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Multi-Institution Phase II Trial of Intraoperative Electron Beam Radiotherapy Boost at the Time of Breast Conserving Surgery with Oncoplastic Reconstruction in Women with Early-Stage Breast Cancer

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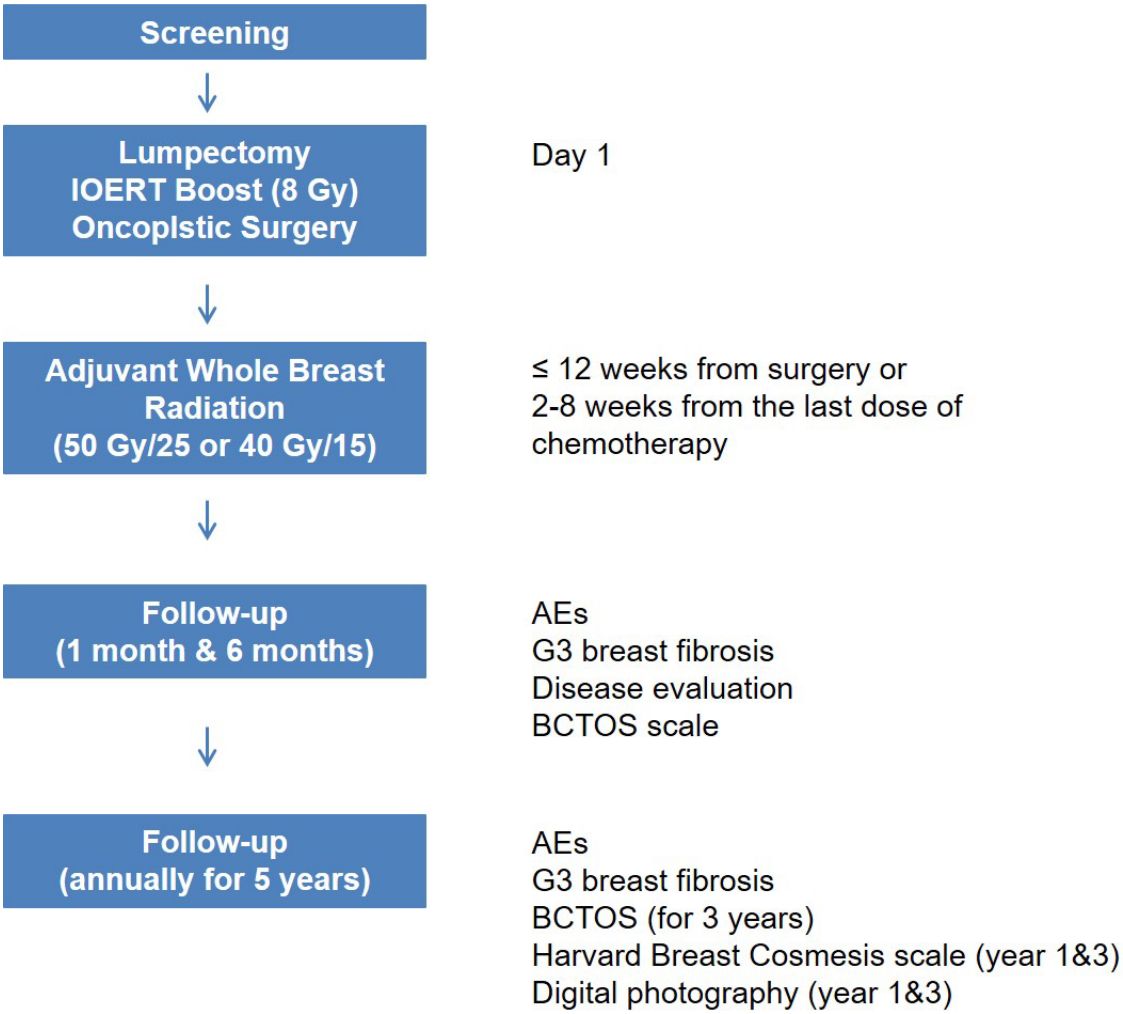
STUDY SUMMARY

Title	Phase II Trial of Intraoperative Electron Beam Radiotherapy Boost at the Time of Breast Conserving Surgery with Oncoplastic Reconstruction in Women with Early-Stage Breast Cancer
Short Title	IOERT Boost with Oncoplastic Reconstruction in Early Stage Breast Cancer
Phase	II
Methodology/Study Design	Single-arm, phase II study to evaluate the safety, toxicity and efficacy of intraoperative electron beam radiotherapy boost at the time of breast conserving surgery in women with early stage breast cancer undergoing oncoplastic reconstruction. Our goal is to safely target the lumpectomy cavity at the time of surgery but prior to oncoplastic reconstruction. We will deliver 1 dose of radiation (8 Gy) after lumpectomy but prior to oncoplastic reconstruction. Women will then receive whole breast radiation therapy after surgery.
Study Duration	48 months for accrual of all patients
Study Center(s)	Multi-center
Objectives	*Primary Objectives:* Determine the rate of grade 3 breast fibrosis at 1 year in women undergoing lumpectomy with oncoplastic reconstruction and immediate intraoperative electron radiotherapy boost followed by adjuvant whole breast radiotherapy *Secondary Objectives:* Determine the rate of 5 year ipsilateral breast tumor recurrence rate Determine the change in self-reported cosmesis using the BCTOS cosmesis scale Analyze physician reported cosmesis by the 4-point Harvard Cosmetic Scale and by digital photography To determine the rate of surgical complications necessitating hospital readmission or return to the operating room within 30 days of surgery + IOERT
Number of Subjects	176

STUDY SCHEMA



AE: Adverse Event
G3: Grade 3
BCTOS: Breast Cancer Treatment Outcome Scale

1.0 OBJECTIVES

This document is a protocol for human research study. This study is to be conducted according to the US and international standards of Good Clinical Practice (FDA Title 21 CFR parts 801, 803, 807, 812, 860, and 892 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

1.1 Primary Objective

The primary objective of this work is:

- To determine the rate of grade 3 breast fibrosis at 1 year in women undergoing lumpectomy with oncoplastic reconstruction and immediate intraoperative electron radiotherapy boost followed by adjuvant whole breast radiotherapy.

1.2 Secondary Objectives

The secondary objectives of this work are:

- To determine the rate of 5 year ipsilateral breast tumor recurrence rate
- To determine the change in self-reported cosmesis using the BCTOS questionnaire
- To evaluate physician-reported cosmetic outcomes using the 4-point Harvard Cosmesis Scale and digital photographs
- To determine the rate of surgical complications necessitating hospital readmission or return to the operating room within 30 days of surgery + IOERT

2.0 BACKGROUND AND RATIONALE

2.1 Local Control in Early-Stage Breast Cancer

Breast cancer remains the most common malignancy and the second most common cause of cancer death in women. Randomized trials with long term follow-up have demonstrated that breast conserving therapy and mastectomy are equivalent in terms of overall survival with long term local control rates of 85-95% with post-lumpectomy radiation therapy (Veronesi 2002; Fisher 2002). As a result, lumpectomy followed by adjuvant whole breast radiation therapy is the standard of care for women with early-stage breast cancer amenable to breast conserving therapy (NIH Consensus Conference 1991; National Comprehensive Cancer Network 2010). The reduction in local recurrence from radiation post lumpectomy has also been associated with improved overall survival compared to surgery alone (Early Breast Cancer Trialists' Collaborative Group 2005).

