment (time from leaving home or work to return to home or work).
- Distance from radiation treatment facility from home or work.
- Means of getting to radiation treatment facility (ask if only one modality used or a combination, if a combination record number of days for each modality).

1) Car

- Approximate cost for parking
- Did patient drive, was patient driven, or a combination

2) Shuttle

- Approximate cost

3) Public transportation

- Approximate cost per visit

4) Foot

5) Taxi/car service

- Approximate total cost per visit (both ways)

- Number of radiation treatments during which at least one other person accompanied patient

8.5 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained.

8.6 Stopping Rules

After 45 patients have been enrolled and followed for 6 months, an interim analysis will be performed of all patients with greater than 6 months of follow up. Based on an expected RT toxicity rate of ≤10%, if greater than 20% of our patients are found to have

non-acute grade 2 or 3 RT toxicities ≥ 6 months after the completion of radiation, this study will be temporarily halted for interim review. Based on an anticipated recurrence rate of < 7%, if ≥ 15% of patients have a documented local recurrence, this study will be temporarily halted for interim review. Once temporarily halted, a team of experts will review the data to determine if it is safe to proceed with the trial or if the trial should be discontinued.

9 STATISTICAL CONSIDERATIONS

9.1 Primary Objective

Overall good to excellent photographic cosmetic of the treated compared to the untreated breast, 24 months after radiation in ≥ 70% of patients, when compared to baseline pre-radiation photographs (See Section 2.4 for data on baseline expected risk). Two year photographic cosmetic scores will be scored according to the EORTC and NCIC photographic assessment system. The primary analysis will be 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. The one sided alternative hypothesis is a good to excellent photographic breast cosmetic assessment in > 70% of patients. Assuming the true rate is 80% (e.g. exact equivalence), a sample of 87 evaluable subjects will provide 80% power at the alpha = 0.1 significance level.

9.2 Secondary Objectives

9.2.1 Patient reported outcomes

An important secondary objective will be one of patient reported outcomes. We've chosen to use the validated Breast-Q breast conservation survey.

Physical well-being, psychosocial well-being, sexual well-being, satisfaction with breast, and satisfaction with overall outcome at 6 months and 24 months after radiation will be evaluated. Scores at 6 months and 24 months post-radiation (relative to pre-RT) will be summarized and compared to prior published data, utilizing a two-sample t-test with a two-sided alternative.

9.2.2 Radiation Toxicity:

Incidence of acute and late radiation complications based on CTCAE 4.0 toxicity. The proportion of patients with acute or late radiation complications, will be estimated. Any event longer than 3 months will be considered a late effect.

The Clinical Cancer Research (CCR) database or data warehouse (as applicable) will be utilized to identify comparison group patients. Fisher's Exact test will be used to compare the rate of toxicity of study participants and comparison groups.

9.2.3 Local and local regional recurrence rate:

The cumulative incidence of local and local regional recurrence will be estimated using the cumulative incidence function treating death as the competing risk. In addition, local and local regional recurrence free survival will be summarized using the Kaplan-Meier estimators. The Clinical Cancer Research (CCR) database or data warehouse (as applicable) will be utilized to identify comparison group patients. The Cox proportional hazards model may be used to compare recurrence of study participants and comparison groups. Follow up time will be censored at the time of a competing event.

