Mayo Clinic Radiation Oncology

A phase III trial of hypofractionated radiotherapy to the whole breast alone after breast conserving surgery

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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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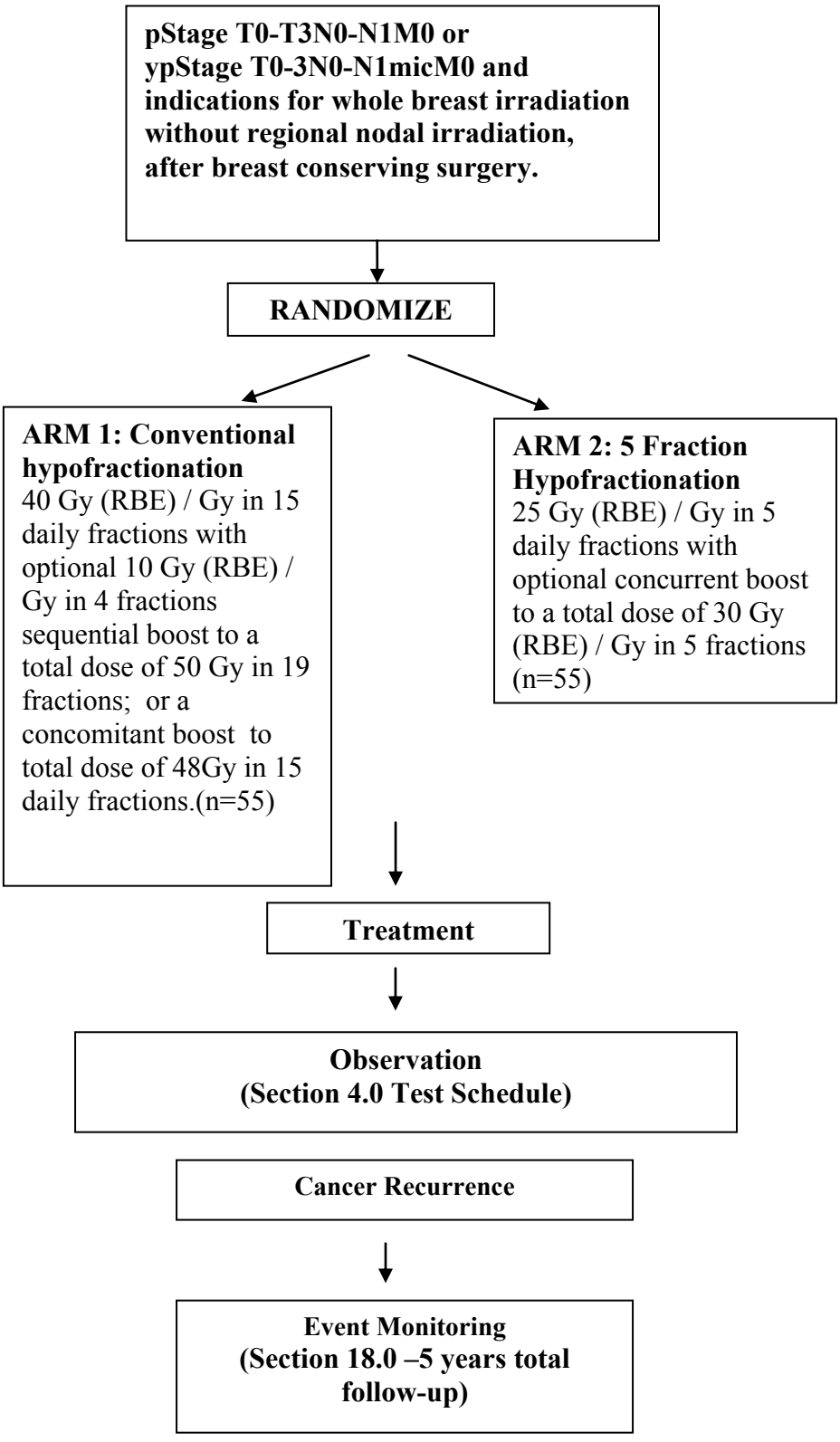
List of Abbreviations

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


pStage T0-T3N0-N1M0 or
ypStage T0-3N0-N1micM0 and
indications for whole breast irradiation
without regional nodal irradiation,
after breast conserving surgery.
RANDOMIZE
ARM 1: Conventional hypofractionation
40 Gy (RBE) / Gy in 15 daily fractions with optional 10 Gy (RBE) / Gy in 4 fractions sequential boost to a total dose of 50 Gy in 19 fractions; or a concomitant boost to total dose of 48Gy in 15 daily fractions.(n=55)
ARM 2: 5 Fraction Hypofractionation
25 Gy (RBE) / Gy in 5 daily fractions with optional concurrent boost to a total dose of 30 Gy (RBE) / Gy in 5 fractions (n=55)
Treatment
Observation
(Section 4.0 Test Schedule)
Cancer Recurrence
Event Monitoring
(Section 18.0 –5 years total follow-up)

N=110 patients

Study Design: This is an open label phase III randomized controlled trial to determine the safety of 5 fraction vs 15 fraction pencil beam scanning proton radiotherapy to the whole breast alone after breast conserving surgery. Proton therapy is recognized as a standard option for the delivery of radiotherapy for breast cancer.

1.0 Background

1.1 Benefits and Risks of Adjuvant Radiotherapy

Breast conserving therapy (BCT), consisting of partial mastectomy, followed by whole breast radiotherapy, is a widely accepted standard of care and the preferred local treatment approach for many women with breast cancer. Women opting for breast conserving therapy have improved body image, quality of life, and sexual function[1,2].

