Mayo Clinic Radiation Oncology

A pilot/phase II trial of hypofractionated radiotherapy to the whole breast alone before breast conserving surgery

Study Chair Arizona: Carlos E. Vargas, M.D.

Study Co-Chair Surgery:

Study Co-Chair Translational Research:

Study Co-chair Arizona:

Study Co-Chair Mayo Rochester:

Study Co-Chair Mayo Florida:

Study Co-Investigators:

[redacted]

Statistician: [redacted]
2nd Statistician: [redacted]

Physics Chair Arizona: [redacted]

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission	Rad Onc Study Coordinator

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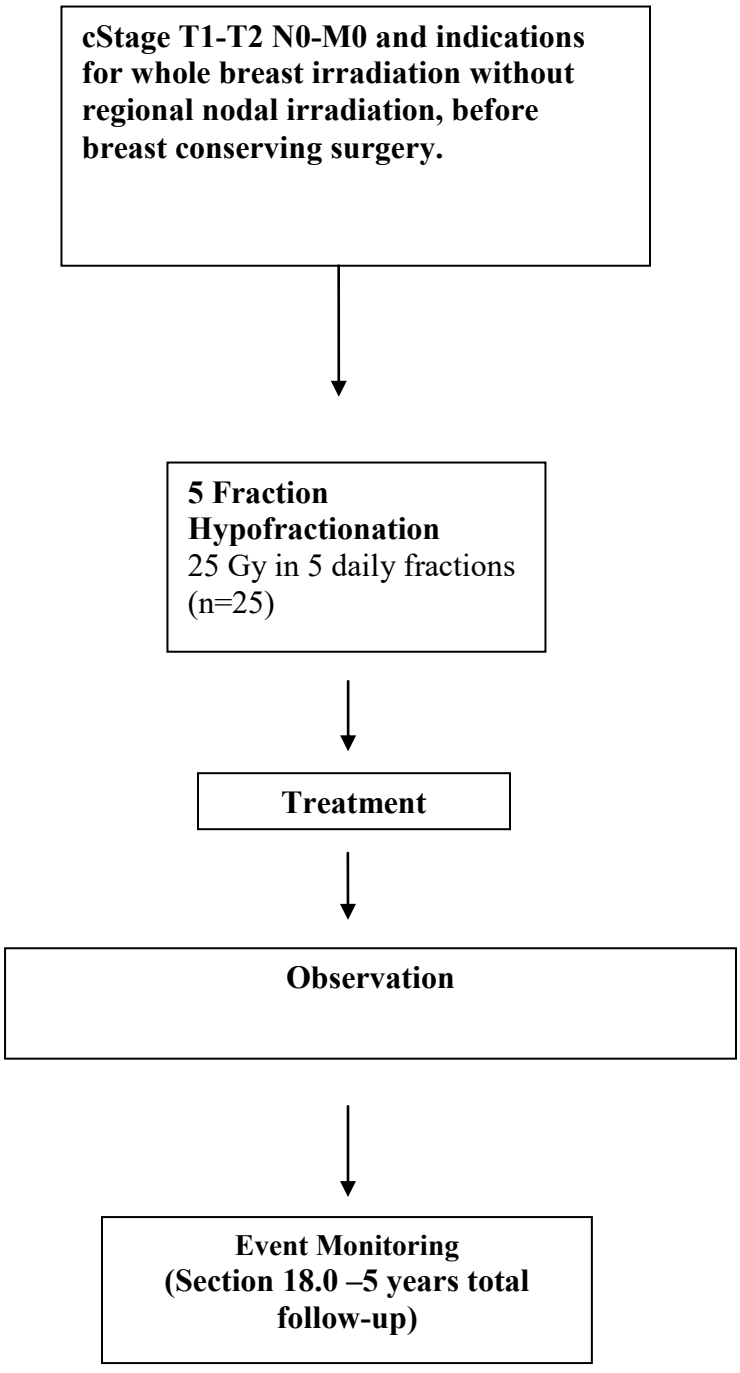
List of Abbreviations

3DCRT	3-D Conformal Radiation Therapy
AE	Adverse Event/Adverse Experience
CBCT	Cone Bean CT
CFR	Code of Federal Regulations
CRF	Case Report Form
CTV	Clinical Target Volume
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBTR	Ipsilateral breast tumor recurrence
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PHI	Protected Health Information
PI	Principal Investigator
PTV	Planning Target Volume
QOL	Quality of Life
RBE	Relative biologic effectiveness
RT	Radiation Therapy
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
XRT	X-ray Radiation Therapy

SCHEMA



N=25 patients

Study Design: This is a phase II trial to determine the effect of 25Gy in 5 fractions to the whole breast alone before breast conserving surgery.

1.0 Background

Breast Conserving Therapy and Breast Radiation

Breast cancer is the most common female malignancy in the United States with over 200,000 new cases being diagnosed annually. In the same manner, breast cancer mortality is one of the leading causes of cancer death among women. In breast cancer patients, the addition of whole breast radiotherapy after breast conserving surgery has been shown to result in improvement in rates of recurrence and survival for women with early stage and locally-advanced breast cancer.

Breast conserving therapy (BCT) refers to breast conserving surgery (BCS) and radiation therapy (RT) to eradicate any microscopic residual disease. The aim of BCT is to achieve equivalent overall survival compared with patients undergoing a mastectomy, with acceptable rates of local recurrence and good to excellent cosmetic results.

Six modern phase III trials have directly compared BCT to mastectomy and a meta-analysis of these trials has shown equivalent survival.[1-11] Furthermore, the EBCTCG has shown the benefit of radiotherapy as an integral part of breast conserving therapy. Although the relative benefit of radiotherapy was similar for different patients, the absolute benefit will vary for different patient populations.[12]

Radiation therapy is considered an integral part of BCT. Despite this, certain subsets of patients may elect to forego radiotherapy given a small absolute benefit. CALGB 9343 and PRIME II have shown that selected elderly patients with early stage favorable breast cancer may safely omit radiotherapy after BCT.[13,14]

Interestingly, a subtype population in the previously described Canadian study looking at the omission of radiotherapy demonstrated that the luminal A subtype of breast cancer (as defined by immuno-histochemical analysis) was prognostic but not predictive of response to radiotherapy.[15] Although the importance of radiation in the management of breast cancer is unquestioned, the ideal timing and overall effect of radiation on breast cancer based on different gene expression signatures is unknown at the present time.

Neo-adjuvant Therapy for Breast Cancer

Neo-adjuvant systemic therapy has been found to have similar outcomes to adjuvant chemotherapy after BCT[16-18] However, certain advantages of neo-adjuvant systemic treatment may include downstaging the tumor to allow for less extensive surgery, improved cosmetic outcomes, and reduced postoperative complications such as lymphedema.[16,19] Neo-adjuvant therapy also permits an early evaluation of the effectiveness of systemic therapy. The presence or absence of residual invasive cancer after neo-adjuvant chemotherapy is a strong prognostic factor for the risk of recurrence.

In addition to the benefits as outlined above, neo-adjuvant therapy gives us the opportunity to obtain imaging, tumor specimens, and blood samples prior to, during, at the time of surgery, and after the preoperative treatment. This information has enabled us to understand the true effect of neo-adjuvant therapy on breast cancer. Furthermore, it has allowed us to understand tumor and patient-specific biomarkers with respect to response or resistance. Given the aforementioned findings, one would expect neo-adjuvant radiotherapy to result in similar outcomes as postoperative radiotherapy, as seen previously with neo-adjuvant systemic chemotherapy. The opportunity to treat patients with neo-adjuvant radiotherapy would provide vital information to help the cancer community better understand the effect of radiation on tumor response, biomarkers, and DNA profiling of breast cancer. This information is crucial if we wish to better define the effect of radiotherapy on breast cancer and tailor our treatment doses to individual patients and their specific type of breast cancer.