9.2.4 Economic Analysis:

Cost-effectiveness (CE) analysis of hypofractionated radiation versus standard fractionation will be explored using cost data and quality adjusted life years (QALYs) (i.e. effectiveness side). A societal perspective will be applied for the analysis because the direct costs (i.e. resource used) relevant to treatments/intervention, indirect costs (i.e. resource lost such as travel time, lost productivity) and side-effects related costs will be considered. Cost for the intervention will be measured for the cost of therapy, medications, hospitalization and medical visits. Costs for treatments due to side effects will be collected. Patient times spent for treatment, travel and lost productivity will be converted to costs using year 2022 mean adult US wage rate. Because costs related to the intervention will be occurred in different years (for example, 2018~2022), they will be adjusted to year 2022 US dollars using the medical component of the Consumer Price Index. If charged amounts relevant to the treatments are available only (i.e. plan paid amounts or reimbursed amounts are not available), they will be converted to costs by using cost-to-charge ratios. We will not compare charges or costs between institutions. The quality of life (QoL) measures will be based on the BREAST-Q and EQ-5D survey and will be used to calculate Quality Adjusted Life Years (QALYs) for the effectiveness side. Because costs and effects will be measured over multiple years, both costs and effects will be discounted at the rate of 3.5%[40]. We will utilize the EQ-5D and Breast-Q to assist in the QALY analysis. See appendix IV. Once parameters are computed: 1) mean differences in cost and effect between treatments, 2) variances for differences in costs and effects, and 3) covariance between effectiveness and cost difference, the incremental cost-effectiveness ratio (ICER) or incremental net benefits summarizing the monetary value of the intervention will be calculated.

$$ICER = \frac{Cost_{\text{Hypofractionated Radiation}} - Cost_{\text{Standard Fractionation}}}{Effect_{\text{Hypofractionated Radiation}} - Effect_{\text{Standard Fractionation}}}$$

A CE acceptability curve will be used to quantify and graphically depict uncertainty in the analysis. To consider uncertainty in parameters, probabilistic sensitivity analysis utilizing Monte Carlo simulation (i.e. second-order simulation) will be conducted. To reflect the uncertainties in costs and in effects, a gamma distribution for costs and a normal distribution for effects will be adopted. And one-way sensitivity analyses will be conducted to consider an uncertainty of one parameter at a time over a range of 95% confidence interval in cost and effectiveness measures.

10 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 4 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

11 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version. Patients who volunteer to complete the Health Care Expense Survey must be provided with the Informed Consent Letter prior to completing the questionnaire.

12.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

12.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved

plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All **phase II** studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

12.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting.

12.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study treatment even if the event is not considered to be related to study treatment. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Events that occur ≤3 months after radiation will be considered early toxicities while events occurring or persisting ≥ 6 months will be considered late toxicities.

Adverse events will be recorded after the start of radiation therapy. All events, even grade 1 will be recorded. AEs recorded until year 3.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.4 (grade 1-5)
2. its relationship to the study treatment (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)

4. action taken (no action taken; study treatment dosage adjusted/temporarily interrupted; study treatment permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study treatment as listed in the dose modification section of this protocol (see section 6 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the treatment is discussed in section 2. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

12.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study treatment
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

Serious adverse events will be recorded after the start of radiation therapy until year 3.

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

12.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, and the IRB, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 business day of first knowledge or notification of event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for this study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational treatment.
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.

- The MedWatch report will be submitted to the FDA through the voluntary reporting method by the Regulatory Coordinator.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements will be reported per local guidelines within 10 working days.
- *MedWatch 3500A form can be found on line at the FDA website.

12.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

12.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

12.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or

- Possible serious or continued noncompliance

12.9 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

12.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

12.11 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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14 APPENDICES

Appendix I: Breast-Q Breast Conservation Module

NOVEMBER

BREAST-Q™- BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0

Patient Study ID: 103976-01-___ ___ ___

Patient Initials: ___ ___ ___

Date of Completion: ____ / ____ / _____

All applicable Breast Conserving modules should be completed at the indicated time points in the study calendar.

- Satisfaction with Breasts
- Adverse Effects of Radiation (to be completed post radiation only)
- Psychosocial Well-Being
- Physical Well-Being: Chest
- Sexual Well-Being

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH BREASTS

The following questions are about your breasts and your breast cancer treatment (by treatment, we mean lumpectomy with or without radiation). If you have had a lumpectomy and radiation of both breasts, answer these questions thinking of the breast you are least satisfied with.