2.2 Tumor Bed Boost

Randomized trials have demonstrated that the addition of a tumor bed boost further significantly reduces the risk of ipsilateral beast tumor recurrences (Romestaing 1997; Bartelink 2015). In the first trial, patients were randomized to 10 Gy boost after 50 Gy whole breast irradiation. At 5 years, the risk of local recurrence was 3.6% vs. 4.5% in the boost vs. no boost group (p=0.044). In the EORTC trial, patients were randomized to a 16 Gy boost after 50 Gy to the whole breast. At 20 years, the cumulative incidence of ipsilateral breast tumor recurrence as a first failure was

9% vs. 13% in the boost vs. no boost group, a proportion reduction of 35%, which was statistically significant ($p<0.0001$). This reduction in ipsilateral breast tumor recurrence was present in all age groups analyzed, but the largest absolute benefit was seen in women ≤40 years old (24.4% vs. 36.0%) and women aged 41-50 years (13.5% vs. 19.4%).

A prior international survey of radiation oncologists demonstrated that 85% of American and 75% of European respondents would deliver a boost even with negative margins after whole breast irradiation (Ceilley 2005). Current guidelines from the National Comprehensive Cancer Network (NCCN) suggest that a boost may not be required in all patients (National Comprehensive Network 2016). This reflects the understanding that the magnitude of benefit of the boost may be smaller in some subgroups of patients as seen in the EORTC boost trial. The consensus guidelines for 2016 indicate that a tumor bed boost is recommend for young patient age, positive axillary nodes, lymphovascular space invasion, or high-grade disease.

In both of the prospective randomized studies in invasive breast cancer testing the use of a lumpectomy cavity boost after whole breast irradiation, the addition of the boost increased the incidence of late effects such as telangectasias and breast fibrosis (Romestaing 1997; Bartelink 2015). Therefore, how an intraoperative boost prior to whole breast irradiation will impact breast cosmesis, risk of complications and treatment efficacy is essential if IOERT boost prior to oncoplastic reconstruction is to be become more widely adopted.

2.3 Lumpectomy Cavity Boost Delineation

There remains controversy regarding the exact definition of the boost target volume from an external beam radiation therapy technical planning perspective. Contemporary randomized trials define the boost target volume as a 1.7 cm isometric expansion on the lumpectomy cavity (RTOG 1005, NRG 9353, and ALLIANCE A011202). However, delineation of the lumpectomy cavity on CT can be challenging, especially in women that receive adjuvant chemotherapy and in cases in which surgical clips are not present. Clearly, enhanced delineation of the lumpectomy cavity will optimize coverage of the desired breast target volume and spare the low-risk breast tissue, which has the potential to both improve cosmetic outcome and local tumor control.

2.4 Intraoperative Electron Beam Radiotherapy Boost Prior to Whole Breast Irradiation

Retrospective studies have evaluated the use of intraoperative electron radiotherapy (IOERT) as a boost prior to whole breast irradiation in women receiving lumpectomy without oncoplastic reconstruction. In one of the first series reported, Lemanski et al. evaluated 50 women with early breast cancer treated with 10 Gy IOERT (9 MeV electrons) followed by standard whole breast irradiation (50 Gy in 25 fractions). At a median follow-up of 9.1 years, 2 local recurrences were observed within the primary tumor bed (9 year ipsilateral breast tumor recurrence rate=4%) and 42 patients remained disease-free. Among the 42 disease-free patients, 6 patients (14%) experienced late grade 2 subcutaneous fibrosis. No grade 3 or greater late effects were observed. Cosmesis was rated as good to excellent in all 42 of the evaluable patients by 2 separate physicians.

In a retrospective matched-pair analysis, Reitsamer et al. compared 190 patients treated with IOERT boost (10 Gy prescribed to the 90% isodose line) to 188 patients treated with conventional external beam radiotherapy boost (12 Gy in 6 fractions using electrons). The 5-year in breast tumor recurrence rate was 0% in the IOERT group compared to 4.3% in the external beam electron boost. No data were reported on late toxicity or cosmesis.

While retrospective, the International Society of Intraoperative Radiotherapy (ISIORT) pooled analysis on IOERT provides the best data regarding its safety and efficacy when used as an intraoperative boost prior to whole breast irradiation (Selmayer 2007; Fastner 2013). This joint investigation by 7 centers in Austria, Germany, Italy and France evaluated the long-term outcome of IOERT as a boost in 1109 women treated from 1998-2005. The median IOERT dose delivered was 10 Gy (range 6-15 Gy) followed by 50-54 Gy whole breast irradiation (1.7-2 Gy per fraction). The median time between delivery of IOERT and initiation of whole breast irradiation was 6.6 weeks (range, 2.9-51 weeks) and was lower in patients that did not receive chemotherapy (3-5 weeks) compared to the 35% of patients that did receive chemotherapy (median delay 18 weeks). The majority of patients (60%, n=655) presented with at least one adverse prognostic factor for local recurrence (tumor size>2 cm, grade 3, age<45 years, or involved axillary nodes). At a median follow-up of 6 years, there were a total of 16 in-breast recurrences accounting for an in-breast tumor control rate of 99.2%. Relapses occurred from 1-13 years after primary treatment. On multivariable analysis, grade 3 disease was found to be associated with higher risk of recurrence (p=0.031). Annual rates of in-breast recurrence were all <1% per year across various age groups: 0.64% (<40 yrs); 0.34% (41-49 yrs); 0.21% (50-59 yrs); 0.16% (≥60 yrs). One major limitation of this study is that late effects and long-term cosmesis were not reported.

2.5 Oncoplastic Reconstruction as Part of Breast Conservation

Recently, the use of oncoplastic techniques in breast conserving surgery has been increasing (Clough 2010, Anderson 2005, Kronowitz 2007, and Rietjens 2007). These techniques are used to prevent the poor cosmetic results that can occur when a large volume of breast tissue is resected. In these cases, the plastic surgeon and/or surgical oncologist resects and/or rearranges additional breast tissue to help provide an esthetically improved shaped breast. The lumpectomy cavity may be incised and separated with different portions ending up in different quadrants of the resected breast. As a result, these represent especially difficult cases for the radiation oncologist to define the lumpectomy target volume, even when surgical clips are employed.