Hypofractionated Breast Radiation

The most robust data for hypofractionated breast radiation comes from the United Kingdom. The Start A and Start B trials compared different hypofractionated radiotherapy regimens with the conventional regimen of 50Gy in 25 treatments over 5 weeks. The Start B trial, analyzed patients receiving a hypofractionated regimen of 40Gy in 15 treatments over 3 weeks, and found that the hypofractionated regimen resulted in less breast shrinkage, telangiectasia, and breast edema as compared to the standard arm. [20] No difference in arm edema or shoulder stiffness was seen among any of the hypofractionated arms as compared to 50Gy over 5 weeks. Interestingly, the hypofractionated 40Gy arm treated over 3 weeks had fewer distant events, which translated into an overall survival benefit at 10-year followup. The study concluded that hypofractionated radiotherapy of 40Gy in 15 treatments over 3 weeks was superior to the standard conventional 50Gy in 25 treatments over 5 weeks in terms of adverse events and cancer specific outcomes.

The UK Fast Trial published the cosmetic results of 390 patients undergoing conventional and hypofractionated radiotherapy. [21] A hypofractionated regimen of 30Gy and 28.5Gy in 5 treatments over 5 weeks was compared to a longer conventional regimen of 50Gy in 25 treatments over 5 weeks. At 2 years post-randomization, 20.8% of patients had mild change and 6.2% had marked change in photographic breast appearance. There was no difference observed for any of the dosimetric parameters confirming the safety of a more hypofractionated approach. Furthermore, the initial results showed three-year rates of physician-assessed moderate/marked adverse effects in the breast were similar for 28.5Gy in 5 treatments over 5 weeks when compared with 50Gy in 25 treatments over 5 weeks.[22]

The Fast Forward Trial has also published comparable acute toxicity among 40Gy in 15 treatments over 3 weeks, and 27Gy or 26Gy in 5 treatments over one week.[23] 190 and 162 patients were recruited for two studies. In the first sub-study, evaluable patients with grade 3 RTOG toxicity were: 13.6% with 40Gy in 15 fractions; 9.8% with 27 Gy in 5 fractions; and 5.8% with 26 Gy in 5 fractions. In the second sub-study only one patient presented with G3 CTCAE toxicity in the 27 Gy in the 5 fraction arm.

Preoperative Radiation

Preoperative radiotherapy has been used successfully in the past for the management of breast cancer. [24-28] Preoperative radiotherapy in patients with locally advanced breast cancer has shown excellent loco-regional control rates even when few patients receive systemic therapy. Pathologic complete response (pCR) was also associated with improved outcomes in patients undergoing preoperative radiotherapy.[28] Matuschek et al. reported that pCR after neo-adjuvant chemo-radiation was 56% for node-positive cases (cN+). The multivariate analysis of this study revealed that a longer time interval to surgery increased the probability for a pCR (HR 1.17 [95% CI 1.05–1.31], $p < 0.01$). Importantly, pCR was the strongest prognostic factor for long-term survival in patients (HR 0.28 [95% CI 0.19–0.56], $p < 0.001$).[27]

Other studies have looked at hypofractionated preoperative radiation as well. Researchers at the University of Maryland evaluated the impact of preoperative hypofractionated radiation on pathologic complete response (NCT01014715). Bondiau et al [29] analyzed five different dose levels during preoperative chemotherapy in high-risk breast cancer patients. Dose levels of 19.5Gy, 22.5Gy, 25.5Gy, 28.5Gy and 31.5Gy were used, with only one grade 3 treatment related AE seen at 8 months. Moreover, pCR was seen in 36% of the patients. However, no pCR was observed in the first dose level of 19.5 Gy, and the majority of pCR (67%) were observed in level 3 (25.5Gy). Given the response with doses of 25.5Gy and higher, a dose of 25.5Gy was selected for future hypofractionated preoperative trials. Horton et al also evaluated extreme preoperative hypofractionated radiation using a single treatment of intensity

modulated radiation therapy with 15 Gy, 18 Gy, or 21 Gy to the tumor with a 1.5-cm margin.[30] No dose limiting toxicity was seen. Tumor response was difficult to evaluate given that surgery was done 10 days after radiotherapy. Multiple studies have shown the safety and excellent cosmetic results of preoperative radiation either in a hypofractionated approach or with standard fractionation. Furthermore, the use of preoperative radiotherapy alone or concurrently with chemotherapy has also been tested and reveals excellent results with minimal toxicity. The literature provide a very compelling argument favoring the use of hypofractionated radiation therapy to a dose of 25Gy in 5 fractions, followed by surgery 8 weeks thereafter to maximize radiation response, as proposed in our current study.

To assess the response of hypofractionated radiation therapy before radiation we would use residual cancer burden in the surgical specimen. We defined a pathological complete response (pCR) as a residual tumor burden of 0-1.[31]

Boost

The EORTC trial showed a small improvement in local control with the use of a boost (4% at 10 years). However, severe breast fibrosis was increased by a similar magnitude at 10-years (3%). Furthermore, no difference was seen between the two groups in terms of breast cancer mortality, overall incidence of breast cancer–related events, disease-free survival, or overall survival.[32] Since, the use of boost has shown an increase in severe breast fibrosis without an improvement in breast related outcomes, we have elected not to use a boost for this trial.

Predicting response to RT

There has been much interest recently in developing more useful biomarkers to identify patients risk and response to radiation therapy in breast cancer. Clinico-pathologic factors as used in the CALGB 9343 study or PRIME II, including age, tumor size, and hormone receptor status, remain imperfect in their risk stratification, and thus identifying overall risk and radiation response remains an unmet clinical need.[13,14] The Danish study has shown that post-mastectomy radiation improved survival in certain cohorts of patients over others.[33,34] However, different studies suggest different benefits based on these biomarkers. These findings lend to the necessity of additional research regarding the response of radiation in cohorts of patients treated uniformly and for whom gene expression profiling is done. Similar to chemotherapy tests such as OncotypeDx and Mammaprint, biomarker testing can ultimately prove beneficial to further delineate the benefit of radiotherapy in our breast cancer patients.

Ideally, breast cancer response to radiation should be addressed by studying the direct effect of radiation on the tumor cells. Gene profiling before and after radiotherapy would help better define the effect of radiation over breast cancer and associated predictive DNA signatures, which remains an active area of interest in the breast cancer field.

Through our research, we hope to better define the breast cancer response to hypofractionated radiation without the confounding factors of other systemic treatments. This research would provide a unique opportunity to address the effect of radiation and describe DNA signatures more likely to be associated with response. We aim to further understand the effect of radiation on cancer cells and, thus individualize the dose and timing of radiation therapy that is necessary to eradicate breast cancer cells.

Summary

At the present time, very little data exists regarding the distinct changes that occur with radiotherapy in the cancer itself. Breast cancer represents a heterogeneous disease with distinct clinical features that can be predicted by differences in the DNA. The analysis of tumor mutation signatures may lead to a better understanding of the effect of radiotherapy in breast cancer. Preoperative radiation of the intact tumor with a hypofractionated regimen can potentially decrease toxicity by allowing the delivery of treatment to intact breast tissue. The potential advantages of preoperative radiation therapy include the delivery of radiation in the intact breast when radiation can be more efficacious as more oxygen can be available in the tissue. Furthermore, complications and cosmetic results are expected to be lower in pre-operative radiotherapy before surgery, as there have been no changes in blood supply to the breast. This lends to the possibility of using lower doses of radiotherapy to patients, and potentially better cancer associated clinical outcomes for our breast cancer patients.

