Mayo Clinic Radiation Oncology

MC1532, A Phase II Study of Accelerated 3 Fraction Photon and Proton Partial Breast External Beam Radiotherapy and Partial Breast Brachytherapy for Early Invasive and Noninvasive Breast Cancer

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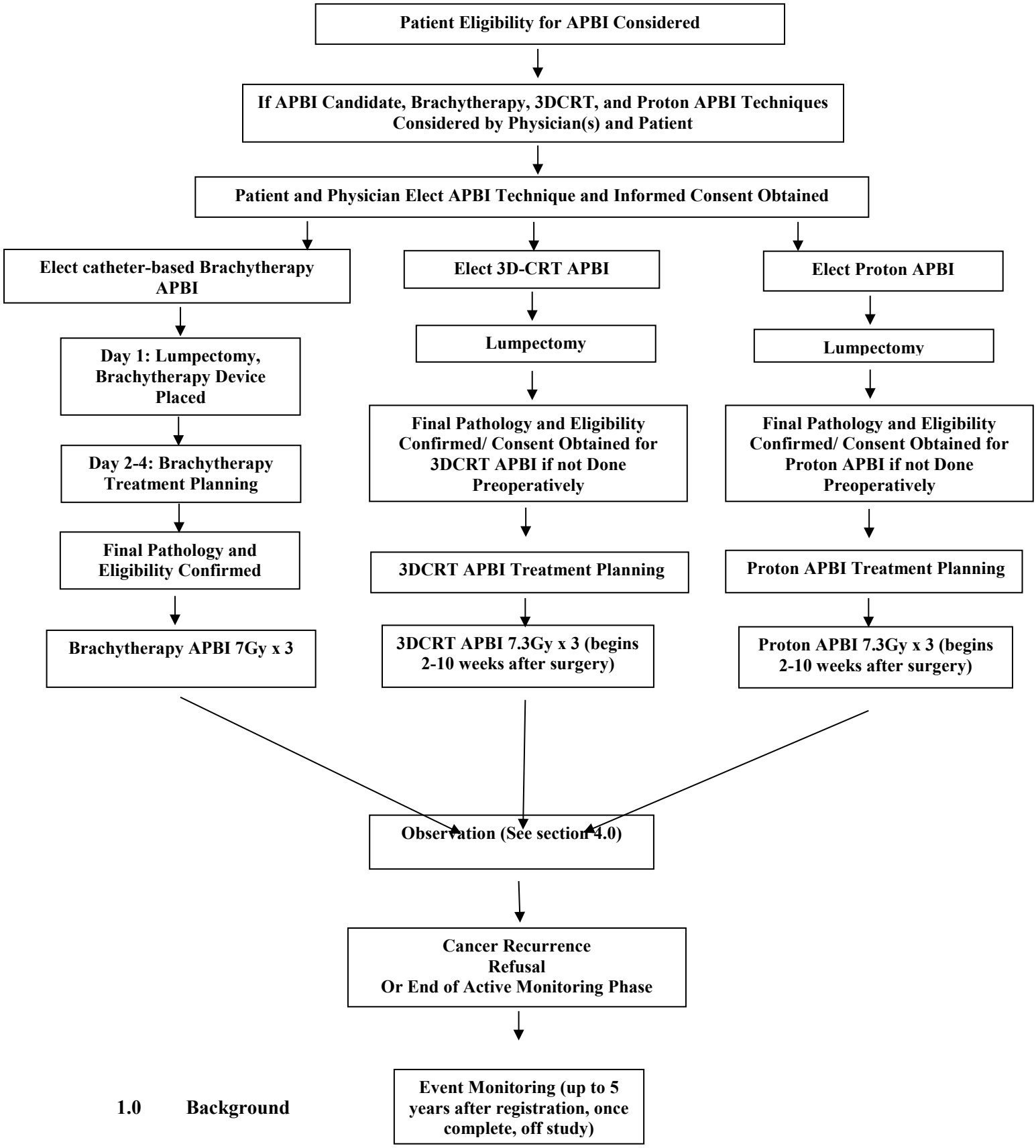
List of Abbreviations