2.6 Advantages of Intraoperative Electron Beam Radiotherapy Boost

One strategy to overcome the problem of lumpectomy cavity delineation in women undergoing oncoplastic resection is to use intraoperative radiation therapy as a “reverse boost” at the time of lumpectomy but just prior to oncoplastic reconstruction. The advantages of this approach include direct visualization of the tumor cavity, exposing only the area at highest risk of harboring microscopic residual disease to high dose radiation, sparing the skin of radiation, and reducing treatment time by 1-2 weeks. Data regarding the use of an IORT electron boost at the time of lumpectomy and prior to oncoplastic reconstruction are limited to 2 case reports.

In 2011, Franchelli et al. reported on 2 cases of lumpectomy with reduction mammoplasty and IOERT. In both cases, the IOERT was delivered to high doses (18-21 Gy) without the use of adjuvant whole breast irradiation. An area of 4-5 cm around the tumor bed was treated. In both cases, the women did not experience postoperative complications within the 6 month follow-up period. Similarly, Munhoz et al. published a report of one woman that underwent lumpectomy followed by 21 Gy IOERT and then reduction mammoplasty. At 2 years from the end of surgery, there was no evidence of recurrence, fat necrosis, ptosis or volume loss in the treated breast.

The lack of data regarding the use of IOERT boost after lumpectomy and prior to oncoplastic reconstruction justifies the need for a prospective trial to investigate this treatment approach in more detail.

2.7 Rationale for IOERT Boost Dose

Standard external beam lumpectomy cavity boost doses range from 10 Gy in 5 fractions to 16 Gy in 8 fractions. Mathematical models have been created to permit comparison of tumor control across various radiation schedules and fraction sizes. The most prevalent model applied to conventionally-fractionated radiation is the linear quadratic (LQ) equation, which allows for comparison across treatment schedules by converting dose and fractionation into a term referred to as the biological effective dose (BED). Different tissues are assigned α/β ratios, which are essentially a reflection of a tissue's sensitivity to changes in fraction size. With regard to tumor cells, a high α/β ratio confers high sensitivity to radiation while a lower α/β ratio predicts lower sensitivity to radiation. It is generally accepted that the α/β ratio for breast cancer cells is ~3. The LQ model defines the BED for a tissue/tumor with α/β=k as

$$BED_k = n*d[1+d/k],$$

Where n=number of fractions delivered and d=daily dose in Gy.

The BED_3 for a lumpectomy cavity boost of 10 Gy in 5 fractions is therefore 16.67 Gy_3. Similarly, the BED_3 for a lumpectomy cavity boost of 16 Gy in 8 fractions is 26.67 Gy_3. Table 1 below compares the BED_3 and BED_4 of various external beam and single fraction IOERT boost approaches.

Table 1: Comparison of biological effective doses between conventionally fractionated external beam radiation therapy boost and intraoperative electron radiotherapy boost for several doses.

Conventional	BED_3	BED_4	**IOERT**	BED_3	BED_4
2 Gy x 5	16.7 Gy_3	15 Gy_4	6 Gy x 1	18 Gy_3	15 Gy_4
2 Gy x 6	20 Gy_3	18 Gy_4	7 Gy x 1	23.3 Gy_3	19.3 Gy_4
2 Gy x 7	23.3 Gy_3	21 Gy_4	8 Gy x 1	29.3 Gy_3	24 Gy_4
2 Gy x 8	26.7 Gy_3	24 Gy_4	9 Gy x 1	36 Gy_3	29.3 Gy_4
			10 Gy x 1	43.3 Gy_3	35 Gy_4

*Abbreviations: BED=biologic effective dose; IOERT=intraoperative electron radiotherapy

The prior studies by Lemanski, Reitsamer, and Fastner have most commonly used 10 Gy in a single fraction as a boost prior to whole breast radiation therapy. However, the BED of this approach is significantly higher compared to the external beam conventionally fractionated dose of 16 Gy in 8 fractions (as used in the EORTC boost trial). Therefore, we have chosen a single fraction of 8 Gy (prescribed to the 90% isodose line) to be delivered as the boost given that the BED_3 of this schedule is slightly higher than the BED_3 of 16 Gy in 8 fractions. This dose should provide sufficient tumor control without excessive risk of subcutaneous fibrosis.

2.8 Hypofractionated Whole Breast Irradiation

Hypofractionation, or delivery of greater than standard 1.8-2 Gy fraction sizes per day, is a method of shortening overall treatment time in breast cancer. There are many potential benefits in delivering postoperative whole breast irradiation in a shorter period of time: greater convenience for patients, broad applicability to nearly all patients following lumpectomy,

improved use of postoperative radiation for breast conservation, decreased treatment costs, and increased utilization of existing RT resources.

Four prospective randomized trials have shown promising results with hypofractionated schedules for whole breast irradiation: OCOG Study (Whelan 2010), UK START A (2008), UK START B (2008), RMH/GOC (Owen 2006). In each of these studies, the goal was to deliver a hypofractionated schedule that is biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions. With 5-10 year follow-up in these studies, there has been similar in-breast local control between the hypofractionated and standard arms and no evidence of worse toxicity or cosmesis with hypofractionated regimens.

Table 2: Summary of the 4 major randomized trials comparing conventionally fractionated whole breast irradiation to hypofractionated whole breast irradiation.

Study	Fractionation	Patients	5-year IBTR	Good/Excellent Cosmesis (%)
Whelan	50 Gy/25	612	3.2%	71.3% (10yr)
	42.5 Gy/16	622	2.8%	69.8% (10 yr)
RMH/GOC	50 Gy/25	470	7.9%	71% (10 yr)
	42.9 Gy/13	466	7.1%	74% (10 yr)
	39 Gy/13	474	9.1%	58% (10 yr)
START A	50 Gy/25	749	3.6%	60% (5 yr)
	41.6 Gy/13	750	3.5%	58% (5 yr)
	39 Gy/13	737	5.2%	66% (5 yr)
START B	50 Gy/25	1105	3.3%	61% (5 yr)
	40 Gy/15	1110	2.2%	66% (5 yr)

*Abbreviations: IBTR=ipsilateral breast-tumor recurrence rate

As a result of the equivalence between conventionally fractionated whole breast irradiation and hypofractionated whole breast irradiation, women on this protocol will be allowed to receive hypofractionated whole breast irradiation. We recommend the UK START B fractionation of 40 Gy in 15 fractions.

3.0 STUDY DESIGN

3.1 General Design

This is a single arm, phase II study to evaluate the safety, toxicity and efficacy of an intraoperative electron beam radiotherapy boost at the time of breast conserving surgery in women with early stage breast cancer undergoing oncoplastic reconstruction. Our goal is to safely target the lumpectomy cavity at the time of surgery but prior to oncoplastic reconstruction.