2.0 Goals

2.1 Primary Objectives

2.1.1 To determine the pathologic complete response (pCR) rate after hypofractionated radiotherapy to the whole breast alone, based on the postsurgical specimen. We define a pCR as residual cancer tumor burden of 0-1.

2.2 Secondary Objectives

2.21 To evaluate acute and late toxicity with preoperative radiation including grade ≥2 pneumonitis.

2.22 To estimate the 5-year locoregional control, distant recurrence, invasive disease-free survival, cause-specific survival, and overall survival.

2.3 Correlative and Exploratory

2.31 To evaluate patient-reported outcomes.

2.32 To evaluate clinical features, treatment technique, dose-volume parameters, histologic and genetic variants associated with adverse events, and fair and poor cosmetic outcomes or unplanned surgical intervention.

2.33 Evaluate tumor mutation signatures before and after radiation; correlate tumor mutation signatures before and after radiation with pathologic information at the time of surgery.

2.34 To describe the pathologic changes seen in breast cancer patients with preoperative radiation.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.2 Age ≥ 18 years.

3.1.3 Histological confirmation of breast cancer.

3.1.4 Clinical Stage T0-T2 N0 M0.

3.1.5 ECOG Performance Status (PS) 0 to 2. (Appendix I)

3.1.6 Able to and provides IRB approved study specific written informed consent.

3.1.7a Study entry must be within 120 days of last biopsy (breast).

3.1.7b Able to complete all mandatory tests listed in section 4.0.

3.1.7c Willing to return to enrolling institution for follow-up (during the active monitoring phase of the study).

3.1.8 Planned breast surgery and indications for whole breast radiotherapy.

3.1.9 No neo-adjuvant therapy

3.2 Exclusion Criteria

3.2.1 Medical contraindication to receipt of radiotherapy.

3.2.2 Severe active co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or providing informed consent.

3.2.4 Active systemic lupus or scleroderma.

3.2.5 Pregnancy.

3.2.6 Women of childbearing potential who are unwilling to employ adequate contraception.

3.2.7 Prior receipt of ipsilateral breast or chest wall radiation.

3.2.8 Recurrent breast cancer.

3.2.9 Indications for comprehensive regional nodal irradiation.

4.0 Test Schedule

	Baseline	Pre-RT	Treatment			Observation / Event Monitoring			
	≤120 days prior to start of RT	≤45 days prior to start of RT	RT	Post-RT[3]	Surgery 8 weeks post-RT (+8/-4 wk)	12 wks post-RT (+/- 4 wk)	6 months post-RT(+/- 3 mo)	12 months (+/- 3 mo), 24 months (+/- 6 mo), 36 months (+/- 6 mo), and 5 years (+/- 6 mo) post-RT	Failure[6]
Procedures									
Informed Consent	X								
Physical Exam/Consult	X								
ECOG performance status (See Appendix I)	X					X	X	X	X
Concomitant medications	X					X	X	X	X
Adverse Event Evaluation (See section 10.0)		X		X		X	X	X	X
QOL surveys (See Appendices II, III, and IV)		X		X		X	X	X	X
Cosmetic assessment (See section 11.3.1)		X		X		X	X	X	
Digital photographs		X[2]		X[2]		X	X	X	
Tumor Assessments									
Biopsy (SOC)	X[4]				X				
Surgery (SOC)					X				
DNA exome sequencing[7]		X			X				
Blood (control)[7]		X			X				
Radiation			X						
PET scan (SOC)									X[1]
Pregnancy (serum)[5] (SOC)	X								

[1] Highly suggested but not mandatory.
[2] Digital photographs can be done at any time before or after treatment at the discretion of the physician.
[3] Last day of treatment +/- 2 days, per discretion of the treating physician.
[4] Outside pathology must be reviewed at treating institution to confirm eligibility.
[5] For women of childbearing potential only, blood pregnancy test to be completed prior to start of radiation.
[6] Failure defined as recurrent disease.
[7] For tissue: total of 4 samples will be collected (2 at pre-RT and 2 at surgery), see section 17.1 for details. For blood: total of 12 samples will be collected (6 at pre-RT and 6 at surgery), see section 14.1 for details.

5.0 Stratification Factors

5.1 None.

6.0 Registration

6.1 Registration Procedures

6.1.1 Patient will be registered to the study when they have consented, met eligibility criteria, and have been logged into the Research Participant Tracking (Ptrax) system.

6.1.2 Baseline tests/procedures (see section 4.0) will be completed within the guidelines specified on the test schedule.

6.1.3 All patients meeting eligibility criteria who have signed a consent form and who have completed treatment will be evaluable for the primary analysis. All patients completing treatment as per the study pre-op RT followed by breast conserving surgery will used to determine the protocol accrual.

6.1.4 Patients consented and enrolled will be monitored in the registry, if patients signed our registry consent (IRB 16000492). All patient meeting accrual as defined in 6.1.3 will be analyzed per study.

7.0 Protocol Treatment

Doses throughout will be prescribed in Gy or Gy(RBE). Radiation therapy must begin within 180 days of the last biopsy date. Concurrent cytotoxic chemotherapy with radiotherapy is not allowed.

7.1 Radiation Therapy

7.2 Dose Specifications

Whole breast irradiation

7.211 Breast: 25 Gy (RBE) in 5 fractions of 5 Gy (RBE)

7.3 Treatment Technique

7.31 Radiation will be delivered using available scanning beam proton equipment at the treating institution or conventional radiation photon (x-ray) radiation.

7.4 Localization, Simulation, Immobilization

7.41 Simulation should be performed with the patient in the supine or prone position

7.42 Patients should be optimally positioned with a custom immobilization device at the discretion of the treating physician.

7.43 Arm position may be up or down.

7.44 The CT should extend cephalad to at least the level of the mandible to include both elbows and extend caudally to encompass the entire lung volume. The CT scan thickness will be 2mm.

7.45 External skin markers, which may include permanent tattoos, are recommended for daily set-up.

7.46 KV image guidance will be performed daily. Other imaging modalities, such as CBCT and Vision RT, real time tracking or others should be performed based on institutional guidelines and/or physician preference.

7.47 Volumetric imaging may be performed with re-planning at the physician's discretion.

7.48 **CT simulation** would be done with **contrast** to better define the tumor volume.

7.5 **Treatment Planning**

7.51 **Radiation Proton Planning**

7.511 For proton planning, 2 or more en face or oblique fields are recommended.

7.52 **Radiation Photon (x-ray) Planning**

7.521 Planning would be done based on tangent fields.

7.522 An inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints and will be used for all left sided breast cancer patients pending insurance approval.

7.523 If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam as defined in Section 7.522 (1) should deliver > 50% of the total number of monitor units for the beam orientation.

7.524 3D field inside of a field would be used if IMRT is not approved by the insurance carriers.

7.53 Additional supraclavicular/axillary radiation

7.531 In cases were more than two SLN are found to have disease or extra capsular extension is found additional radiation to the SCF/axilla area can be given at the discretion of the treating radiation oncologist. Doses fields and techniques would be defined by the treating physician. A matching anterior oblique field with an IMRT gradient based on prior dose distribution is encouraged.

7.54 Image guidance

7.541 Cone beam CT would be done daily pre-treatment. Alternatively, if is not available CT on rails can be used. Kv guidance can be used for proton therapy if volumetric guidance is not available. Kv guidance can be used if conebeam is not an option

7.6 **Target Volumes**

The definitions for the CTV and normal structures for this protocol will generally follow the RTOG (Radiation Therapy Oncologic Group)-endorsed consensus guidelines for delineation for breast cancer [redacted] with exceptions described below.