3DCRT	3-D Conformal Radiation Therapy
AE	Adverse Event/Adverse Experience
ALI	Angiolympatic Invasion
APBI	Accelerated Partial Breast Irradiation
BCT	Breast Conserving Therapy
BED	Biological Effective Dose
CFR	Code of Federal Regulations
CRF	Case Report Form
CTV	Clinical Target Volume
DCIS	Ductal Carcinoma In Situ
DSMP	Data and Safety Monitoring Plan
EBRT	External Beam Radiation Therapy
EIC	Extensive Intraductal Component
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDR	High Dose Rate
HIPAA	Health Insurance Portability and Accountability Act
IBTR	Ipsilateral Breast Tumor Recurrence
IORT	Intraoperative Radiation Therapy
IRB	Institutional Review Board
LDR	Low Dose Rate
MIB	Multicatheter interstitial Brachytherapy
NSABP	National Surgical Adjuvant Breast and Bowel Project
PI	Principal Investigator
PHI	Protected Health Information
PTV	Planning Target Volume
QOL	Quality of Life
RTOG	Radiation Therapy Oncologic Group
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
WBI	Whole Breast Irradiation

Summary

This is an open label phase II study to determine the safety and efficacy of a novel 3 fraction daily dosing regimen for accelerated partial breast irradiation (APBI) for early invasive and noninvasive breast cancer. The three techniques utilized are recognized as standard options for the delivery of APBI, and there is no evidence that either technique is superior or inferior to any other. The APBI technique utilized will be at the physician's discretion and will be based on technical considerations, availability at the treating radiation facility, insurance coverage, as well as patient preference.

Schema



1.0 Background

1.1 Rationale for Accelerated Partial Breast Irradiation

The combination of breast conserving surgery and radiotherapy has been confirmed to provide equivalent disease-free and overall survival in multiple prospective randomized controlled trials with follow-up periods of over 20 years in early stage breast cancer.[1-3] Despite the cosmetic and potential emotional advantages of BCT (breast conserving therapy), many patients may choose mastectomy or decline radiation following lumpectomy due to the protracted nature of a conventional course of whole breast irradiation (WBI), which is delivered to the whole breast and frequently followed by a boost to the tumor bed, usually over 3-6.5 weeks.

The optimal volume of breast irradiation remains an area of ongoing study.[4] Several lines of evidence suggest that WBI is unnecessary in a substantial number of patients with appropriately defined histological and clinical characteristics. For example, in a review of 217 mastectomy specimens, treated in Nijmegen, the Netherlands, residual disease was rarely identified more than 2 cm beyond the edge of the primary tumor unless an extensive intraductal component (EIC) was present.[5] A pathologic analysis of reexcision specimens at William Beaumont Hospital demonstrated that in 90% of 134 patients with negative initial lumpectomy margins, any residual disease present was limited to <10mm from the edge of the original lumpectomy margin.[6] Clinical validation of these histologic findings comes from analyses of patterns of failure after BCT which have shown that a majority of local recurrences in the first 5-10 years after BCT occur in close proximity of the original tumor, and the rate of recurrences outside of this area in the treated ipsilateral breast are similar to the rate of contralateral breast failures.[7-10] With increasing follow-up, a larger proportion of recurrences are seen in other quadrants of the breast.[7] Similar findings have also been seen in patients treated with lumpectomy without radiation, implying that an "in breast recurrence" may be due to growth of residual tumor cells left following the initial therapy (the target of adjuvant radiation), or the development of new primary tumors without relation to the initial breast cancer diagnosis.[11,12] The impact of WBI in reducing local recurrence therefore appears to be primarily related to irradiation of the lumpectomy cavity and the immediately surrounding breast tissue.

In response to this clinical data, the patient inconvenience of protracted conventional WBI, and the possibility that unnecessary prophylactic treatment of uninvolved breast tissue may place the patient at greater risk of acute and chronic toxicity, accelerated partial breast irradiation (APBI) has been studied as a viable alternative to WBI. In general, APBI involves treating the surgical cavity with a 1-2cm margin. This substantial reduction in the volume of exposed breast tissue has enabled much shorter treatment schemes than WBI, making treatment more convenient for patients, and potentially decreasing the overall cost of treatment substantially.[13] The results of multiple large, multicenter randomized controlled studies, including the National Surgical Adjuvant Breast and Bowel Project B 39 & Radiation Therapy Oncology Group 0413, are underway comparing ABPI to WBI and will be reported in the years ahead. To date, a small number of phase III and multiple phase I-II studies of various APBI techniques and fractionation schemes have been published. The sum of this data suggests that local recurrence rates with APBI are low in properly selected, low-risk women. However, the optimal technique, dose and length of treatment to be used for APBI remains undefined. The rationale for the proposed dose and fractionation of 7.3Gy x 3 is delineated in section 1.3.2.