Patients will be registered on trial after meeting all eligibility criteria. Eligible patients that provide informed consent will receive breast conserving surgery with an intraoperative boost to the lumpectomy cavity of 8 Gy prescribed to the 90% isodose line using the Mobetron device. Upon completion of IOERT, oncoplastic reconstruction will be performed. All patients will then initiate whole breast radiotherapy to a dose of 40 Gy in 15 fractions or 50 Gy in 25 fractions that must begin no later than 12 weeks (84 days) from the date of surgery or 2-8 weeks after the date of last chemotherapy dose delivered.

3.2 Primary Study Endpoint

The primary endpoint of the study will be the rate of grade 3 fibrosis (using the LENT SOMA scale, Appendix I) at 1 year from the end of whole breast radiotherapy. Based on data from whole breast radiation alone (Meric 2002) and lumpectomy+IOERT boost (Kraus-Tiefenbacher 2006, Wenz 2010), our hypothesis is that the rate of grade 3 fibrosis in our study will be ≤ 5%.

3.3 Secondary Study Endpoints

Secondary endpoints will include evaluation of the 5 year rate of ipsilateral breast tumor recurrence (IBTR). We will evaluate IBTR by standard clinical and pathologic variables to analyze trends. We hypothesize that the overall 5 yr IBTR rate will be ≤ 5%. We will also analyze self-reported cosmesis using the BCTOS cosmesis scale (Stanton 2001, Appendix II). The BCTOS will be collected at baseline, after informed consent has been obtained, prior to adjuvant radiation, 1 month and 6 months after radiation, and 1, 2 and 3 years after completion of adjuvant radiation. The primary endpoint will focus on the mean change from baseline to 3 years. Physician reported cosmesis using the 4-point Harvard Breast Cosmesis scale and digital photographs will also be evaluated at baseline, and at 1 and 3 years after completion of radiation therapy (Appendix III).

4.0 SUBJECT SELECTION AND WITHDRAWAL

Patients must have baseline evaluations performed prior to delivery of IOERT and must meet all inclusion and exclusion criteria. Results of all baseline evaluations will be reviewed by the treating physician prior to enrollment, to verify that all inclusion and exclusion criteria have been satisfied. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria

4.1.1 Pathologically proven diagnosis of breast cancer

4.1.2 The patient must be female.

4.1.3 The patient must be ≥ 18 years old

4.1.4 Must have clinical anatomic stage I-III breast cancer prior to any breast cancer therapy

4.1.5 Appropriate stage for protocol entry including no clinical evidence for distant metastases based upon the following minimum diagnostic workup:

- History/physical examination, documentation of weight and Zubrod Performance Status 0-2 within 60 days prior to study entry

4.1.6 Women of childbearing potential must be willing to use highly effective form of contraception throughout the study duration, and until after the final dose of radiation therapy or chemotherapy, whichever occurs last.

4.1.7 Patients must provide study specific informed consent prior to study entry

4.2 Exclusion Criteria

4.2.1 Clinical or pathological stage IV breast cancer

4.2.2 Prior invasive non-breast malignancy (except non-melanoma skin cancer, carcinoma in situ of the cervix) unless disease free for a minimum of 3 yrs prior to study entry

4.2.3 Prior invasive or in-situ carcinoma of the ipsilateral breast (prior LCIS is eligible)

4.2.4 Two or more cancers not resectable through a single lumpectomy incision

4.2.5 DCIS only

4.2.6 Non-epithelial breast malignancies such as sarcoma/lymphoma

4.2.7 Male breast cancer

4.2.8 Paget's disease of the nipple

4.2.9 Prior radiotherapy to the region of the ipsilateral breast that would result in overlap of radiation fields

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

4.2.11 Active systemic lupus erythematosus, or any history of scleroderma, dermatomyositis with active rash

4.2.12 Medical, psychiatric or other condition that would prevent the patient from receiving the protocol therapy or providing informed consent

4.3 Gender/Minority/Pediatric Inclusion for Research

This study includes females and minority patients. Males and pediatric patients are excluded.

4.4 Subject Recruitment and Screening

Patients who are ≥ 18 years old with non-metastatic stage I, II or III breast cancer are eligible for the study. Patients can be recruited from PI or co-investigators' clinical practices. Potential study subject should be notified to PI and study designated research nurse/research associate. Appropriate laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria will be ordered through the recruiting physician. Treating physician will screen and determine the final eligibility of the subject for enrollment.

4.5 Subject Registration Procedures

For subsite patients, sites must send the signed consent form, documentation of the consent process, and the Screening Form (refer to Supplemental Forms Document) within 1 business day of initial consent.

Patients will be registered after meeting all entry requirements and signing of the informed consent.

OSU patients will be registered by the OSU research coordinator, as per their standard

practice.

Subsite patients will have eligibility verified and will be entered on study centrally at The Ohio State University by the Multi-Center Trial Program. All subsites must email the Multi-Center Trial Program Coordinator to verify slot availabilities prior to consenting patients. Once a patient signs consent, the signed consent document and documentation of the consenting process must be securely emailed to the Multi-Center Trial Program. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and securely e-mailed to the Multi-Center Trial Program Coordinator:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form
- Signed Patient HIPAA Authorization Form (if separate)
- Consent Documentation Note
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria

Upon receipt of registration documents, the Multi-Center Trial Program will send an email confirmation of receipt. If confirmation of receipt is not received within 1 hour of submission, please call or page the Multi-Center Trial Program Coordinator to confirm receipt.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the Multi-Center Trial Program Coordinator will:

- Assign the patient a study sequence ID
- Register the patient on the study
- E-mail to the subsite the completed Registration Form with the assigned study sequence ID as confirmation of patient registration

Following registration, patients should have the first protocol treatment (breast IOERT/ surgery) within 45 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator and Multi-Center Trial Program Coordinator as soon as possible. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled, after discussion with the PI and Multi-Center Trial Program Coordinator.

Patient sequence IDs will be assigned in the following fashion:

- [Site ID]-XXX
    - Site ID = NCI issued institutional ID

- XXX = sequential numbers by order of enrollment

4.6 Early Withdrawal of Subjects

4.6.1 When and How to Withdraw Subjects

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

1. Intercurrent illness
2. Occurrence of an unacceptable adverse event
3. A treatment delay in radiation therapy >1 weeks
4. Patient request
5. Protocol violations
6. Non-compliance
7. Administrative reasons
8. Failure to return for follow-up
9. General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

4.6.2 Data Collection and Follow-up for Withdrawn Subjects

According to FDA regulations, when a subject withdraws from the study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

A subject who is withdrawing needs to state whether he/she wishes to provide continued follow-up and further data collection subsequent to withdrawal from the study.

4.6.3 Data Submission for Subsites

The study will be managed per the Multi-Center Trial Program policies. Data must be submitted to the Multi-Center Trial Program Data within 2 weeks of completion of each cycle. Data will be submitted using case report forms and the Data Submission Form (refer to Supplemental Forms Document) supplied by the Multi-Center Trial Program. All data submitted must be accompanied by supporting source documents. Access to the OSU OnCore database may be provided to external participating for direct electronic data entry.