7.61 <u>Breast target volumes</u>

7.611 **High tangents volume:** Alternatively, breast target volume can be defined by traditionally treated volume. All palpable breast tissue and all tissue encompassed by a standard tangent fields would be considered breast tissue. A medial tangent would be placed at the costo-condral

junction and a lateral tangent would be placed at the mid axillary line or more posterior as necessary to cover all breast tissue laterally. The caudal border would be 1 cm below all breast tissue. The superior border would be placed at the second intercostal space. Position would be verified on CT and in general it should not be closer than 1.5 cm from the inferior border of the humeral head and no more than 2 cm distally.

7.612 **Manual modifications:** alternatively, volumes can be defined using the RTOG breast atlas as above. However, for uniformity of the posterior margin the breast volume would include muscle tissue as needed to maintain a uniform distal edge. Please see breast CTV (section 7.6.1.3.2).

7.613 Tumor: Contour around the radiologic marker(s) including architectural distortion.

7.6.1.3.1 **Tumor CTV**: Tumor + 5mm 3 D expansion. Limit the CTV 5 mm from skin and not extending into the pectoralis muscle or chest wall.

7.6.1.3.2 **Breast CTV**: the breast would be the same as the CTV high tangents or low tangents without further expansions. The Tumor CTV is also included. The breast CTV volume is limited 5mm from the skin. The breast CTV posteriorly, would be limited by the chest wall.

7.7 Critical Structures

7.71 **Breast skin evaluation:** Will be defined as the first 3 mm of tissue under the body surface anterior to the Breast CTV.

7.72 **Heart:** To be contoured on all cases. The contour should begin just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA) and should extend to its most inferior extent near the diaphragm. The esophagus, ascending and descending aorta and inferior vena cava should be excluded from the heart contour.

7.73 **Left anterior descending (LAD) interventricular branch (optional)**: To be contoured on left-sided cases. “Originates from the left coronary artery and runs in the interventricular groove between the right and left ventricles. If it is difficult to see, raising the level and lowering the window may help (e.g. level 50, window 150)”.[35]

7.74 **Right coronary artery (RCA) (optional):** To be contoured on all right-sided cases. “Originates from the right side of the ascending aorta. Due to the native heart position in the chest, on axilla CT, it appears to start inferior to the left coronary artery. It moves significantly with cardiac motion, so often the location can seem noncontiguous from axial CT slice to slice, as the position of the AV groove changes.”[35]

7.75 **Ipsilateral lung**: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.76 **Contralateral lung**: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.77 **Total lung**: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.78 **Contralateral breast**: Dose to the contralateral breast will not be constrained in treatment planning and therefore contouring of the contralateral breast is not required in this protocol. However, efforts should be made to limit inadvertent dosing of the contralateral breast.

7.8 Prescription and Normal Tissue Constraints

7.8.1 Breast CTV:
7.8.1.1 Per protocol ≥ D95% will receive ≥95% of prescription; Variation acceptable ≥ D90% receives ≥ 90% of prescription

7.8.2 Tumor CTV
7.8.2.1 Per protocol D95% receives ≥95% of dose; variation acceptable D90% receives ≥90% of the boost dose

7.8.3 Robustness analysis **for Protons**
7.8.3.1 Breast CTV coverage would be evaluated for 5mm movements or 3% range changes. Per protocol Breast CTV V90% receives ≥95% of the prescription dose; variation acceptable ≥ V90% receives ≥90% of the prescription dose.

7.8.3.2 Under the same robustness evaluation criteria, plans will be evaluated for D max. Variation acceptable D0.01cc % ≤120%

Protons DVH summary table

		Goal	Major violation
Breast CTV		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Tumor CTV		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Breast CTV robustness		V90% >90% of prescription	V90% <90% of prescription
Heart	Max dose	≤25% of prescription	>33% of prescription
	Mean	<0.1Gy	>1Gy

Breast Skin	Max dose	≤105% of prescription	>110% of prescription
Lung Ipsilateral	V50% of prescription	≤10%	>15%
	V20	record	
Lung contralateral	V50%	≤7%	>10%
Lung Total	Mean dose	record	
	V20Gy	record	
	V50%	record	
LAD (optional)	Mean dose	record	
	Max dose	record	
RCA	Mean dose	record	
	Max dose	record	

Photons (x-rays) DVH summary table

		Goal	Major violation
Breast CTV		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Tumor CTV		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Breast CTV robustness		V90% >90% of prescription	V90% <90% of prescription
Heart	Max dose	≤33% of prescription	>50% of prescription
	Mean	<1Gy	>2Gy
Breast Skin	Max dose	≤107% of prescription	>115% of prescription
Lung Ipsilateral	V50% of prescription	≤10%	>15%
	V20	record	
Lung contralateral	V50%	≤7%	>10%
Lung Total	Mean dose	record	
	V20Gy	record	
	V50%	record	
LAD (optional)	Mean dose	record	
	Max dose	record	
RCA	Mean dose	record	
	Max dose	record	

7.9 Quality Assurance Documentation

7.9.1 At a minimum, the initial 3 treatment plans per physician will be centrally reviewed by the principal investigator or designee prior to the start of treatment.

7.10 Axillary management

7.10.1 Only clinical N0 patients are eligible. If 2 or less positive LN are found in the SLNB without ECE no additional radiation would be considered

7.11 Surgery

7.11.1 Surgical treatment will be done at the discretion of the treating surgeon.

7.11.2 Surgery will be done at 8 weeks after the completion of radiation. Acceptable range is 4-16 weeks after.

7.12 Endocrine therapy or chemotherapy

7.12.1 Systemic management would be done at the discretion of the treating medical oncologist after the surgery

8 Radiotherapy Dose Modifications Based on Adverse Events

This study has no pre-specified interruptions due to adverse events. Treatment interruptions are discouraged. No dose modifications should be done for treatment interruptions.

9.0 Ancillary Treatment/Supportive Care

Skin changes are common complications of breast cancer radiation therapy. Usual care will be provided as per the treating institution's standard of practice. If the skin becomes erythematous and/or there is pruritus, topical steroid cream may be prescribed. The addition of antihistamines may be used for severe pruritus. Patients experiencing pain will be prescribed pain medication.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event – Any grade 4 or 5 adverse event as defined by CTC AE v4.0. Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include in general:

- Death
- Life threatening adverse experience where emergent lifesaving treatment is necessary.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1)

death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting unless as otherwise stated in the table below.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

[redacted]

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.22 Assessment of Attribution
Only G4 or G5 adverse events will require an attribution. Any change in the grade of an adverse event within the list of monitored AEs will be recorded and considered to be related to treatment. Any new adverse not listed occurring within the Radiated area or in close proximity will be graded and attribution defined by the study PI.
Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the treatment and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.31 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.311 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.312 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
General	Pain	X	X	CTCAE
Skin and subcutaneous tissue disorders	Dermatitis Radiation	X	X	CTCAE
	Skin hyperpigmentation	X	X	CTCAE
	Skin hypopigmentation	X	X	CTCAE
Musculoskeletal	Fibrosis	X	X	CTCAE
Vascular	Lymphedema	X	X	CTCAE
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X	CTCAE

10.5 Submit via appropriate *reporting mechanisms* the following AEs experienced by a patient and not specified in Section 10.4:

10.52 Grade 4 and 5 AEs regardless of attribution to the study treatment or procedure.

10.53 Grade 5 AEs (Death)

10.531 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.532 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation

11.1 Patients will be evaluated at baseline, then according to the Assessment Schedule (Section 4.0)

11.2 At the time of reevaluation, patients will be classified in the following manner:

11.2.1 No evidence of disease (NED).

11.2.2 Recurrence of disease (REC). Consider biopsy of the site and PET scan.

11.2.3 The site of recurrence (or failure) will also be collected and classified as local vs. regional vs. distant recurrence.