With your breasts in mind, in the past week, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	**1**	**2**	**3**	**4**
b.	The shape of your lumpectomy breast when you are wearing a bra?	**1**	**2**	**3**	**4**
c.	How normal you feel in your clothes?	**1**	**2**	**3**	**4**
d.	Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
e.	How your lumpectomy breast sits/hangs?	**1**	**2**	**3**	**4**
f.	How smoothly shaped your lumpectomy breast looks?	**1**	**2**	**3**	**4**
g.	The contour (outline) of your lumpectomy breast?	**1**	**2**	**3**	**4**
h.	How equal in size your breasts are to each other?	**1**	**2**	**3**	**4**
i.	How normal your lumpectomy breast looks?	**1**	**2**	**3**	**4**
j.	How much your breasts look the same?	**1**	**2**	**3**	**4**
k.	How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0 ADVERSE EFFECTS OF RADIATION

If you have had radiation on both breasts, answer these questions thinking of the breast you are least satisfied with.

With your radiated breast(s) in mind, in the past week, how much have you been bothered by:

	Not at all	A little	A lot
a. Your radiated breast skin looking different (e.g. too dark or too light)?	**1**	**2**	**3**
b. Marks on your breast skin caused by radiation (e.g. small visible blood vessels)?	**1**	**2**	**3**
c. Your radiated breast skin feeling dry?	**1**	**2**	**3**
d. Your radiated breast skin feeling sore (sensitive) when touched (e.g. changes in water temperature when you bathe/shower)?	**1**	**2**	**3**
e. Your radiated breast skin feeling unnaturally thick (rough, tough) when you touch it?	**1**	**2**	**3**
f. Your radiated breast skin feeling irritated by clothing that you wear?	**1**	**2**	**3**

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0
PSYCHOSOCIAL WELL-BEING

With your breasts in mind, in the past week, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	**1**	**2**	**3**	**4**	**5**
b. Emotionally able to do the things that you want to do?	**1**	**2**	**3**	**4**	**5**
c. Emotionally healthy?	**1**	**2**	**3**	**4**	**5**
d. Of equal worth to other women?	**1**	**2**	**3**	**4**	**5**
e. Self-confident?	**1**	**2**	**3**	**4**	**5**
f. Feminine in your clothes?	**1**	**2**	**3**	**4**	**5**
g. Accepting of your body?	**1**	**2**	**3**	**4**	**5**
h. Normal?	**1**	**2**	**3**	**4**	**5**
i. Like other women?	**1**	**2**	**3**	**4**	**5**
j. Attractive?	**1**	**2**	**3**	**4**	**5**

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0
PHYSICAL WELL-BEING: CHEST

In the past week, how often have you experienced:

	None of the time	Some of the time	All of the time
a. Difficulty lifting or moving your arms?	**1**	**2**	**3**
b. Difficulty sleeping because of discomfort in your breast area?	**1**	**2**	**3**
c. Tightness in your breast area?	**1**	**2**	**3**
d. Pulling in your breast area?	**1**	**2**	**3**
e. Tenderness in your breast area?	**1**	**2**	**3**
f. Sharp pains in your breast area?	**1**	**2**	**3**
g. Aching feeling in your breast area?	**1**	**2**	**3**
h. Difficulty laying on the side of your lumpectomy breast?	**1**	**2**	**3**
i. Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery?	**1**	**2**	**3**

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) 2.0 SEXUAL WELL-BEING

Thinking of your sexuality, since your lumpectomy surgery, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Sexually attractive in your clothes?	**1**	**2**	**3**	**4**	**5**
b.	Comfortable/at ease during sexual activity?	**1**	**2**	**3**	**4**	**5**
c.	Confident sexually?	**1**	**2**	**3**	**4**	**5**
d.	Satisfied with your sex-life?	**1**	**2**	**3**	**4**	**5**
e.	Confident sexually about how your breast(s) look when unclothed?	**1**	**2**	**3**	**4**	**5**
f.	Sexually attractive when unclothed?	**1**	**2**	**3**	**4**	**5**

Appendix II – Health Care Expense Survey

NOVEMBER

Health Care Expense Survey

Patient Study ID: 103976-01-____ ____ ____

Patient Initials: ____ ____ ____

Date of Completion: ____ / ____ / _____

Health Care Expense Survey

Before you were diagnosed with breast cancer, did you do paid or unpaid work outside the home?