4.6.4 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in minutes. For each dose level, the Principal Investigator, study coordinator,

and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments. The Principal Investigator of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the Principal Investigator and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator will also submit progress reports that will be reviewed by the committee per the DSMC plan. All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be held every three months and moderated by the Multi-Center Trial Program. All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the Multi-Institution Program protocol files.

5.0 RADIATION THERAPY

5.1 IOERT Boost

- IOERT is performed on a Mobetron with variable electron energies in the range of 4-12 MeV
- Planning target volume (PTV) is defined as a 3D volume of at least 2 cm beyond the former macroscopic tumor edge
- IOERT dose is specified at the point of maximum dose on the central axis depth dose curve. The PTV should be encompassed by 90% of the prescribed dose (8 Gy). A dose inhomogeneity of -10% within the target volume is acceptable. In the beam entrance region, a small volume of under dosage as low as 80% of the prescribed dose is acceptable.
- The depth of the 90% isodose (8 Gy) has to be reported. In case of beveled angles, the depth is specified along the clinical axis.
- The choice of electron energy has to account for minimum PTV requirements.
- Optionally, additional thoracic wall protection by lead shielding can be performed.
- Tissue depth measurement has to be documented.

5.2 Whole Breast Radiation Therapy

5.2.1 Dose Specifications

Standard Whole Breast Irradiation with Sequential Boost

Breast: 40 Gy in 15 fractions of 2.67 Gy. Optional: 50 Gy in 25 fractions of 2 Gy.

Note: Patients that are found to have lymph-node positive disease are able to receive regional nodal irradiation at the discretion of the treating radiation oncologist. All patients that

are to receive regional nodal irradiation will be treated with conventional fractionation (50 Gy in 25 fractions), not hypofractionation (40 Gy in 15 fractions).

5.2.2 Technical Factors

- Each of the target volumes and normal structures listed below must be delineated on each slice from the 3D planning CT in which that structure exists.
- Megavoltage photon beams with energies ≥ 6 MV and megavoltage electron beams are required. Proton beams are not allowed.

5.2.3 Localization, Simulation, and Immobilization

- Simulation and treatment may be performed with the patient in the supine or prone position.
- Patients should be optimally positioned with alpha cradle casts, breast boards, wing boards and/or other methods of immobilization at the discretion of the treating physician.
- Methods to minimize the cardiac exposure to RT like heart block, gating or breathhold are allowed at the discretion of the treating physician
- For large-breasted patients, including those with a large inframammary skin fold, devices to improve positioning of the breast are permissible.
- A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV) and planning target volumes (PTV).
    - The CT required for generation of a virtual plan with 3DCRT or IMRT must be post-lumpectomy
    - Radio-opaque markers must be placed on external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) The lumpectomy incision 2) The outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock 3) The superior border of the breast tissue at 12 o'clock based on palpation. Additional markers to define the borders of "clinical" tangent fields (e.g. based on the palpable breast tissue and boney landmarks) are often helpful.
    - The CT should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.5 cm should be employed.
- External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.
- For obese patients: while every effort should be made to include the full external contour in the planning CT, it is permissible to use CT with cutoff of a portion of the body image due to the limited field-of-view of the CT scanner only if: (1) the treated breast is fully included in the CT, (2) no treatment beam goes through the cutoff portion, and (3) maximum doses in cutoff normal structures (e.g. contralateral lung, contralateral breast) can still be evaluated.

5.2.4 Target Volumes and Normal Tissues

- The definitions for the CTV, PTV and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer (http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) and the 1993 ICRU report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

- Target Volumes and Normal Structures

Lumpectomy volumes:

Lumpectomy GTV: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended).

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

Lumpectomy PTV: Lumpectomy CTV + 7 mm 3D expansion (excludes heart). *Lumpectomy PTV Eval*: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval which is edited. This Lumpectomy PTV Eval is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung) when pertinent. The lumpectomy PTV should not cross midline. This Lumpectomy PTV Eval is the structure used for DVH constraints and analysis. This Lumpectomy PTV Eval cannot be used for beam aperture generation.

Breast volumes:

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

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

Breast PTV Eval: Since a substantial part of the Breast PTV often extends outside the patient, the Breast PTV is then copied to a Breast PTV Eval which is edited. This Breast PTV Eval is

limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and posteriorly is limited no deeper to the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis. This Breast PTV Eval cannot be used for beam aperture generation.

Contralateral breast

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

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

Refer to the breast contouring atlas:
http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx

Ipsilateral lung. This may be contoured with auto-segmentation with manual verification.

Contralateral lung. This may be contoured with auto-segmentation with manual verification

Heart

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

Thyroid

The thyroid is easily visible on a non-contrast CT due to its preferential absorption of Iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured.

5.2.5 Treatment Planning

CT-based planning with tissue inhomogeneity correction is required

IMRT or 3D-CRT are permitted

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

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

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

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

4. If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the 3D composition dose distribution and DVHs should be generated.

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

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

7. The patient specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

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

- The plans generated using forward-planning methods or segmental techniques such as “field-in-field” to meet dose-volume constraints are considered as 3D-CRT plans. These forward-planned or segmental treatment techniques are those intended to mainly improve the uniformity of the dose distribution, but not to produce steep dose gradients to protect critical structures (e.g., heart or lung).
- The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms.

Whole Breast Radiation Therapy

The breast PTV is used to generate the beam apertures with an additional margin to take into account penumbra. Fields should include the entire breast PTV and boost PTV. The aperture margin generally needed beyond the PTV is 5 mm. The goals of treatment planning are to encompass the breast PTV and minimize inclusion of the heart and lung.

Field arrangements for 3D conformal and IMRT of the Breast PTV are at the discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the Breast PTV and normal tissues outlined below.

Standard Whole Breast Irradiation

All efforts should be made to adhere to the following planning target volume objectives and normal tissue constraints. Please see section 5.2.7 for issues related to quality assurance of the whole breast radiation treatment plans.

Breast PTV Eval:

- Per Protocol: At least 95% of the breast PTV Eval will receive at least 95% (47.5 Gy) of the whole breast prescribed dose of 50 Gy (or 38 Gy if hypofractionation whole breast fractionation used).

  Variation Acceptable: At least 90% of the breast PTV Eval will receive at least 90% (45 Gy) of the whole breast prescribed dose of 50 Gy (or 36 Gy if hypofractionation whole breast fractionation used).

- Per Protocol: The maximal point dose will not exceed 115% of the prescription whole breast dose, e.g. will not exceed 57.5 Gy for a prescribed dose of 50 Gy or will not exceed 46 Gy for a prescribed dose of 40 Gy if hypofractionation whole breast fractionation is used.

  Variation Acceptable: The maximal point dose will not exceed 120% (will not exceed 60 Gy for a prescription whole breast dose of 50 Gy or will not exceed 48 Gy if hypofractionated 40 Gy is used.