11.2.4 Secondary Treatment. The date of the first retreatment and extent of retreatment post-recurrence (i.e. secondary resection or re-irradiation for primary disease), will be collected. Pathology, if available, and operative reports are required to be submitted per Section 18.0.

11.3 Cosmesis evaluation and Patient Reported Outcomes

11.3.1 The Harvard/NSABP/RTOG Cosmesis Scale will be used to score cosmesis by trained nurses for the primary endpoint according to the schedule outlined in section 4.0.

Excellent: Treated breast nearly identical to untreated breast

Good: Treated breast slightly different than untreated (minimal but identifiable effects of the treated breast). Mild reddening or darkening of the breast may be present. Thickening or scar tissue causes only a mild change in the shape or size.

Fair: Obvious difference in the size and shape of the treated breast. **The change involves one-quarter or less of the breast**. Severe thickening or scarring can be present.

Poor: Marked change in appearance or shape involving **more than one-quarter or less of the breast.** Treated breast seriously distorted (severe sequelae of breast tissue)

11.3.2 Digital photographs should be performed according to the schedule outlined in section 4.0 and should include three poses: from the front with hands on hips, both oblique and lateral views with hands behind the back. Recommended framing should go from the sternal notch to the umbilicus. If possible, patients should be photographed against a solid colored background such as a white sheet.

11.3.3 The Breast Cancer Treatment Outcome Scale (BCTOS) is a self-report instrument that has high reliability and validity and will be used for evaluating patient-rated cosmesis according to the schedule outlined in section 4.0.

11.4 Quality of life questionnaires are being done as part of the standard of care for all patients. We will correlate results of this standard of care questionnaires with clinical outcomes.

Unplanned surgical intervention will be adjudicated by a plastic surgeon and a general surgeon.

11.5 Pathologic complete response. At time of surgery the residual tumor would be measured and a score of 0-1 would be considered a pCR. Residual cancer burden (RCB) measurement is currently considered SOC for all three sites for surgical specimens after neo-adjuvant therapy. We would use the current grading used at the three Mayo sites to determine RCB.[31]

12.0 Descriptive Factors

- Breast: left vs. right
- Tumor Size: 0-2cm vs 2-5cm
- Pathologic Lymph Nodes: N0 vs N1
- Pathologic complete response: yes vs. none [31]

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Follow-up data will collected and entered after the observation phase outlined in section 4.0. If the patient is still alive after 5 years have elapsed from the on-study date, no further follow-up is required by this protocol.

13.1 Patients who have a recurrence while receiving therapy or during observation will go to the event-monitoring phase and be followed

13.2 Patients who discontinue treatment or observation for reasons other than recurrence will go to the event-monitoring phase and be followed

13.3 Patients who will not receive any radiation treatment or who will receive radiation treatment elsewhere will move to event monitoring phase.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.5 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Bio-specimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Collection Tube	Volume to Collect per Tube (Total Number of Tubes to Collect)	Time point: Before radiation	Time point: After radiation
EDTA tubes	10 mL (8)	X(4)	X(4)
No additive tubes (for Serum)	10 mL (4)	X(2)	X(2)

14.2 BAP will process and store specimens per standard operating procedures. The baseline sample will be obtained prior to the start of radiation. It would be used as our control for the DNA exome sequencing section 17.0.

14.3 We will send to Rochester two EDTA tubes with 10cc of blood taken prior to radiation and two after radiation for a total of 4 EDTA tubes.

15.0 Drug Information

Not Applicable

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase II trial to determine the pathologic complete response (pCR) rate (at time of definitive surgical procedure) seen in breast cancer patients with preoperative ionizing radiation.

16.2 Primary and Secondary Endpoints

16.21 Primary Endpoint: The pathologic complete response (pCR) rate observed at time of definitive surgery in breast cancer patients receiving preoperative ionizing radiation. A residual tumor cancer burden 0-1 would be considered a pCR.[31] All patients meeting eligibility criteria who have signed a consent form and who have begun treatment will be evaluable for the endpoint.

16.22 Secondary Endpoints:

16.221 Acute and late adverse events including grade ≥2 pneumonitis.

16.223 Locoregional control, invasive disease-free, distant recurrence, disease-free survival, cause-specific survival, overall survival.

The following definitions are used for the secondary endpoints of interest:

- *Pathologic complete response:* We defined a pathological complete response (pCR) as a residual tumor burden of 0-1 in the surgical specimen.[31]
- *Acute adverse events* (up to 180 days post-RT): any adverse event, regardless of attribution, that occurs in the first month post-RT.
- *Late adverse events* (up to 5 years post XRT): any adverse event that occurred after the first month post-RT and up to 5 years post-RT.
- *Ipsilateral breast tumor recurrence (IBTR):* this is defined as local recurrence from trial registration as a first event at 5 years. IBTR is defined as both invasive and non-invasive breast cancer involving the same breast parenchyma as the original tumor.
- *Regional recurrence:* invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast at 5 years.
- *Distant recurrence:* metastatic cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer at 5 years.
- *Invasive disease- free survival:* this is defined as the time from study registration until the occurrence of one of the events in a composite endpoint. This endpoint includes invasive IBTR, regional invasive breast cancer recurrence, distant breast cancer recurrence, death due to any cause,
- *Disease- free survival:* this is defined as the time from study registration until the occurrence of one of the events in a composite endpoint. This endpoint includes any IBTR, regional invasive breast cancer recurrence, distant breast cancer recurrence, death due to any cause,
- *Cause specific survival:* is defined as the time from registration to death due to breast cancer. If the cause of death is unknown or difficult to establish, patients with a distant failure at the time of death would be censored as dying from breast cancer
- *Overall survival:* is defined as the time from registration to death due to any cause.

16.3 Exploratory endpoints:

16.31 Patient self-reported cosmesis, i.e. fatigue, breast pain, and other patient reported outcomes.

16.32 Clinical features, treatment technique, dose-volume parameters, histologic and genetic variants associated with adverse events, and fair and poor cosmetic outcomes or unplanned surgical intervention.

16.33 Tumor mutation signatures before and after radiation; correlate tumor mutation signatures before and after radiation with pathologic information at the time of surgery.

16.34 Pathologic changes seen in breast cancer patients with preoperative radiation.

The following definitions are used for the exploratory endpoints of interest:

- *Patient Reported Outcomes/Quality of life:* Elements of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be used for patient self-reporting of toxicities. The Breast Cancer Treatment Outcomes Scale (BCTOS) will be used to measure patient reported functional status (pain, mobility). Other measures of fatigue, pain, and arm function are listed in the appendix.

- *Provider reported cosmetic outcomes:* the physician or mid-level reported outcome will be assessed using the Harvard Cosmesis Scale baseline, EOT, 3 months, 12 months, and yearly after.
- *Patient self-reported cosmetic outcomes:* the patient self-reported outcome will be assessed using a modified Harvard Cosmesis Scale and the BCTOS at baseline, 2 years, and 5 years.
- *Panel assessed cosmetic outcome:* in addition to patient self-reported and physician reported outcomes, cosmesis will be assessed by a panel of breast cancer medical providers using digital photographs from baseline and at 2 years.