1.2 Clinical Studies of Partial Breast Irradiation

Few randomized trials have been published to date with long-term outcomes comparing APBI to WBI. The first was conducted from 1982 to 1987 in Manchester, England, and randomized 708 evaluable patients with breast carcinoma 4cm or less in diameter to receive radiotherapy to the tumor bed only (40-42.5Gy in 8 fractions delivered over 10 days, typically using 10MeV electrons to an average field size of 8 x 6cm, prescribed to the 100% isodose line) or to the whole breast and regional lymph nodes (40 Gy in 15 fractions over 21 days, delivered with a 4-MV linear accelerator without the use of wedges). There was no axillary dissection or systemic therapy used and most patients did not have pre or postoperative mammographic evaluation. Moreover, there was no microscopic assessment of specimen margins and no CT planning for radiation so dose delivered to the target is uncertain. The 7-year actuarial breast recurrence rate (first event) for patients with infiltrating ductal carcinoma was 15% and 11% for the tumor bed only and whole breast/regional nodes arms, respectively. For patients with infiltrating lobular tumors, the respective recurrence rates were 34% and 8%.[14]

The Hungarian National Institute of Oncology trial randomized 258 patients with T1 N0-1mi, grade 1-2, nonlobular breast cancer without the presence of an EIC and resected with negative margins to lumpectomy followed by WBI (50Gy in 25 fractions, n=130) or APBI using either a high-dose-rate (HDR) multicatheter interstitial brachytherapy (MIB) technique (7 x 5.2Gy, n=88) or limited-field external-beam APBI with electrons (50Gy in 25 fractions, using 6-15MeV en face electron fields to the tumor bed extended with a margin of 2cm, n=40). The 5-year actuarial rate of local recurrence was 4.7% in the WBI and 3.4% in the APBI arms, respectively (p=0.50), and there was no significant difference in overall survival, cancer-specific survival, and disease-free survival. The rate of good to excellent cosmesis was significantly better in the APBI arm: It was 77.6% with APBI (81.2% after HDR brachytherapy, 70.% after electron APBI) and 62.9% following WBI (52.2% in patients treated with cobalt, 65.6% after 6-9MV photons), p=0.009.[15]

Multiple non-randomized phase I-II trials using various techniques to deliver APBI have been reported. Overall, these data suggest that with proper patient selection APBI appears to result in outcomes similar to those seen with WBI. The William Beaumont Hospital reported the largest American series of 199 patients treated with the MIB technique. Most patients had tumors smaller than 3cm in size, negative margins (≥2mm), were over the age of 40, and had negative lymph nodes. A total of 120 patients (60%) were treated with a low-dose-rate (LDR) implant of 50Gy over 96 hours, and seventy-nine patients (40%) were treated with a HDR implant of either 32Gy in 8 fractions or 34Gy in 10 fractions, separated by 6 hours. With a median follow-up of 60 months, the cumulative incidence of local recurrence was 1%, and was not different than WBI patients on matched-pair analysis.[16]

The Radiation Therapy Oncology Group (RTOG) performed a multi-institutional phase I-II trial of MIB APBI based on the favorable results at William Beaumont and other institutions. Eligibility for RTOG 9517 included tumors <3cm, unifocal disease, negative margins, and three or fewer lymph nodes without the presence of extra-capsular extension, and no EIC. Patients were treated with either LDR (45Gy in 3.5-5days) or HDR (34Gy in 10 twice-daily fractions within 5 days) APBI. The target volume was defined as 2 cm beyond the lumpectomy cavity peripherally and 1 cm superficially and

deeply.[17] With a median follow-up of 7years, the estimated 5-year in-breast failure rate for the 99 eligible patients was 4%. Of the 6 patients that failed within the treated breast, just two had failure outside of the treated volume.[18] Five patients experienced grade 3 or 4 acute adverse effects. The most common toxicities during follow-up were skin thickening and fibrosis, and late grade 3 toxicities were lower in patients treated with HDR compared with the LDR group (6% versus 18%).[17]