Contralateral Breast

- Per Protocol: The maximum dose to contralateral breast does not exceed

  310 cGy (244 cGy if hypofractionation used) and no more than 5% exceeds 186 cGy (144 cGy if hypofractionation used).

  Variation Acceptable**:** The maximum dose does not exceed 496 cGy (384 cGy if hypofractionation used) and no more than 5% exceeds 310 cGy (240 cGy if hypofractionation used)

Ipsilateral Lung

- Per Protocol**:** No more than 15% of the ipsilateral lung exceeds 20 Gy (16 Gy if hypofractionation used).

  Variation Acceptable**:** No more than 20% of the ipsilateral lung exceeds 20 Gy (16 Gy if hypofractionation used).

- Per Protocol**:** No more than 35% of the ipsilateral lung exceeds 10 Gy (8 Gy if hypofractionation used).

  Variation Acceptable**:** No more than 40% of the ipsilateral lung exceeds 10 Gy (8 Gy if hypofractionation used).
- Per Protocol**:** No more than 50% of the ipsilateral lung exceeds 5 Gy (4 Gy if hypofractionation used).

  Variation Acceptable**:** No more than 55% of the ipsilateral lung exceeds 5 Gy (4 Gy if hypofractionation used).

Contralateral Lung

- Per Protocol**:** No more than 10% of the contralateral lung exceeds 5 Gy (4 Gy if hypofractionation used).

  Variation Acceptable: No more than 15% of the contralateral lung exceeds 5 Gy (4 Gy if hypofractionation used)

Heart

- Per Protocol**:** No more than 5% of the whole heart exceeds 20 Gy for left- sided breast cancers (16 Gy if hypofractionation used) and 0% of the heart exceeds 20 Gy for right-sided breast cancers (16 Gy if hypofractionation used).

  Variation Acceptable**:** No more than 5% of the whole heart exceeds 25 Gy (20 Gy if hypofractionation used) for left-sided breast cancers, and 0% of the heart exceeds 25 Gy for right- sided breast cancers (20 Gy if hypofractionation used).

- Per Protocol**:** No more than 30% of the whole heart exceeds 10 Gy for left sided breast cancers (8 Gy if hypofractionation used) and no more than 10% of the heart exceeds 10 Gy for right-sided breast cancers (8 Gy if hypofractionation used).

  Variation Acceptable: No more than 35% of the whole heart exceeds 10 Gy for left sided breast cancers (8 Gy if hypofractionation used) and no more than 15% of the heart exceeds 10 Gy for right-sided breast cancers (8 Gy if hypofractionation used).

- Per Protocol**:** The mean heart dose does not exceed 400 cGy (320 cGy if hypofractionation used).

  Variation Acceptable**:** The mean heart dose does not exceed 500 cGy (400 cGy if hypofractionation used).

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

5.2.6 Treatment Verification

Before first treatment

Portal films or images of each 3DCRT beam and an orthogonal pair for all patients must be obtained and approved by a physician prior to initiation of treatment.

Subsequent images or films

Subsequent treatment images may be obtained every fraction. At the minimum, orthogonal

pair films or treatment images should be obtained prior to fraction number 5 and every 5 fractions subsequently. The imaging modality and process should be performed based on the institutional guidelines.

5.2.7 Quality Assurance

To evaluate whether the dose distribution from the whole breast radiation portion of the treatment impacts the development of breast fibrosis, we will collect the DVH data for the target volumes and normal tissues listed in Section 5.2.5 on separate case report forms. Treatment plans will be scored as acceptable if: all specified DVH requirements identified as "Per Protocol" or "Variation Acceptable" in Section 5.2.5 have been met for all structures. Treatment plans will be scored as unacceptable if: the specified DVH requirements for "Variation Acceptable" in Section 5.2.5 are not met for ≥1 structure.

6.0 ADVERSE EVENTS

6.1 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse events will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE version 5.0 for toxicity and Adverse Drug Experience reporting. A copy of the CTC version 5.0 can also be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

All appropriate treatment areas will have access to a copy of the CTCAE version 5.0

All adverse events should be treated appropriately. Once an adverse event is detected, it should be followed until its resolution or baseline, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

6.2 Serious Adverse Events

Definition of an SAE: Any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant disability/incapacity to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition,

Any pregnancy occurring on study must be reported as a medically significant event.

Any unexpected late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported within 10 days of discovery.

6.3 SAE Reporting Requirements

The OSU principal investigator is required to submit all adverse events or injuries that are serious, unexpected, ***and*** related to the OSU IRB within **10 days** of the investigator's or research staff member's learning of the event.. All AE/SAEs will be reported to the Data and Safety Monitoring Committee (DSMC) at the quarterly DSMC review meetings; however, the investigator determines corrective action is necessary, and "ad hoc" DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported to the OSU IRB and the DSMC within the required time frame per institutional, IRB, and DSMC policies. Fatalities not related to the study must also be reported within the institutional required timeframe.

The Ohio State University
Office of Responsible Research Practices
1960 Kenny Road
Columbus, Ohio 43210
Phone: 614 292-5958
Fax: 614 688-0366

6.3.1 Subsite SAE Reporting Requirements

NOTE: External participating sites are not permitted to report directly to the OSU IRB or FDA. All external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program. The Multi-Center Trial Program will facilitate submission of external site SAEs to the OSU IRB and other regulatory authorities, if applicable.

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the OSU Principal Investigator and Multi-Center Trial Program within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form and the "SAE Submission Form" cover sheet (refer to the Supplemental Forms Document for cover sheet and case report form).

Copies of de-identified source documentation pertaining to the SAE must be submitted to OSU. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to OSU as soon as possible but no later than 5 calendar days.

7.0 SURGERY

According to Anderson, oncoplastic surgery refers to one of several surgical techniques by which segments of malignant breast tissue are removed to achieve wide surgical margins while the remaining glandular tissue is transposed to achieve the best possible cosmetic outcome (Anderson 2005). The oncoplastic procedure can be performed by either the breast surgeon or plastic surgeon according to institutional standards. The choice of oncoplastic procedure will be based on the individual patient/tumor location and will be determined by the surgeon/plastic surgeon at the time of consultation.

The patient will first undergo resection of the tumor. Intraoperative radiotherapy will then be applied to the tumor bed. In oncoplastic procedures that require rearrangement of the tumor bed, this will occur after completion of IOERT.

8.0 DRUG THERAPY

8.1 Chemotherapy

Chemotherapy may be given at the discretion of the patient's medical oncologist. The use of chemotherapeutic agents during radiation therapy is not allowed. Chemotherapy is permitted as neoadjuvant or adjuvant to surgery. Adjuvant chemotherapy may be given prior to whole breast irradiation (in which case initiation radiotherapy should be 2-8 weeks after the last cycle of adjuvant chemotherapy) or upon completion of whole breast irradiation according to institution standard.