Six randomized studies with long term follow up have established the equivalent overall survival of breast conserving therapy to mastectomy[3-8] . The breast radiotherapy component of BCT has been shown to improve rates of local control, reduce distant recurrence, and improve survival [9,10]. Despite the strong evidence for breast conserving therapy, there is underutilization of both breast conserving surgery [11] and adjuvant radiotherapy[12] . While many factors likely contribute, convenience of therapy, access to treatment facilities[13], cost, and perceived toxicity of therapy may all represent barriers to radiation therapy[14].

Survival rates for breast cancer are high, as most women diagnosed will not die of their disease[15]. As such, recent oncologic emphasis has highlighted survivorship, with strategies aimed to improve treatments, treatment-related adverse effects, and long term quality of life [16,17]. These improvement strategies aim to improve the therapeutic ratio, with enhanced benefits of therapy, reduced toxicity, or both.

Careful study of photon breast radiotherapy techniques has highlighted potential long term toxicities and opportunities to enhance the therapeutic ratio. Data demonstrating late cardiovascular toxicity, particularly for women with left-sided tumors, and risk of secondary malignancy have garnered particular attention in recent years,[18] and these toxicities have been shown to partially offset the cause-specific survival benefit of adjuvant radiotherapy[9,19].

Cardiovascular toxicity has been studied in great detail and appears to be primarily mediated by a vascular etiology, likely with macro- and microvascular contributions. Amongst women undergoing adjuvant radiotherapy for breast cancer, Correa and colleagues[20] demonstrated a likelihood of left anterior descending artery (LAD) stenosis in excess of what would be expected, providing indirect evidence of radiation-mediated coronary artery disease. Darby and co-authors[19] found that the risk of major coronary events (myocardial infarction, coronary revascularization, or death from ischemic heart disease) was related to the mean heart dose and not the LAD, suggesting a microvascular etiology. Radiation related cardiovascular toxicity is likely multifactorial, and multiple dose-volume relationships are likely important risk factors of subsequent cardiac disease, including dose to the LAD, heart (mean heart dose and volumetric parameters such as V_{25}) and left ventricle[21]. Efforts to minimize cardiac exposure to radiotherapy, while studying the potential dose relationships are of utmost importance, particularly in the

modern systemic therapy era, which now includes more agents with known cardiac effects, including anthracyclines and trastuzumab.

Adjuvant radiotherapy for breast cancer has also been associated with an elevated risk of developing a secondary malignancy[9]. Specifically, radiotherapy is associated with increased risk of developing and dying from ipsilateral lung cancer[9,22]. Radiotherapy is also associated with increased risk of contralateral breast carcinoma[9]. This is a result of inadvertent and unnecessary dose delivered to normal organs adjacent to disease targets.

Radiotherapy to the breast may also result in breast fibrosis, breast shrinkage, worsening of cosmesis, and arm and shoulder pain.[23,24,25] There is evidence that these late effects are potentially dose dependent.

In summary, breast conserving therapy is a standard of care and offers many advantages to women, and radiotherapy is necessary to achieve optimal oncologic outcomes. However, in the modern era of enhanced technology and improved emphasis on survivorship, there is strong rationale for the development and evaluation of novel strategies that reduce unnecessary radiation exposure to normal tissue, as well as novel dose and fractionation regimens which may improve the therapeutic ratio, while reducing costs and increasing convenience of delivery. We propose a prospective phase III trial that will evaluate the use of hypo-fractionation with either x-rays or proton therapy

1.2 Rationale for Proton Therapy in Breast Cancer

Enhanced radiotherapy delivery techniques may enable better treatment delivery with reduced toxicity. Proton therapy, in particular, may reduce treatment toxicity, as there is less non-target tissue exposed to radiation therapy. Relative to photons, protons have fundamental physical advantages in the treatment of tumors adjacent to radiosensitive normal structures. By exploiting the Bragg peak of proton beams, target tissues may be covered with a similar or better dose distributions as with photons, with reduced unintended dose to other tissues, including reduced integral dose [26,27]. Thus, interest in the possible benefits of breast cancer radiotherapy with protons is emerging, with hopes of being able to maintain or improve the locoregional control and cause-specific survival, with potential to reduce toxicity.

Clinical experience with proton beam radiotherapy (PBT) in the treatment of breast cancer patients remains limited, though increased institutional experiences are reported, and a multi-center randomized study in node positive patients has been initiated (CITE PCORI). A recent review examined published experience with PBT for breast cancer[28]. This report highlights the limited published clinical experience with proton beam for breast cancer, in particular demonstrating very little data for whole breast radiotherapy without regional nodal treatment. The two such cited studies were retrospectively planned proton versus plan comparisons, rather than clinical experience, yet each supported a dosimetric advantage to PBT for left sided breast cancer patients undergoing BCT, with a reduction in mean heart dose, coronary artery dose, and ipsilateral lung dose[29,30].