MIB requires a considerable amount of physician technical expertise and the majority of radiation oncologists who treat breast cancer routinely do not have training to perform these procedures. The MammoSite® (Hologic Inc., Marlbourough, MA) breast brachytherapy applicator was designed to treat a similar volume of tissue around the lumpectomy cavity as MIB but with a single skin entry point, greater simplicity and less user-dependence.[19] The American Society of Breast Surgeons (ASBS) MammoSite Breast Brachytherapy Registry Trial reported the outcomes of 1440 patients treated with this technique between 2002 and 2004 at 97 institutions. With a median follow-up for surviving patients of 53.7 months, the 5-year actuarial rate of ipsilateral breast tumor recurrence (IBTR) was 3.8% (3.86% for the 1249 patients with invasive breast cancer, 3.39% for the 194 patients with DCIS). In patients with invasive breast cancer, the 5-year actuarial rate of regional nodal failure was 0.84%. Negative estrogen receptor status was the only variable significantly associated with ipsilateral breast tumor recurrence (IBTR) and was limited to the development of breast failures several centimeters from the primary site and believed to be a new primary cancer. 90.6% of patients had a good or excellent cosmetic result at 5 years, and the only factor significantly associated with favorable cosmesis was increasing balloon-to-skin distance.[20]

Multi-lumen balloon catheter devices (Mammosite® ML and Contura® [SenoRx, Irvine, CA]) and non-balloon bundled-catheter device (SAVI® [Strut Adjusted Volume Implant], Cianna Medical, Aliso, Viejo, CA]) were developed to provide greater conformality to the lumpectomy cavity while enabling better tailoring of dose around normal tissue structures like the skin, chest wall, and heart compared with single-lumen applicators. Fisher et al. reported their results of treatment of 117 patients with APBI brachytherapy between 2004 and 2010.[21] Seventy-seven were treated with single-lumen balloon catheter Mammosite® and 40 with the SAVI® applicator, all to total doses of 34Gy in 10 fractions. Of the 40 patients treated with the SAVI® device, 12 had tumor bed-to-skin spacing of less than 7mm. None of these patients required device explantation, compared to 57% of patients treated with Mammosite when distances were <7mm. All 12 SAVI patients with minimal skin spacing had good or excellent cosmesis at short interval follow-up of 13 months thus far.[21]

Three-dimensional (3D) conformal external-beam photon radiotherapy (3D-CRT) APBI is attractive because it is non-invasive, is widely available, and provides a more homogeneous radiation dose. The RTOG 0319 was a phase I-II trial designed to determine the feasibility and reproducibility of 3D-CRT APBI in a multi-institutional setting. 58 patients with stage 1 or 2 invasive ductal carcinoma with tumors ≤3cm and negative surgical margins were enrolled. A total dose of 38.5Gy was administered in 10 fractions over 5 days. The clinical target volume (CTV) included the lumpectomy cavity plus a 10-15mm margin. The Planning target volume (PTV) included the CTV plus a 10-mm margin. The primary endpoint of reproducibility was met, as only 4 cases had major protocol violations.[22] With a median follow-up of 4.5 years, a total of three ipsilateral breast failures were noted on RTOG 0319, with a four-year actuarial estimate of 6%. The

3DCRT technique was therefore included on the phase III NSABP B-39/RTOG 0413 clinical trial and has been the most utilized APBI approach on that study.

Formenti et al. 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 delivered over 10 days with port film verification at each treatment. 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.[23]

Proton beam APBI is a particularly promising alternative to other forms of APBI. Like 3D-CRT APBI delivered with photons, it is noninvasive and has less dosimetric inhomogeneity compared with brachytherapy delivery methods.[24] Due to unique physical properties of protons including their characteristic Bragg Peak, protons can be directed to treat deep-seated tumors while significantly sparing surrounding normal tissue, resulting in improved dose conformity. The Massachusetts General Hospital group recently reported long-term outcomes of their initial clinical experience with proton APBI on a phase 1 dose-escalation trial.[25] Patients with unifocal, T1 tumors with tumor-free margins of ≥2mm and pathologically negative axillary nodes were eligible. The dose was 32Gy in 8 fractions given twice daily and could be delivered with either protons, photons, or mixed photons and electrons. At 7 years, the local failure rate for all 98 evaluable patients was 6%. Physician rated cosmesis was good or excellent in 94% of photon patients, compared with 62% among the 19 patients treated with protons (p=0.03). Similarly, skin toxicity was more common in the proton group. The higher than expected level of skin toxicity is likely a result of suboptimal dose, beam arrangement and number of beams.[24] For example, a single field was used each fraction in the proton arm in order to minimize machine time. In contrast, Bush et al. from Loma Linda recently reported very favorable cosmetic and toxicity outcomes in 100 patients treated on a phase II study of proton APBI.[26] Eligibility included non-lobular carcinoma of the breast, pathologically negative margins by at least 2mm, and primary tumors ≤3cm. In this study, 40Gy was delivered in 10 daily fractions over 2 weeks and multiple fields were treated each day. With a median follow-up of 5 years, good or excellent cosmesis was noted in 90% of patients by both physician and patient reports. There was no acute or late grade 3 skin toxicity. Grade 1 telangiectasias were seen in just 7% of patients. The 5 year ipsilateral breast tumor recurrence-free survival was 97%.