8.2 Hormonal Therapy

Patients with ER-positive and/or PR-positive tumors should be treated with hormonal therapy. The type and duration of hormonal therapy will be determined by the treating medical oncologist. Hormonal therapy may be initiated before, during or after completion of radiotherapy at the discretion of the medical oncologist.

8.3 Anti-HER2 Therapy

Anti-HER2 therapy is permitted at the discretion of the medical oncologist for patients whose tumors are HER2 positive. The dose and schedule of these agents should be per standard treatment protocol. Anti-HER2 therapy during radiotherapy is permitted.

9.0 OTHER THERAPY

9.1 Permitted Therapies

9.1.1 Anti endocrine therapy (Tamoxifen, aromatase inhibitors, etc.) are allowed at any time (see Section 8.2)

9.1.2 Chemotherapy (see Section 8.1)

9.1.3 Anti-HER2 therapy (see Section 8.3)

9.2 Non-permitted Therapies

9.2.1 The use of chemotherapeutic agents during radiation therapy is not allowed.

10.0 PATIENT ASSESSMENTS

10.1 Study Parameters

See Appendix IV for a summary of assessments and time frames.

10.1.1 A breast cosmetic assessment will be conducted at baseline, prior to the start of adjuvant radiation (post-IOERT-boost and surgery), at 1 year and 3 years after completion of adjuvant radiation. This assessment will include inspection of the breast being treated and toxicity assessment. Palpation of the breast during this assessment is optional at the discretion of the treating physician.

10.1.2 A breast examination will be conducted at baseline, prior to the start of adjuvant radiation (post-IOERT-boost and surgery), at 1 month, 6 months and 1 year after completion of adjuvant radiation and then yearly thereafter. This assessment will include inspection of the breast being treated and toxicity assessment. Palpation of the breast during this assessment is optional at the discretion of the treating physician.

10.2 Cosmetic and Functional Outcomes

Breast Cancer Treatment Outcome Scale (BCTOS) - a 22-item measure of perceived aesthetic (e.g., breast shape) and functional status (e.g., pain, mobility) after breast-conserving surgical treatment (BCT) and radiotherapy.

This brief self-report instrument has high reliability and validity, and it has been used in a variety of previous studies on recovery from breast cancer treatment. These endpoints will be assessed at baseline prior to study entry, prior to start of adjuvant RT, 1 month and 6 months after radiation, and 1, 2 and 3 years after completion of radiation. This tool was also used and at these same time points to facilitate comparisons with the outcomes from RTOG 0413/NSABP B39 and RTOG 1005. This tool includes items that focus specifically on radiotherapy-relevant symptoms (e.g., reports of skin problems, tenderness in the breast, hardness in the breast due to enhanced fibrosis, and pain).

Physician reported cosmetic outcome has been consistently reported from prospective studies evaluating new methods for breast radiation. It is important to demonstrate that physician reported cosmetic outcomes are non-inferior with this novel method as well. Physician assessed cosmetic outcome will be assessed at baseline prior to study entry, prior

to start of adjuvant RT, and at 1 year and 3 years after adjuvant RT using a 4 point scale (Harvard/EORTC). This scale has been used in prior RTOG studies (NSABP B39/RTOG 0413 and RTOG 1005).

Digital images (photographs) will be taken of the breasts. Optimally, the photos should be taken at a distance of 3 feet. For practical reasons, these digital images will be taken at only 4 points in time: at baseline (prior to surgery), prior to start of adjuvant whole breast irradiation, at the 1-year and at the 3-year assessment points. A minimum of three digital images will be taken at each of these assessment points. The front view will include the clavicles and shoulders with the patient's arms at side. An oblique view will involving turning the patient 45 degrees (clockwise for left breast, counterclockwise for right breast) and moving the distal arm back slightly. A lateral view will involve turning the patient an additional 45 degrees (clockwise for left breast, counterclockwise for right breast) and moving the distal arm back slightly (DiBernardo 1998). For each image, we will take care to exclude patient's face.

Subsites will submit photographs to OSU using secure email. Instructions for sending secure email will be included in the MCTP regulatory start-up packet. If subsites are unable to submit photographs to OSU using secure email, subsites will be able to submit images through a secure platform that has been approved by OSU IT Security. OSU MCTP team will provide additional information on submitting images through a secure platform when needed. Digital photos will be saved as jpegs in a restricted folder on a secure OSU server. Access to the server requires a unique username and password. Access to the study folder will be limited to study personnel only. Study PI will grant access accordingly. Photographs will be stored with the patient's study ID, time point and date of visit. Photographs will be collected and stored in this manner for five years following study closure and final data analysis. At that time, all digital images will be deleted from the server.

These digital images will later be evaluated for cosmetic results by a panel of physicians using diagnostic criteria established in previous RTOG trials (e.g., degree of scarring, extent of pock marks and /or dimpling, degree of symmetry between the breasts, extent of changes in skin). We think it is of interest and important to obtain multiple measures of cosmetic outcome in order to assess the degree of correspondence between physician-generated and patient-generated outcomes.

10.3 Measurement of Response

Ipsilateral breast tumor recurrence (IBTR) is a secondary endpoint of this study. We will evaluate the 5-year rate of IBTR.

10.4 Criteria for Discontinuation of Protocol Treatment

10.4.1 A delay in protocol treatment, as specified in Section 4.5.1

If study therapy is stopped but she still allows the study doctor to follow her care, she should continue to be followed according to the study schedule. Follow up and data collection will continue as specified in the protocol.

11.0 STATISTICAL CONSIDERATIONS

11.1 Safety/Feasibility

The first 30 patients enrolled will be used to determine the safety and feasibility of this approach (lumpectomy+IOERT and oncoplastic reconstruction) in a multi-institutional setting. Safety will be evaluated by the rate of surgical complications involving the breast treated with IOERT necessitating hospital readmission or return to the operating room within 30 days of surgery + IOERT. Greater than 15% incidence rate of surgical complications is unacceptable. Specific complications evaluated will include: incisional infections, return to the operating room for any reason other than re-excision due to positive margins, wound dehiscence, pneumonia and rare but serious events including deep venous thrombosis requiring therapy, pulmonary embolism, acute renal failure, stroke/CVA, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, sepsis/septic shock, urinary tract infection, re-intubation. Previous studies have reported a complication rate of 15% (Eck 2012, Vitug 2007). The following table summarizes the stopping criteria based on the number of complications for every 10 patients treated and the exact binomial distribution with a hypothesized probability of success of 0.15. If we observe 4 or more complications in the first 10 patients, 7 or more out of the first 20 patients or 9 or more out of 30 patients then the study will be deemed not safe to continue. If the safety criteria are met, then we plan to accrue additional patients to study the primary endpoint. The first 30 patients will be included in this analysis as well.