Clinical experience in the node positive setting is published. MacDonald et al [31] recently published early outcomes for a small cohort of 12 patients treated with proton radiotherapy following mastectomy. All patients received chest wall irradiation and eleven received radiotherapy to the supraclavicular, level 3, and internal mammary lymph

node chains. Nine patients had grade 2 skin toxicity and 3 patients had grade 1 skin toxicity. There was no ≥ grade 3 skin toxicity reported. During treatment 6 patients experienced grade 1 fatigue, 5 patients experienced grade 2 fatigue, and there was one incident of grade 3 fatigue. By 4 weeks follow-up fatigue had completed resolved in all but 1 patient who continued to have grade 1 fatigue. There were no reported cases of pneumonitis. The average mean dose to the heart was 0.44 Gy and the average mean V20 of the lung was 12.7%. Cuaron et al. recently reported the results of treatment of the largest cohort of patients treated with proton therapy for breast cancer.[32] Four patients were treated after lumpectomy, 24 after mastectomy (including 14 patients with implant reconstruction and 1 patient with autologous reconstruction) and 2 patients received proton therapy after wide local excision of a chest wall recurrence. Grade 2 dermatitis occurred in 20 patients (71.4%), 8 of whom (28.6%) also experienced moist desquamation. Grad 2 esophagitis was observed in 8 patients (28.6%). There was 1 grade 3 reconstructive complication. The median mean heart dose was 0.88Gy and the median V20 of the ipsilateral lung was 16.5%. This early data suggests that post-mastectomy and post-lumpectomy proton therapy is feasible and well tolerated with reduced dose to the heart and lung, warranting further study.

In addition to the clinical experience in the locally advanced setting, several institutions have examined PBT for partial breast radiotherapy. One such initial report showed high rates of acute skin toxicity, pigmentation changes, and worse physician reported cosmesis [33]. However, the planning techniques reported therein, including passive scatter and a single beam treated per day for many, possibly contributed to these outcomes. A larger series from Loma Linda with 60 month follow up and 100 patients reported good to excellent cosmetic outcome in >90% throughout 5 years of follow up[34]. No patient had acute grade 3 or higher skin toxicity. Ispilateral tumor recurrence rates at 5 years were 3%. In addition to differences in dose and technique, once daily treatments were used.

Much of the published PBT experience is with passively scattered protons. A concern with this technique is the high entrance skin dose which may be associated with higher skin toxicity and adverse cosmesis.[33] This higher skin dose may be of particular concern in patients who undergo breast conserving surgery. Scanning beam proton therapy, the technique proposed in this study, offers potential advantages over passively scattered protons including increased conformality with even less unintended dose to normal tissues, including the skin.[35] However, this technique is also potentially more sensitive to uncertainties including inter-fractional as well as intra-fractional motion which must be taken into account in treatment delivery. Rigorous clinical studies of scanning beam proton therapy are needed to determine the disease control and toxicity outcomes with this technique and to determine whether the physical dose advantages of proton therapy translate to substantial and lasting improvements in patient outcome.

In summary, there is strong interest in prospectively designing and understanding proton therapy in breast cancer. Data for proton therapy in breast cancer are limited, particularly in the intact breast setting, yet there is compelling rationale for study of proton beam therapy for breast cancer to reduce radiation dose to non-target tissue and potentially improve outcomes for breast cancer survivors. In view of the need to gain experience, a clinical study is supported.

1.3 Rationale for Hypofractionation in Breast Cancer

Hypofractionated, or shorter course, radiotherapy presents an opportunity to enhance access to care, increase convenience and acceptability of therapy, while reducing cost and potentially improving toxicity. Although the use of proton therapy for breast cancer is still in early development, concerns regarding proton therapy have primarily been related to costs, rather than technical feasibility in the clinic. Proton therapy departments are more expensive to build as they require huge accelerators to deliver the beam. While proton therapy is considered more expensive than conventional forms of radiation, cost-benefit studies have suggested cost-effectiveness in the long term due to decreased long term toxicity. [36-38] An important driver of cost of both photon and proton radiotherapy is the number of treatments delivered to individual patients, with shorter courses resulting in lower expenditures[39]. Studies are needed to evaluate whether equivalent or improved outcomes can be achieved with shorter courses of therapy.

Furthermore, the optimal dose and fractionation regimen for whole breast irradiation, whole breast and regional nodal irradiation, and postmastectomy radiotherapy remains unknown. While there is widespread clinical experience with standard fractionation, newer preclinical and clinical data support a shorter course of radiotherapy.

For fraction sizes up to approximately 8 Gy, The linear-quadratic formula model is the preferred method of predicting the relationship between fraction size and tissue response of varying radiotherapy regimens. Its origins stem from what has been described as a two-component survival curve for mammalian cells represented by the curvilinear dose-response curve for the log of cell survival.[40] In it, the biologically effective dose (BED) of a given fractionation regimen is related to the α/β ratio in the following equation, where α represents the $\log_e$ of the cells killed per gray and β is the $\log_e$ of the cells killed per gray squared:

$BED = nd(1 + d/\alpha/\beta)$
d = dose per fraction
n = # of identical fractions

The ratio of α/β is the dose at which the linear and quadratic components of cell killing are the same. In general, early-responding tissues such as skin desquamation have a high ratio whereas late-responding tissues such as dermal contraction have a low ratio and are very sensitive to increases in fraction size.[41]