16.4 Statistical Design:

Pathologic complete response (pCR) will be assessed at the time of definitive surgery. The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 20%. The following Simon's Optimum design uses 22 evaluable patients to test the null hypothesis that the proportion of successes is at most 5%

16.41 Decision Rules:

16.411 If 2 or fewer successes are observed in the first 22 evaluable patients that have a definitive surgical procedure, we will consider this regimen to be ineffective in this patient population. If 3 or more successes are observed in the first 22 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.412 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.42 Sample Size

The one-stage design to be utilized is fully described in Section 16.21. A minimum of 22 evaluable patients will be accrued to this phase-II study unless undue toxicity is encountered. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 25 patients. We anticipate pre-registering 40 patients to register a total of 25 patients necessary for the study design.

16.43 Accrual Time and Study Duration

We anticipate enrolling 25 patients and thus plan to finish accrual of patients in 1.5-2 years after opening the study, leaving year 5 for follow-up and analysis. Therefore, the overall study duration is expected to be 84 months.

16.44 Power and Significance Levels

Assuming the number of successes is binomially distributed, the significance level is 0.10 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is …	0.05	0.10	0.15	0.20	0.25

Then the probability of declaring that the regimen warrants further studies is…	0.09	0.38	0.66	0.85	0.94

16.45 Other Considerations
Adverse events observed in this study as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.5 Analysis Plan

The analysis for this trial will commence at the planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such decision will be made by the Statistician and Study chair, in accord with the Cancer Center Statistics (CCS) Standard Operating procedures, availability of data for secondary endpoints, and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via a manuscript, abstract, or presentation format is when 22 patients have had definitive surgical treatment.

16.51 Primary Analysis: The primary analysis will be to estimate the pathologic complete response (pCR) rate observed at time of definitive surgery in breast cancer patients receiving preoperative ionizing radiation. All patients meeting eligibility criteria who have signed a consent form and who have begun treatment will be evaluable for the primary analysis.

16.511 Estimation: The proportion of successes (number of patients achieving pCR at time of definitive surgery) will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner [74].

16.512 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence limits.

16.52 Secondary Analyses

16.521 *Acute adverse events (up to 180 days post-RT)*: All patients who were registered to the study and started treatment will be included in the acute adverse event analysis. An acute adverse event is an AE, regardless of attribution, that occurs up to 180 days post-RT. The maximum grade for each type of acute AE will be recorded for each patient. Data will be summarized as frequencies and relative frequencies. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.522 *Late adverse events*: All patients who were registered to the study and started treatment will be included in the late adverse event analysis. A late adverse event is an AE, regardless of attribution, that after one month post-RT and up to 5 years post-RT. The maximum grade for each type of late AE will be recorded for each patient. Data will be

summarized as frequencies and relative frequencies by treatment arm. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.523 *Locoregional control*: The cumulative incidence of locoregional recurrence will be estimated using a competing risks method (Gooley et al.). The competing risks will be distant breast cancer recurrence and death.

16.524 Invasive *disease-free survival*: i-DFS is defined as the time from registration until the time of disease recurrence or death due to any cause. The i-DFS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.525 *Disease-free survival*: DFS is defined as the time from registration until the time of disease recurrence or death due to any cause. The DFS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.526 Cause specific survival: The CSS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.527 *Overall survival*: The OS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.53 Exploratory Analyses:

16.531 *Quality of life*: The subscales of the BCTOS, elements from CTCAE-PRO, and other patient reported measures such as fatigue, breast pain, breast shape, and arm related morbidity outlined in the appendix will be summarized as the mean ± SD and median (minimum value, maximum value). Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Analysis will include percent change from baseline using t-tests and generalized linear models to test for changes at each time point and non-zero slope respectfully.

16.532 *Cosmesis*: The values of the cosmesis instruments (patient self-reported and panel-assessed) will be summarized with the frequencies and confidence intervals of fair or poor cosmesis events at baseline, 2 years, and 5 years.

16.533 Tumor mutation signatures will be analyzed before and after radiotherapy as compared to pathologic information at the time of surgery. Continuous variable will be compared using unpaired t tests and monimal variables will be compared using contingency tables and Chi square analyses.

16.534 Pathologic changes due to preoperative radiotherapy observed at the time of definitive surgery will be described.

16.6 Data & Safety Monitoring

16.61 The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.62 Adverse Event Stopping Rules: The stopping rules specified below are based on knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended if at any time we observe the following events that are possibly, probably or definitely related to treatment:
If 4 or more patients in the first 10 treated patients or 6 patients at any point in the study experience (end/during radiation, 3 months after radiation, at 12 months and yearly after) a grade 3 or higher skin induced radiation dermatitis, pain over the treated area, swelling over the breast area, pneumonitis, radiation in-field wound infection, or poor cosmetic outcome (change from excellent/good cosmesis to fair or poor, or from fair to poor via Harvard cosmesis scale).

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event. However, any grade 4 or higher regardless of the attribution could be used for temporary suspension of the protocol at that time. The study team will review all grade 4 or 5 AEs, if they are clearly “unrelated” the study can remain active while the MCCC reviews the adverse event. In all other cases the grade 4 or 5 toxicity will determine a temporary closure of the study while it is reviewed by the MCCC DSMB.

The study will continue to be monitored by the MCCC DSMB till all patients in the study complete treatment and are followed by 180 days. Patients will continue to be followed and monitored in the study for 5-years by the radiation oncology clinical research team.

16.7 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the “ClincialTrails.gov” website. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 24 months after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has undergone definitive surgical procedure.

16.8 Inclusion of Women and Minorities

16.81 This study will be available to all eligible patients, regardless of race, or ethnic origin.

16.82 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist. Male breast cancer is a relatively rare entity in whom APBI would not be appropriate therapy and male gender is an exclusion criteria.Although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.83 The geographical region served by the Mayo Clinic, has a population which includes approximately 5% minorities. We expect about 5% of patients will be classified as minorities by race and about 100% of patients will be women.

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	0	2
Not Hispanic or Latino	23	0	23
Ethnic Category: Total of all subjects	25	0	25
American Indian or Alaskan Native	1	0	1
Asian	0	0	0
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	23	0	23
Racial Category: Total of all subjects	25	0	25

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens

	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Process at Site? (Yes or No)
Diagnostic	Mandatory	Formalin Fixed and Flash Frozen tumor	See below	Yes
Definitive surgery	Mandatory	Formalin Fixed and Flash Frozen tumor	See below	Yes

Tissue requirements:

Paraffin blocks: Two (2) of the initial diagnostic core biopsy and two (2) blocks of the cancer at the time of surgery, if available.

Alternate to paraffin blocks:
Two 2 mm core sampling of the existing tumor block from an area rich in tumor cells or a similar size fragment cut from the original block

Flash frozen tissue at the time of surgery: One 18g needle core of the initial diagnostic core biopsy and a 25-50mg tissue sample of the cancer at the time of surgery, if available.
We will send 25 mgs of the tumor to RST. We will send 25-50 mgs of the tumor and sentinel lymph node tissue to RST, if available.