Halt if Number of Complications is equal or more than	Total Patients Treated
4	10
7	20
9	30

11.2 Primary Endpoint

The primary endpoint of the study will be the rate of grade 3 fibrosis (using the LENT SOMA scale, Appendix I) at 1 year from the end of therapy. Based on data from whole breast radiation alone (Meric 2002) and lumpectomy+IOERT boost (Kraus-Tiefenbacher 2006, Wenz 2010), our hypothesis is that the rate of grade 3 fibrosis in our study will be ≤5%.

11.3 Secondary Endpoints

Secondary endpoints will include evaluation of the 5 year rate of ipsilateral breast tumor recurrence (IBTR). We will evaluate IBTR by standard clinical and pathologic variables to analyze trends. We hypothesize that the overall 5 yr IBTR rate will be ≤5%. We will also analyze self-reported cosmesis using the BCTOS cosmesis scale (Stanton 2001, Appendix II). The BCTOS will be collected at baseline, after informed consent has been obtained, prior to adjuvant radiation, 1 month and 6 months after radiation, and 1, 2 and 3 years after completion of adjuvant radiation. The secondary endpoint will focus on the mean change from baseline to 3 years. Physician reported cosmesis using the 4-point Harvard Breast Cosmesis scale will also be evaluated at baseline, before the adjuvant radiation, and 1, and 3 years after completion of radiation therapy (Appendix III). Physician reported cosmesis using digital photographs will be evaluated at baseline, prior to the start of adjuvant whole breast

irradiation, and at 1 and 3 years after completion of radiation therapy. Finally, the rate of surgical complications necessitating hospital readmission or return to the operating room within 30 days of surgery + IOERT will be evaluated for all patients on the study.

11.4 Statistical Analysis

We will calculate the proportion of patients with an overall response rate of grade 3 fibrosis at 1 year from the end of therapy along with the exact binomial confidence interval for the rate. We will use the same method to calculate and report the 5 year rate of ipsilateral breast tumor recurrence (IBTR). The mean and standard deviation of the self-reported cosmesis using the BCTOS cosmesis scale will be summarized over time. We will examine the change over time using a repeated measures model or non-parametric methods if appropriate. Summary statistics will be used to report all complications.

11.5 Sample Size Determination

The primary endpoint of the study will be the rate of grade 3 fibrosis at 1 year from the end of therapy. Based on a rate 5% for these adverse events from whole breast radiation alone (Meric 2002) and lumpectomy + whole breast radiation + IOERT boost (Kraus-Tiefenbacher 2006, Wenz 2010), the investigators have determined a rate of 9% or more for these adverse events with lumpectomy+IOERT and oncoplastic reconstruction would be unacceptable. The following table summarizes the power and sample size needed if the true adverse event rate ranges from 3% to 5% and the specified unacceptable rate of adverse events is 9% based on a one-sided binomial test for non-inferiority with target alpha 0.05:

Non-inferiority proportion	Actual Proportion	Target alpha	Actual Alpha	Sample Size	Power
9%	3%	0.05	0.0474	100	82%
9%	4%	0.05	0.0479	158	82%
9%	5%	0.05	0.0496	266	82%

Based on the above table, a sample size of 158 evaluable patients will have 82% power to conclude that the treatment has an unacceptable rate of the specified adverse events if the rate of adverse events is at least 9% and the true adverse event rate is 4%.

While the study was originally planned to have a sample size of 158 evaluable patients, we adjusted the sample size from 158 to 116 evaluable patients due to emerging data from a study in Europe (Fastner) that found the rate of grade 3 fibrosis at year one to be around 1%, much lower than our original estimate of 4%. With a sample size of 116 evaluable patients, the study will have 80% power to conclude the treatment has an unacceptable rate of grade 3 fibrosis if the rate of grade 3 fibrosis is at least 9% and the true adverse event rate is 3.2%, a conservative estimate which is closer to the recent data published.

A total of 129 patients will be enrolled to adjust for approximately 10% that do not start the protocol or are lost to follow up to obtain 116 evaluable patients.

11.6 Accrual

Patient accrual is projected to be 4 cases per month in the multi-institutional setting with a ramp up period in the first 6 months. The estimated time for accrual is approximately 48 months.

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13.0 APPENDIX

APPENDIX I: LENT SOMA Scale for Breast Fibrosis

Grade 1: Barely palpable, increased density

Grade 2: Definite increased density and firmness

Grade 3: Very marked density, retraction and fixation

APPENDIX II: BCTOS SCALE

	Difference between treated and untreated breast and area			
	None	Slight	Moderate	Large
1. Breast size……..	1	2	3	4
2. Breast texture (hardening) ……	1	2	3	4
3. Arm heaviness……..……	1	2	3	4
4. Nipple appearance……	1	2	3	4
5. Shoulder movement ……	1	2	3	4
6. Arm movement ……	1	2	3	4
7. Breast pain……	1	2	3	4
8. Ability to lift objects……..	1	2	3	4
9. Fit of shirt sleeve……..	1	2	3	4
10. Breast tenderness……	1	2	3	4
11. Shoulder stiffness……	1	2	3	4
12. Breast shape……	1	2	3	4
13. Breast elevation (how high the breast is)……	1	2	3	4
14. Scar tissue……	1	2	3	4
15. Shoulder pain……..	1	2	3	4
16. Arm pain……..	1	2	3	4
17. Arm swelling……	1	2	3	4
18. Breast swelling……	1	2	3	4
19. Arm stiffness……	1	2	3	4
20. Fit of bra……	1	2	3	4
21. Breast sensitivity……	1	2	3	4
22. Fit of clothing……	1	2	3	4

APPENDIX III: Harvard Breast Cosmesis Grading Scale

Table 1

Harvard/NSABP/RTOG Breast Cosmesis Grading Scale

1. Excellent	When compared to the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast, but not enough to change the appearance.
2. Good	There is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3. Fair	Obvious difference in the size and shape of the treated breast. This change involves one-quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4. Poor	Marked change in the appearance of the treated breast involving more than one-quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

APPENDIX IV: STUDY CALENDAR

Assessments	Study Entry / Registration (Pre-IOERT/Surgery)	Prior to Start of Adjuvant RT (Post-IOERT/Surgery)	+/- 14 days of the last Adjuvant RT	1 Month After RT Completion	6 Months After RT Completion	1 year After RT Completion Then Annually x 5 years
Visit Window (+/- days)	-	-	-	30	90	90
History & Physical, Zubrod, and weight	X[1]	X[2]		X	X	X
Breast examination	X[1]	X[2]		X	X	X
Adverse Event Evaluation	X	X[2]	X	X	X	X
Doctor cosmetic assessment (questionnaire and photos)	X[3]	X[2]				X (year 1 and year 3)
Patient questionnaire (BCTOS)	X[3]	X[2]		X	X	X (for 3 years)
Breast fibrosis		X[2]		X	X	X

[1] Within 60 days prior to study entry

[2] At time of follow up visit prior to CT simulation or at the time of CT simulation

[3] Within 60 days to study entry