Emerging evidence suggests that the α/β ratio of breast cancer may be low and more in line with that of late responding tissues and therefore breast cancer patients may not benefit from prolonged fractionation regimens.[42,43] Indeed, the most robust data to date suggesting this relationship has come from the UK Standardization of Breast Radiotherapy (START) trials, two modern breast cancer randomized controlled trials examining various fractionation regimens that have recently been reported with 10-year follow-up. In START-A, a regimen of 50Gy in 25 fractions to the whole breast over 5 weeks was compared with 41.6Gy or 39 Gy in 13 fractions over 5 weeks. There was no significant difference in local-regional relapse between the 41.6Gy and 50Gy regimens (6.3% vs 7.4%, p=0.65) or the 39Gy and 50Gy regimens (8.8 vs 7.4%, p=0.41).[24] Moderate or marked breast induration, telangiectasia, and breast edema was less common in the 39Gy group compared with the 50Gy group, and rates of these toxicities were no different between the 41.6Gy and 50Gy groups. The treatments in each arm were given over the same time period, enabling an estimate of sensitivity of breast cancer to changes

in fraction size that was not confounded by differences in treatment time. An α/β ratio for local-regional relapse of breast cancer was determined from a meta-analysis of START-A and the START pilot trial (349 events, 3646 women) as 3.5 Gy (95% CI 1.2-5.7). The α/β ratio for normal tissue toxicity endpoints included 3.5Gy (95% CI 0.7-6.4) for breast shrinkage, 4Gy (2.3-5.6) for breast induration, 3.8Gy (1.8-5.7) for telangiectasia, and 4.7 Gy (2.4-7.0) for breast edema, suggesting that normal tissue toxicity may not be reduced and may even be increased when breast cancer radiotherapy fractionation regimens are prolonged with small daily fractions.

Further evidence supporting hypofractionated regimens for breast cancer came from the START-B clinical trial, in which 50Gy in 25 fractions over 5 weeks was compared with 40Gy in 15 fractions over 3 weeks. There was no difference in local-regional relapse at 10 years between 40Gy and 50Gy groups, (4.3% vs 5.5%, p=0.2) but breast shrinkage, telangiectasia, and breast edema were significantly less common with the shorter fractionation regimen. These data are consistent with the results of the Canadian hypofractionation trial which compared 42.5Gy in 16 fractions in 3.2 weeks to 50Gy in 25 fractions over 5 weeks and suggest that the use of smaller fractions is of no benefit in terms of tumor control or reduction in toxicity, at least in the doses used in these studies, and may potentially be deleterious.[24,44]. Interestingly, if one applies an α/β ratio for both normal tissue toxicity and tumor control of 3.5 from START-A, the 40Gy regimen from START-B is equivalent to 44.9Gy in 2 Gy fractions. This may imply that differences in overall treatment time of a course of radiation therapy may be more important than originally thought, potentially allowing further dose reduction when fractionation regimens are shortened, as we propose here.[45,46].

Other moderate hypofractionated radiotherapy treatments support excellent local control and comparable toxicity outcomes. Ahlawat el al, reported on 83 women treated after breast conserving surgery 36.63 Gy in 11 fractions of 3.33 Gy per day, with a 4 fraction boost of an addition 3.33 Gy[47]. Three year local recurrence free survival was 95.9%, and breast cosmesis was good or excellent in 94% of evaluable patients.

In the FAST trial, 915 women aged ≥ 50 years with node negative early breast cancer after wide local excision were randomly assigned to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks versus 28.5 Gy or 30Gy in 5 fractions once weekly fractions of 5.7 Gy or 6.0 Gy. Three-year rates of physician-assessed moderate/marked adverse effects in the breast were 17.3% (13.3-22.3%, p<0.001) for 30Gy and 11.1% (7.9-15.6%, p=0.18) for 28.5Gy compared with 9.5% (6.5-13.7%) after 50Gy.[48] Further follow-up is needed to determine local control of these three regimens but promisingly at a median follow-up of 37.3 months in survivors, only 2 ipsilateral breast recurrences were noted.

Rovea, et al reported outcomes with 5 fractions of 6 to 6.5 Gy delivered once weekly for 291 elderly patients[49]. 5 year Local control was excellent at 98%. Late skin fibrosis was Grade 2 in 4.2% and grade 3 in 1.4%. Breast edema was low, at 7%, 4.2%, and 1.4% for Grade 1, 2, and 3, respectively. Good to excellent cosmetic outcome was reported in 86.4%. Similarly, favorable acute toxicity results were reported among 42 women with early stage breast cancer, treated to the whole breast with 30 Gy in 5 weekly fractions, with or without a boost, despite the majority of women having an obese BMI[50].

Min reported a modern cohort of patients treated according to an older French trial[51]. 82 patients were treated to 23 Gy over 4 fractions, delivered on days 1 and 3 and 15 and 17.

Five year local control was 99%, with low rates of acute toxicity. 63 of 74 (86%) reported good or excellent cosmesis at last follow up. An included cost analysis supported substantial cost savings, compared with both standard fractionated and moderate hypofractionated schemes[52].

Despite strong interest and rationale for study of hypofractionated radiotherapy in breast cancer, there are no data available presently on the role of hypofractionation for breast cancer with scanning beam proton therapy.[31]

The overlying hypothesis of this study is that the low α/β of breast cancer can be exploited with carefully designed hypofractionated proton therapy regimens to further optimize the therapeutic ratio, improve patient convenience, and reduce cost. The goal of this phase III randomized controlled trial is to determine whether the hypofractionated proton regimens proposed are non-inferior compared with standard fractionated proton radiotherapy and therefore worthy of further investigation.