☐Yes ☐No

If you worked outside the home, which of the following best applies to you?

Paid work outside the home ☐Yes ☐No

Unpaid work outside the home ☐Yes ☐No (including work in a family farm or business).

Self-employed / business owner ☐Yes ☐No

If you worked outside the home:

How many days per week did you work? __ (days)

How many hours per day did you work? __ __ (hours)

What is your profession?

_____

In what industry do you work?

_____

What is / was your job title?

_____

NOTE: This section is designed to capture the out of pocket expenses associated with radiation therapy.

How many hours were spent in total for each radiation treatment (time from leaving home/other accommodation or work to return to home/other accommodation or work)?

__ __ (hours)

What is the distance from the radiation treatment facility from home/other accommodation or work? __ __ __ (miles)

Did you commute daily to radiation treatment from your home? ☐Yes ☐No

(If yes), method of transport used to get to the radiation therapy facility (Check all that apply)

Car ☐Yes ☐No

(If yes) approximate cost for parking per visit $__ __.__ __

Did you drive yourself? ☐Yes ☐No

Were you driven? ☐Yes ☐No

Was it a combination of driving yourself or being driven ☐Yes ☐No

Shuttle ☐Yes ☐No

(If yes) Approximate cost per visit $__ __.__ __

Public transport ☐Yes ☐No

(If yes) Approximate cost per visit $__ __.__ __

On foot ☐Yes ☐No

Taxi/car service ☐Yes ☐No

(If yes) Approximate cost per visit (both ways) $__ __ __

(If no), which of the follow apply (check one):

☐ I was in a health care facility during radiation

☐ I was living with a friend/family member during radiation (answer the commuting questions above)

☐ I stayed hotel, apartment, or similar facility during radiation (answer the commuting questions above)

If hotel, apartment or similar facility, estimated cost of lodging during your radiation treatment $__ __ __ __

Number of radiation treatments during which at least one other person accompanied patient __ __

Number of visits to radiation treatment facility since completing radiation therapy (follow up visits) __ __

From the 1st day of starting radiation, until 40 days after the completion of radiation:

Number of days the patient was unable to go to work at all __ __

Number of days the patient went to work part-time __ __

If part time, number of hours reduced from typical work day __ __

Estimate child care costs due to radiation therapy $__ , __ __ __

Estimate wages lost due to radiation therapy $__ __ , __ __ __

Appendix III - **HEALTH CARE EXPENSE DIARY FOR SURVEY COMPLETION**

Use this diary to record your health care-related expenses from the time you start radiation therapy until 6 to 10 weeks after you have completed radiation therapy. A copy of the survey questions is included with this diary for your reference.

Date	Type of expense

Appendix IV – EQ-5D-3L

NOVEMBER

EQ-5D-3L

Patient Study ID: 103976-01-____ ____ ____

Patient Initials: ____ ____ ____

Date of Completion: ____ / ____ / _____

Health Questionnaire

English version for the USA

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety / Depression

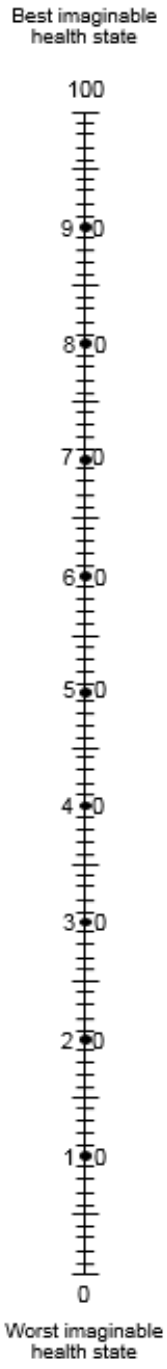
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

Appendix V – ECOG/KPS Conversion

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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