17.2 Flow cytometry

For formalin fixed tissue samples excess paraffin is removed with a scalpel from either side of 40-60um scrolls then processed according to our published methods. Briefly each sectioned piece is collected into individual microcentrifuge tubes then washed three times with 1 ml Xylene for 5 minutes to remove remaining paraffin. Each sample is rehydrated in sequential ethanol washes (100% 5 minutes x2, then 95%, 70%, 50% and 30% ethanol) and washed 2 times in 1ml 1 mM EDTA pH 8.0. A 1 ml aliquot of 1 mM EDTA pH 8.0 is added to the samples and incubated at 95^{o}C for 80 minutes to facilitate the removal of protein cross-links present in FFPE tissue. Samples are then cooled to room temperature for $\geq$ 5 minutes, followed by addition of 300 ul PBS pH 7.4 and gentle centrifugation for 2 minutes at 3.6 x g. The supernatant is carefully removed and the pellet washed three times with 1 ml PBS pH 7.4/0.5mM $CaCl_2$ to remove EDTA. Each sample is digested overnight (6-17 hours) in 1ml of a freshly prepared enzymatic cocktail containing 50 units/ml of collagenase type 3, 80 units/ml of purified collagenase, and 100 units/ml of hyaluronidase in PBS pH 7.4/0.5mM $CaCl_2$ buffer. Following overnight digestion 500 ul NST is added to each sample to facilitate pelleting. Samples are centrifuged for 5 minutes at 3000 x g, after which pellets are resuspended in 750 ul of NST/10% fetal bovine serum and then passed through a 25 G needle 10-20 times.

Prior to sorting biopsies (formalin fixed or flash frozen) are minced in the presence of NST buffer and DAPI according to published protocols. Each sample is filtered through a 35 um mesh and collected into a 5 ml Polypropylene round bottom tube. The mesh is

rinsed with an additional 750 ul of NST/10% fetal bovine serum and placed on ice while processing remaining samples. The total volume in the tube for each sample is approximately 1.5 ml. An equal volume of 20ug/ml DAPI is added to each tube to achieve a final concentration of 10ug/ml DAPI for flow sorting with a BD Influx cytometer with ultraviolet excitation (Becton-Dickinson, San Jose, CA). The optimal settings for sorting FFPE samples with the Influx sorter are as follows: Drop formation was achieved with piezzo amplitude of 6-10 volts and a drop frequency of 30 khertz. The sort mode is set to purity yield with a drop delay of 31.5-32. Sheath fluid pressure was typically 17-18 psi with a 100 um nozzle. For single parameter DNA content assays DAPI emission is collected at >450nm. DNA content and cell cycle were then analyzed using the software program MultiCycle (Phoenix Flow Systems, San Diego, CA). All flow sorting will be done in the Barrett laboratory located in the Collaborative Research Building on the MCA Scottsdale campus.

17.3 DNA extraction

DNA from sorted nuclei is extracted using an amended protocol from QIAamp® DNA Micro Kit from Qiagen (Valencia, CA). Briefly each sorted sample is resuspended in 180ul buffer ATL and 20ul proteinase K (20mg/ml) then incubated for 3 hours at 56°C for complete lysis. Samples are bound and washed according to QIAamp® DNA Micro Kit instructions, eluted into 50ul of H20, then precipitated overnight with 5ul 3 M sodium acetate and 180 ul 100% EtOH. Each sample is then centrifuged for 30 minutes at 20,000 x g, washed in 1 ml of 70% EtOH for 30 minutes at 20,000 x g. The samples are carefully decanted and the DNA pellet is dried by speed vacuum then resuspended in a small volume (e.g. 10-50ul) of H20 for final concentrations suitable for accurate quantitation. All DNA extractions will be done in the [redacted].

17.4 Exome capture and sequencing

For each patient we will prepare sufficient DNAs from each sorted tumor population, as well as a patient matched control sample, for exome sequencing. Residual DNAs will be stored at MCA for future studies. All sequencing will be done within Mayo Clinic Medical Genome Facility (MGF) using established protocols for whole exome analysis. Briefly, whole exon capture is carried out using the protocol for Agilent's SureSelect Human All Exon 71 MB v6 kit. 500 ng of the prepped library is incubated with whole exon biotinylated RNA capture baits supplied in the kit for 24 hours at 65 °C. The captured DNA: RNA hybrids are recovered using Dynabeads MyOne Streptavidin T1 (Dynal). The DNA is eluted from the beads and desalted using purified using Ampure XP beads (Agencourt). The purified capture products are then amplified using the SureSelect Post-Capture Indexing forward and Index PCR reverse primers (Agilent) for 12 cycles. Libraries are loaded onto paired end flow cells at concentrations of 4-5 pM to generate cluster densities of 600,000-800,000/mm^2 using the Illumina cBot and HiSeq Paired end cluster kit version 3.The flow cells are sequenced as 101 X 2 paired end reads on an Illumina HiSeq 4000 using TruSeq SBS sequencing kit version 3 and HiSeq data collection version 1.4.8 software. Base-calling is performed using Illumina's RTA version 1.12.4.2

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Treatment** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
Patient Eligibility	
Demographics	
On-Study	
Pathology of Ipsilateral Breast	
Adverse Events- Baseline	
Patient Status: Baseline	
Patient Assessment	
	*6 months after accrual
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	End of Treatment	12 weeks post-RT / Observation Phase[4]	Event Monitoring[5]
Radiation Therapy	X		
Radiation Lumpectomy Therapy	X		
Patient Assessment	X	X	
Adverse Events Solicited	X	X	
Adverse Events: Other	X[2]	X[2]	
Off Treatment	X[2]	X[2]	
Patient Status Form	X	X	X
Specimen Submission: Tissue (Recurrence)		X[2]	
Consent Withdrawal	X[2]	X[2]	
Lost to Follow-up	X[2]	X[2]	
Breast Radiotherapy Questionnaire[3]	X	X	

[1] Complete at each evaluation during Active Treatment (see Section 4.0).
[2] When applicable
[3] Survey will need to be entered manually if has not alternately been scanned or entered electronically
[4] Active monitoring observation phase, Day 15 (+/-3 days), D90 (+/- 1 month), D180 (+/- 2 months), D365 (+/- three months), annually for 4 years (+/-6 months, total 5 years follow-up). If patient progresses within observation, they will move to the event monitoring phase where they will be followed until 5 years of follow-up information has been completed from the end of treatment time point.
[5] If patient has a recurrence prior to being off radiation therapy for 5 years, continue to follow yearly.

18.2 Data Handling and Record Keeping

18.21 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 14)

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.22 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access.

18.23 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was

not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

18.24 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;
1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Venipuncture, DNA analysis, and Biobanking

19.3 Other budget notes: The Marley Grant and the Mayo Clinic Radiation Oncology Unit are funding this study and will cover all costs related to running this study

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party. The principal investigator would maintain control and use of all data used in the study during the study and after the study has been completed.

21.0 References

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Appendix I

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

Appendix II
Mayo Breast Patient Survey

Mayo Breast Patient Survey

Survey Date (mm/dd/yyyy):

DIRECTIONS: For each question below, please mark one response that describes how you would rate your symptoms DURING THE PAST DAY.

1. How you would describe…

   Your overall quality of life? *Response scale 1 to 10, with 1 = as bad as it could be; 10 = as good as it could be*

   The severity of your pain, on average? *Response scale 1 to 10, with 1 = no pain; 10 = Pain as bad as it could be*

   Your level of fatigue, on average? *Response scale 1 to 10, with 1 = no fatigue; 10 = fatigue as bad as it could be*

DIRECTIONS: For each question below, please mark one response that describes how you would rate your symptoms IN THE LAST 7 DAYS.