1.4 Rationale for Doses Selected

Table 1

Arms	Tx	Tumor dose 2Gy
50Gy in 2Gy	25	50Gy
45Gy in 2.26Gy	20	50Gy
33.4Gy in 3.34Gy	10	50Gy
24.7Gy in 4.98Gy	5	50Gy

As described above, a linear quadratic model can be used to define the alpha-beta of the normal structures and tumor as well biologic effective doses. Plausible population averaged radiobiologic parameters for breast cancer (95% confidence level) are α/β = 2.88 (0.75–5.01) Gy; a = 0.08 ± 0.02 Gy_1; potential doubling time Td = 14.4 ± 7.8 day.[43] The fractionation regimens in table 1 (modified from Qi et al.)[43] is based on the fitting of clinical data including the hypofractionated randomized trials mentioned above and justifies the five fraction regimen proposed for arm 2. The concurrent boost dose of 6 Gy x 5 is also based in part on the work of Formenti et al. who recently reported the 5-year results of a prospective trial of 3D-CRT APBI of 100 patients treated in the prone position to a total dose of 30Gy in 6Gy fractions. At a median follow-up of 64 months, there has been just one local recurrence and one contralateral recurrence and cosmesis was rated as good/excellent in 89% of patients with at least 36 months follow-up.[53] Livi et al has also shown excellent 5-year toxicity, cosmetic outcome and local failure results employing a dose of 30Gy in 5 treatments.[54]The control arm for this study will be 15 fractions based on the favorable long term follow-up of the UK START B[55]. More recently the initial toxicity results of the fast forward trial have been published. Very low rates of grade 3 toxicity were seen using either the 40 Gy over 3 weeks, or 26 Gy or 27 Gy over one week.[56] It is possible that the spot proton RBE may be different than 1.1 for hypo-fractionated treatments. Trials like the currently proposed would be critical to define differences in RBE with spot scanned hypofractionated radiation as well as the cancer and normal tissue alpha/beta.

2.0 Goals

2.1 Primary Objectives

2.1.1 To determine the 24-month complication rate of 5 fraction whole radiotherapy +/- concurrent boost as compared to 15 fraction radiotherapy +/- sequential boost. Complications will be defined as one or more of the following events: 1) grade 3 or higher late adverse event, 2) deterioration of cosmesis from excellent/good to fair/poor or from fair to poor.

2.2 Secondary Objectives

2.21 To evaluate acute and late toxicity
2.22 To estimate the 5-year locoregional control, invasive disease-free survival and overall survival.

2.3 Correlative and Exploratory

2.31 To evaluate fatigue, and other patient-reported outcomes.

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

2.32 To evaluate the costs and comparative effectiveness of treatment

2.33 Compare the use of photon therapy with spot scanning proton therapy in two different hypo-fractionated whole breast schemas.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.12 Age ≥ 18 years.

3.13 Histological confirmation of breast cancer.

3.14 Pathologic Stage T0-T3N0-N1M0. (8^{th} edition)

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

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

3.17a Study entry (randomization) must be within 12 weeks of last surgery (breast or axilla) or last chemotherapy (if applicable).

3.17b Willing to return to enrolling institution for follow-up (during the active monitoring phase of the study).

3.18 Fair, good or excellent cosmesis, as determined by trained nurse assessment using the Harvard Cosmetic Scale.

3.19 Radiotherapy must begin within 12 weeks of the last breast cancer surgery or the last dose of adjuvant chemotherapy.

3.20 Breast conserving surgery and indications for whole breast radiotherapy.

3.3 Exclusion Criteria

3.31 Medical contraindication to receipt of radiotherapy.

3.32 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.

3.33 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.

3.34 Active systemic lupus or scleroderma.

3.35 Women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception.

3.36 Prior receipt of ipsilateral breast or chest wall radiation.

3.37 Positive margins on ink after definitive surgery either for DCIS or invasive cancer.

3.38 History of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior study entry.

3.39 Recurrent breast cancer.

3.40 Indications for comprehensive regional nodal irradiation.

3.41 Male subjects.

3.42 Patient requires bilateral breast radiation treatment.

4.0 Test Schedule

	Baseline	Pre-treatment	EOT	Observation [12]			
	≤120 days prior to start of treatment	≤45 days prior to start of treatment[6]	Last day of Treatment (+/- 5 days)	12 weeks (+/- 4 weeks) post-treatment	6 months (+/- 2 months)	12 months (+/- 3 months), 24 months (+/- 6 months), 36 months (+/- 6 months), 48 months (+/- 6 months) and 5 years (+/- 6 months) **post completion of treatment**	Failure*
Consent	X						
cal exam[1]	X						
xam/ECOG us (see Appendix	X		X[8]	X		X	X
ment (see Section		X[9]	X[8]	X		X[13]	X
hs[3]		X	X	X		X	
dices 2,3,4)[11]		X[9]	X	X	X	X	X
valuation (see		X[9]	X	X		X	X
nts							
l specimen	X[5]						X[2]
							X[7]

1. A general history & physical exam should include height and weight (optional at Rochester site)
2. Review of pathology at failure if obtained clinically
3. Photographs can be done at any time before or after treatment at the discretion of the physician
4. Last day of treatment +/-2 days per discretion of treating physician
5. Outside pathology must be reviewed at treating institution to confirm eligibility within 365 days.
6. Blood pregnancy test to be completed prior to start of treatment on day 1 (for women of childbearing potential only).
7. PET Scan at failure optional
8. Per discretion of treating physician for Arm 2 (5 days)
9. These tests can be done before or up 3 days into treatment
10. Limited physical exam to include ECOG; weight (optional for Rochester site)
11. As collected clinically
12. Patients that cannot come back to Mayo within the time constraints of the follow-up schedule; efforts to obtain outside records and complete QOL's will occur, however the required items may not be captured.
13. If follow up visit occurred at an outside institution, Cosmetic Assessment will not be required.

***Failure defined as recurrent disease5.0 Stratification Factors**

5.1 Treatment modality: Photons vs. spot scanned proton therapy.
Of the total 110 patients in this study, fifty-five would be treated in each arm. We will

allow a maximum of 28 patients per arm per treatment modality (photons/x-ray or protons).

6.0 Registration / Randomization Procedures

6.1 Registration Procedures

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

6.2 Screening tests/procedures (see section 4.0) will be completed within the guidelines specified on the assessment schedule.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups. [57]

7.0 Protocol Treatment

Doses throughout will be prescribed in Gy (RBE) / Gy or Gy. One Gy will be the equivalent of one Gy (RBE) / Gy for proton therapy for the purposes of the descriptions below. Radiation therapy must begin within 12 weeks of the last breast cancer surgery or the last dose of adjuvant chemotherapy and no sooner than 14 days since the last chemotherapy. The dose, schedule, and timing (neoadjuvant vs adjuvant) of chemotherapy and endocrine therapy are at the discretion of the treating oncologists. Concurrent cytotoxic chemotherapy with radiotherapy is not allowed. Use of anti-HER2 therapy during radiotherapy is permitted.

The treatment technique (photon/x-ray vs. proton) utilized will be at the physician's discretion and will be based on technical considerations, availability at the radiation oncology facility, insurance coverage considerations, and patient preference. See section 7.4.

7.1 Radiation Therapy, Arm 1

Patients who had breast conserving surgery and are randomized to arm 1 (standard fractionation) will receive whole breast radiotherapy delivered to the breast CTV with or without a sequential boost to the lumpectomy cavity CTV. Boost indications will be left to physician discretion. Potential risk factors suggesting increased absolute benefit from a boost include but are not limited to age < 40, close margins, extensive DCIS adjacent to the invasive tumor.[58,59]

7.2 Radiation Therapy, Arm 2

Patients who had breast conserving surgery and are randomized to arm 2 (5 fraction hypofractionation) will receive whole breast radiotherapy in 5 daily fractions delivered to the breast CTV with or without a concurrent boost to the lumpectomy cavity CTV. Boost indications will be left to physician discretion. Potential risk factors suggesting increased absolute benefit from a boost include but are not limited to age < 40, close margins, extensive DCIS adjacent to the invasive tumor.[58,59]

7.3 **Dose Specifications**

7.31 **Arm 1 Post-lumpectomy whole breast irradiation +/- sequential boost**

7.311 Breast: 40.05Gy (RBE) / Gy/Gy in 15 fractions of 2.67 Gy (RBE) / Gy/Gy

7.312 Lumpectomy cavity (optional): Sequential boost dose will be 10 Gy (RBE) / Gy in 2.5 Gy (RBE) / Gy fractions for a total dose of 50.05Gy (RBE) / Gy / Gy. Simultaneously integrated boost is allowed to a total dose of 48Gy (RBE) / Gy over 15 fractions.

7.32 **Arm 2 Post-lumpectomy whole breast irradiation +/- concurrent boost**

7.321 Breast: 25 Gy (RBE) / Gy in 5 fractions of 5 Gy (RBE) / Gy

7.322 Lumpectomy cavity (optional): Dose to the lumpectomy cavity (concurrent boost dose) will be 30 Gy (RBE) / Gy in 5 fractions of 6 Gy (RBE) / Gy

7.4 **Treatment Technique**

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

7.42 Only one breast will be treated on the protocol.

7.43 While planning the scanning target volumes, care must be taken to not put Bragg Peaks either in the Chest Wall or in the first 5 mm from the external surface of the body.

7.5 **Localization, Simulation, Immobilization**

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

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

7.53 Arm position may be up or down.

7.54 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.

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

7.56 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.

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

7.6 **Treatment Planning**

7.61 For proton planning, 1 or more en face or oblique fields are recommended.

7.7 **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.

7.71 Post-lumpectomy breast target volumes (Arms 1 and 2)

7.711 **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.

7.712 **Low tangents volume:** would be defined in the same manner; with the exception that the superior border should be between 2-4 cm from the inferior border of the humeral head.

7.713 **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 7.7.1.4.2).

7.714 Lumpectomy Cavity: Contour using the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips and/or fiducials are strongly recommended).

7.7.1.4.1 **Lumpectomy Cavity CTV**: Lumpectomy Cavity + 5mm 3 D expansion. Limit the CTV 5 mm from skin.

7.7.1.4.2 Breast CTV: the breast would be the same as the CTV high tangents or low tangents without further expansions. The lumpectomy CTV is also included. The breast CTV volume is limited 5mm from the skin. The breast CTV posteriorly, would be limited 5mm from the lung excluding the chest wall.

7.715 Photon therapy

7.7.1.5.1 PTV-eval (PTV evaluation): PTV evaluation would be used for photon patients. PTV eval would equal to the breast CTV as defined above. The breast CTV as defined above matches the definition of the RTOG 1005 “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 no deeper to the anterior surface of the ribs (excludes boney thorax and lung).”

7.8 **Critical Structures**

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

7.82 **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.

7.83 **Left anterior descending (LAD) interventricular branch**: 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)".[60]

7.84 **Right coronary artery (RCA).** 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."[60]

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

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

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

7.88 **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.

7.89 **Chest wall:** from patient's midline, at the mid plane of the sternum, to the patient's posterior axillary line. The thickness would be defined by measuring the distance from the lung-chest wall interface to the posterior edge of the pectoralis muscle and creating virtual structure. It can be manually modified to exclude the pectoralis muscle at the discretion of the treating physician. No breast tissue should be included in this structure. The CTV should not be included in this structure plus 2mm.