2. **In the last 7 days**, how much did anxiety interfere with your usual or daily activities?
   ☐Not at all
   ☐A little bit
   ☐Somewhat
   ☐Quite a bit
   ☐Very much

3. **In the last 7 days**, how much did insomnia, including falling asleep, staying asleep, or waking up early INTERFERE with your usual or daily activities?
   ☐Not at all
   ☐A little bit
   ☐Somewhat
   ☐Quite a bit
   ☐Very much

4. **In the last 7 days**, what was the SEVERITY of your shortness of breath at its WORST?
   ☐Not at all
   ☐A little bit
   ☐Somewhat
   ☐Quite a bit
   ☐Very much

5. **In the last 7 days**, what was the SEVERITY of your cough at its WORST?
   ☐Not at all
   ☐A little bit
   ☐Somewhat
   ☐Quite a bit
   ☐Very much

6. **In the last 7 days**, how much did problems with concentration INTERFERE with your usual or daily activities?
☐Not at all
☐A little bit
☐Somewhat
☐Quite a bit
☐Very much

7. **In the last 7 days**, how much did sad or unhappy feelings INTERFERE with your usual or daily activities?
☐Not at all
☐A little bit
☐Somewhat
☐Quite a bit
☐Very much

8. **In the last 7 days**, what was the SEVERITY of your skin burns from radiation at their worst?
☐Not at all
☐A little bit
☐Somewhat
☐Quite a bit
☐Very much

9. **In the last 7 days**, what was the SEVERITY of your difficulty swallowing at its WORST?
☐Not at all
☐A little bit
☐Somewhat
☐Quite a bit
☐Very much

10. **In the last 7 days**, how SEVERE have the following problems been (at their WORST)?

Flaking or peeling of the treated breast or chest wall; *response options 0 to 10, 0 = not at all, 10 = flaking as much as could be*

Bleeding of or leaking fluid from the treatment breast or chest wall; *response options 0 to 10, 0 = not at all, 10 = bleeding as much as could be*

Blistering of the treated breast or chest wall; *response options 0 to 10, 0 = not at all, 10 = blistering as much as could be*

Itching of the treated breast or chest wall; *response options 0 to 10, 0 = not at all, 10 = as itchy as it could be*

Skin burns from radiation on your back; *response options 0 to 10, 0 = not at all, 10 = as itchy as it could be*

11. If you had to do it all over again, would you have this **RADIATION** treatment again?
☐Yes
☐No

12. Have you been diagnosed with an infection at your breast cancer surgical site that required treatment with antibiotics or surgery?
☐Yes
☐No

We are interested in your evaluation of your physical appearance and functioning. Please rate the following items from 0 to 10, according to how you feel **AT THIS POINT IN TIME**.

Is the color of your treated breast/chest wall skin different than the other side (red, tan, or lighter)? *response options 0 to 10, 0 = not at all, 10 = as different as it could be*

Do you have visible small blood vessels (spider veins) on your treated breast/chest wall? *response options 0 to 10, 0 = not at all, 10 = as many as it could be*

Do you have pain with swallowing? *response options 0 to 10, 0 = not at all, 10 = as painful as could be*

Do you have numbness or a tingling sensation in the arm on the side that was treated? *response options 0 to 10, 0 = not at all, 10 = as much as it could be*

Do you have tightness, pulling, or stretching in the arm, breast, or chest area (in the side that was treated?) response *options 0 to 10, 0 = not at all, 10 = as much as it could be*

Do you have tenderness or discomfort on the treated breast/chest wall? *response options 0 to 10, 0 = not at all, 10 = as much as it could be*

Overall, how would you rate the cosmetic results of your breast treatment?
☐Excellent ☐ Good☐ Fair☐ Poor

Please rate the following items according to your evaluation **at this point in time:**

Breast/chest wall texture (hardening)	☐ None	☐ Slight	☐Moderate	☐Large
Arm heaviness	☐ None	☐ Slight	☐Moderate	☐Large
Shoulder movement	☐ None	☐ Slight	☐Moderate	☐Large
Arm movement	☐ None	☐ Slight	☐Moderate	☐Large
Breast/chest wall pain	☐ None	☐ Slight	☐Moderate	☐Large
Ability to lift objects	☐ None	☐ Slight	☐Moderate	☐Large
Fit of shirt sleeve	☐ None	☐ Slight	☐Moderate	☐Large
Breast/chest wall tenderness	☐ None	☐ Slight	☐Moderate	☐Large
Shoulder stiffness	☐ None	☐ Slight	☐Moderate	☐Large
Scar tissue	☐ None	☐ Slight	☐Moderate	☐Large
Shoulder pain	☐ None	☐ Slight	☐Moderate	☐Large
Arm pain	☐ None	☐ Slight	☐Moderate	☐Large
Arm swelling	☐ None	☐ Slight	☐Moderate	☐Large
Breast/chest wall swelling	☐ None	☐ Slight	☐Moderate	☐Large
Arm stiffness	☐ None	☐ Slight	☐Moderate	☐Large
Breast/chest wall sensitivity	☐ None	☐ Slight	☐Moderate	☐Large
Fit of clothing	☐ None	☐ Slight	☐Moderate	☐Large
Axillary (arm pit) fullness or numbness	☐ None	☐ Slight	☐Moderate	☐Large

Please complete the following questions if you had breast conserving therapy or mastectomy with reconstruction.

Please rate the following items according to your evaluation **at this point in time**

Breast size	☐ None	☐ Slight	☐Moderate	☐Large
Nipple appearance	☐ None	☐ Slight	☐Moderate	☐Large
Breast shape	☐ None	☐ Slight	☐Moderate	☐Large
Breast elevation (how high the breast is)	☐ None	☐ Slight	☐Moderate	☐Large
Fit of bra	☐ None	☐ Slight	☐Moderate	☐Large
Breast heaviness	☐ None	☐ Slight	☐Moderate	☐Large

Appendix III
Mayo Patient Survey PRO-CTCAE Mayo 10

Survey Date (mm/dd/yyyy):

Please answer the following questions about your symptoms.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
In the last 7 days, how much did anxiety INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
In the last 7 days, how much did insomnia including difficulty falling asleep, staying asleep, or waking up early INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
In the last 7 days, how much did decreased appetite INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
	Never	Rarely	Occasionally	Frequently	Almost Constantly
In the last 7 days, how OFTEN did you have nausea:	☐	☐	☐	☐	☐
	Not at all	A little bit	Somewhat	Quite a bit	Very much
In the last 7 days, how much did shortness of breath INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
In the last 7 days, how much did problems with concentration INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
In the last 7 days, how much did sad or unhappy feelings INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
	None	Mild	Moderate	Quite a bit	Very severe
In the last 7 days, what was the SEVERITY of your constipation at its WORST:	☐	☐	☐	☐	☐
	Not at all	A little bit	Somewhat	Quite a bit	Very much
In the last 7 days, how much did numbness or tingling in your hands or feet INTERFERE with your usual or daily activities:	☐	☐	☐	☐	☐
	Never	Rarely	Occasionally	Frequently	Almost Constantly
In the last 7 days, how OFTEN did you have loose or watery stools (diarrhea):	☐	☐	☐	☐	☐

Appendix IV
Mayo Patient Survey

Survey Date (mm/dd/yyyy):

Please respond to each item by choosing one number per row.

	Excellent	Very Good	Good	Fair	Poor
In general, would you say your **health** is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, would you say your **quality of life** is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your **physical health**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your mental health, including your **mood and your ability to think**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your satisfaction with your **social activities and relationships**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, please rate how well you carry out your usual **social activities and roles** (Includes activities at home, work, community, parenting, marriage, friends.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	Completely	Mostly	Moderately	A little	Not at all
To what extent are you able to carry out your **everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	Never	Rarely	Sometimes	Often	Always
In the past 7 days… How often have you been bothered by **emotional problems such as feeling anxious, depressed, or irritable**?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

How would you rate your **fatigue** on average?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Worst pain imaginable

How would you rate your **fatigue** on average?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No pain Worst pain imaginable