7.9 Prescription and Normal Tissue Constraints

7.91 **Arms 1 and 2 (protons and photons/x-rays)**

7.911 Breast CTV:

7.9.1.1.1 Per protocol ≥ D95% will receive ≥95% of prescription; Variation acceptable ≥ D90% receives ≥ 90% of prescription

7.912 Tumor CTV

7.9.1.2.1 Per protocol D95% receives ≥95% of dose; variation acceptable D90% receives ≥90% of the boost dose

7.913 Robustness analysis **for Protons**

7.9.1.3.1 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.

7.9.1.3.2 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[1]
Breast CTV		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Tumor Bed 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 (optional)	Mean dose	record	
	Max dose	record	

1. Major violations do not exclude patients from the protocol as it is an intent to treat analysis

Photons (x-rays) DVH summary table

		Goal	Major violation
PTV Eval		≥ V95% will receive ≥95% of prescription	V90% <90% of prescription
		Dmax <107%	Dmax >115%
Tumor Bed 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 (optional)	Mean dose	record	
	Max dose	record	

1. Major violations do not exclude patients from the protocol as it is an intent to treat analysis

Quality Assurance Documentation

7.92 At a minimum, the initial 2treatment plans per institution will be centrally reviewed by the principal investigator or designee prior to the start of treatment.

8.0 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: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

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 v5.0 grading unless otherwise stated in the table below. Version 4 is allowed if v5 is not available, however, AEs will have to be updated to V5 once is available:

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
	Superficial Soft Tissue Fibrosis	X	X	CTCAE
	Breast edema (lymphedema)	X	X	CTCAE

Vascular	Lymphedema -arms	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 3, 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 Quality of Life (QOL) questionnaires are adapted from the Breast Cancer Treatment Outcome Scale (BCTOS). PRO-CTCAE will also be used for QOL questionnaires.

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.

11.4.1 The Quality of Life (QOL) questionnaires are adapted from the Breast Cancer Treatment Outcome Scale (BCTOS). PRO-CTCAE will also be used for QOL questionnaires.

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

12.0 Descriptive Factors

- Breast: left vs. right
- AJCC Stage: 0 vs IA vs IB vs IIA vs IIB vs IIIA
- Tumor Size: 0-2cm vs > 2-5cm vs > 5cm
- Lymph Nodes: N0 vs N1

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 *withdrawn* if 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 N/A

15.0 Drug Information

Not Applicable

16.0 Statistical Considerations and Methodology

16.1 Overview: This is an open label phase III randomized controlled trial to determine the safety of 5 fraction vs 15 fraction radiotherapy after breast conserving surgery. The goal is to determine whether the difference in 24-month complication rates between the experimental arm and the control arm is acceptable. Of interest is whether the experimental arm results in an unacceptable increase in the 24-month complication rate. If it does not, then the experimental arm will be recommended for further study. If the 24-month complication rate is found to be unacceptable, then the recommendation would be to do no further studies of the experimental arm.

16.2 Primary and Secondary Endpoints

16.21 Primary Endpoint: The 24-month complication rate, defined as the percentage of women evaluable at 24 months who develop one or more of the following events:

1) grade 3 or higher late adverse event OR

2) deterioration of cosmesis from excellent/good to fair/poor or from fair to poor at the 24-month evaluation (using the Harvard/NSABP/RTOG Cosmesis Scale)

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:

- *Acute adverse events*: any adverse event, regardless of attribution, that occurs in the first 90 days post-RT.
- *Late adverse events* (up to 5 years post RT): any adverse event that occurred after the first 90 days 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 unkonw or difficult to stablish 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 evaluate fatigue, breast pain, arm function and other patient reported outcomes.

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.
- *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. The Panel will be blinded to treatment allocation.

16.4 Sample Size Determination

This study requires 100 evaluable women for the primary endpoint analysis (50 evaluable patients per arm).

Ninety-two percent of expected patients completed a 3-year assessment of cosmesis in the randomized phase III study reported by Olivotto et al.[61] Expected was defined as patients who were projected to have had their 3-year follow-up visit based on the date of random assignment and who did not experience recurrence, undergo mastectomy, or die. Therefore to be conservative we will anticipate enrolling 10 (5 per arm) additional patients to account for ineligibility, cancellation, major treatment violations, or other reasons. The maximum projected enrollment is therefore 110 women.

In a large randomized controlled trial Whelan and colleagues compared cosmetic outcomes between conventional and hypofractionated whole breast radiotherapy after lumpectomy. At baseline, 84% of patients in the hypofractionated arm were rated as having good or excellent cosmesis by trained nursing assessment. At 3 years, the percentage was 77%, or an absolute change of 7%.[62] In the study proposed here, a subset of patients may receive a boost to the lumpectomy cavity which has been associated with a slightly higher risk of fibrosis and adverse cosmesis.[63,64] Therefore, the sample size proposed for arms 1-2 is based on an assumed value of a 10% complication rate in the control arm. The rate of grade 3 or higher late toxicity in this population is expected to be ≤1 % (Whelan ASCO 2011). Since the local failure rate and death rate at 2-years in the UK start B trial[24] was less than 3% we assume that an additional 10% to account for patients lost to follow, failures, deaths and others should be adequate (Total enrollment of 110 patients).

16.5 Study Decision Rule and Operating Characteristics

The primary endpoint for this trial is the 24-month complication rate. Complications will be defined as at least one of the following events: 1) grade 3 or higher late adverse event OR 2) deterioration of cosmesis from excellent/good to fair/poor or from fair to poor (using the Harvard/NSABP/RTOG Cosmesis Scale)

The proposed analysis would be to compute the difference in the 24-month complication rate between the experimental arm and the control arm. A one-sided 90% confidence interval (with the upper bound of the interval) was computed by assuming a 10% complication rate in the control arm and a 15% "non-inferiority margin" of the difference (i.e. the maximum the difference can be between the experimental arm and control arm, the largest difference we're willing to accept). The decision rule would be of the following:

- *Upper bound of the one-sided confidence interval (CI) for the difference (experimental arm 24-month complication rate minus control arm 24-month complication rate) lies above 15%* then **recommend that the experimental arm is not investigated further**. The 24-month complication rate of the experimental arm is unacceptably high.
- *Upper bound of the one-sided confidence interval (CI) for the difference (experimental arm 24-month complication rate minus control arm 24-month complication rate) is less than 15%* then **recommend that the experimental arm undergo further investigation**. The 24-month complication rate of the experimental arm is potentially acceptable.

With 100 evaluable patients, this study has 80% power with a 1-sided alpha of 0.05 to test a null hypothesis that the control arm complication rate is10% and experimental arm control rate is 25% versus an alternate hypothesis that the complication rate in both arms is 10%. Sample size was computed using PASS v.15 software.

Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure 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.

16.6 Analysis Plan

The analysis for this trial will commence at the planned time points and at the time the patients have become evaluable for the primary endpoint.

16.61 Primary Analysis: The primary analysis will be to estimate the difference in the complication rate (adverse cosmesis and grade 3+ toxicities) which is defined as the 24-month complication rate in experimental arm minus that in the control arm. All patients meeting the eligibility criteria who have signed a consent form and started treatment will be in the primary analysis. The complication rate will include all women evaluable at 24 months. Those who have recurrent disease or die before 24 months will not be included in this calculation. We expect that <3% of patients will not be found eligible based on failure or death.[24] The complication rate will be estimated using a binomial estimator in both experimental arm

and control arm, and a one-sided 90% confidence interval of the difference will be computed with normal approximation. As mentioned above, the following decisions will be made based on the 90% CI:

- ***The upper bound of the 1-sided 90% CI of the difference lies below 15%***: The experimental arm regimen is acceptable.
- ***The upper bound of the 1-sided 90% CI of the difference lies above 15%***: The experimental arm regimen is unacceptable.

16.62 Secondary Analyses

16.621 *Acute adverse events*: 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 90 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 by treatment arm. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Rates will be compared between arms using chi-squared tests.

16.622 *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 appears or persists after 90 days 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. Rates will be compared between arms using chi-squared tests.

16.623 *Locoregional control*: The cumulative incidence of locoregional recurrence will be estimated using a competing risks method (Gooley et al.) by treatment arm. The competing risks will be distant breast cancer recurrence and death. Comparison between arms will employ Fine-Gray regression.

16.624 Invasive *disease-free survival*: i-DFS is defined as the time from registration until the time of invasive disease recurrence (not including DCIS) or death due to any cause. The i-DFS will be estimated with a Kaplan-Meier estimator and curve by treatment arm. Estimates will be given for specific time points along with 95% CIs. Comparison between arms will employ a log-rank test.

16.625 *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 by treatment arm. Estimates will be given for specific time points along with 95% CIs. Comparison between arms will employ a log-rank test.

16.626 Cause specific survival: The CSS will be estimated with a Kaplan-Meier estimator and curve by treatment arm. Estimates will be given for specific time

points along with 95% CIs. Comparison between arms will employ a log-rank test.

16.627 *Overall survival*: The OS will be estimated with a Kaplan-Meier estimator and curve by treatment arm. Estimates will be given for specific time points along with 95% CIs. Comparison between arms will employ a log-rank test.

16.631 *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). Mixed models will be used to estimate changes at fixed time points as well as compare outcomes between arms.

16.632 *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 by treatment arm. Comparisons between arms will employ chi-squared tests.

16.7 Data & Safety Monitoring

16.71 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.

16.72 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 events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 4 or more patients in the first 10 treated patients (per treatment arm) experience a grade 3 or higher adverse event, besides acute dermatitis, at least possibly related to treatment at any time following completion of the protocol treatment within 90 days post-treatment.
- After the first 10 patients have been treated (per treatment arm): if ≥ 20% of all patients experience a grade 3 or higher adverse event, besides acute

dermatitis, at least possibly related to treatment at any time following the completion of protocol treatment within 90 days post-treatment.

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.

16.8 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 48 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 been observed for 24 months.

16.9 Inclusion of Women and Minorities

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

16.92 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. 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.

16.93 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	3	0	3
Not Hispanic or Latino	105	0	105
Hispanic or Latino	5	0	5
Ethnic Category: Total of all subjects	110	0	110
American Indian or Alaskan Native	1	0	1
Asian	1	0	1
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
White (Hispanic and non-Hispanic)	107	0	107
Racial Category: Total of all subjects	110	0	110

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 to be Collected for this Protocol
None

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	
On Study: Neoadjuvant Chemotherapy	
Surgery	
Pathology of Ipsilateral Breast	
Adjuvant Therapy	
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/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

CRF	End of Treatment	12 weeks post/Observation Phase[4]	Event Monitoring[5]
Specimen Submission: Pathology Report (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. **Refer to test schedule in section 4.0**If patient has a recurrence prior to being off radiation therapy for 5 years, continue to follow yearly.

18.3 Data Handling and Record Keeping

18.31 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.

18.32 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.

18.33 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.

18.37 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 Other budget concerns: The Mayo Clinic Radiation Oncology Unit is funding the study and will cover costs related to running the 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.

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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