Electronic and intraoperative APBI devices have recently gained in popularity. Although the convenience of single fraction intraoperative radiation (IORT) is attractive, target and normal tissue dosimetery is limited and follow-up to date is short. TARGIT-A (targeted intraoperative radiation therapy), is a phase III prospective non-inferiority trial comparing whole breast EBRT to 20 Gy single fraction IORT delivered to the surface of the tumor bed with 50kV x-rays using spherical applicators. Patients aged 45 or older with unifocal invasive ductal carcinoma and tumor sizes <3.5cm were eligible and enrolled between March 24, 2000 and June 25, 2012. If final pathology demonstrated pre-specified adverse features, EBRT was added to the TARGIT arm. The primary outcome was absolute difference in local recurrence in the conserved breast, with a prespecified non-inferiority margin of 2.5% at 5 years. For the whole cohort, the median follow up was 2 years and 5 months. 1721 patients were randomized to TARGIT and 1730 patients to EBRT. Supplemental EBRT after TARGIT was given in 15.2% of patients treated with TARGIT. The 5-year risk for local recurrence were 3.3% (95% CI 2.1-5.1) and 1.3% (0.7-2.5, p=0.042) for the TARGIT and EBRT arms respectively, p=0.042, with an

absolute difference within the pre-specified non-inferiority margin.[27] Significantly fewer non-breast cancer deaths were noted with TARGIT compared to EBRT (1.4% [0.8-2.5] vs 3.5% [2.3-5.2]; p=0.0086).

In the Electron IntraOperative Therapy (ELIOT) phase III trial, patients aged 48-75 years with invasive tumors ≤2.5cm were randomized to 21Gy in 1 fractions to the tumor bed using 6-9MEV electrons prescribed to the 90% isodose line (n=651) or whole breast EBRT to 50Gy followed by a 10Gy boost.[28] 88.4% of patients on the study received endocrine therapy and 21.5% had chemotherapy. The study was designed with an assumed 5-year local recurrence rate of 3% in the EBRT group and equivalence of the two groups if the 5-year local recurrence rate in the ELIOT group did not exceed 7.5%. The 5-year event rate for IBTR was 4.4% (95% CI 2.7-6.1) in the ELIOT group, which was significantly higher compared to the 0.4% (0.0-1.0) rate in the conventional group, p=0.0001. The hazard ratio for the development of IBTR was 9.3 [95% CI 3.3-26.3]. The rate of IBTR in the intraoperative radiotherapy group, however, was within the prespecified equivalence margin. The 5-year IBTR exceeded 10% in patients with tumors >2cm, patients with four or more positive lymph nodes, grade 3 tumors, ER negative tumors, and triple negative tumors. In multivariable analysis, tumor size greater than 2cm (HR 2.24, 95% CI 1.03-4.87), the presence of four or more positive lymph nodes (2.61, 0.91-7.50), grade 3 (2.18, 1.00-4.79), and triple-negative subtype (2.40, 0.94-6.10) were associated with elevated risk of IBTR. The 5-year occurrence of IBTR was 1.5% in the 452 women who did not have one of these unfavorable characteristics. The development of distant metastasis and overall survival at 5 years did not differ significantly between the two groups. There was significantly less erythema, dryness, hyperpigmentation, and pruritus in the ELIOT group, but a higher occurrence of fat necrosis.

1.3 Rationale For the Current Study Design

1.3.1 Patient Selection

In order to limit the risk of local failure, only patients who have tumors that are limited in their spread beyond the index lesion, and unlikely to be at increased risk of chest wall, skin, or regional nodal recurrence if these sites are not fully irradiated should be offered APBI. Therefore, patients with positive axillary nodes, angiolymphatic invasion (ALI), large (>2.5 cm) or multicentric/multifocal tumors, those with lobular histology or an EIC, those with ER negative disease will be excluded.[14,28,29] Patients with unifocal DCIS will be included based on multiple lines of evidence suggesting low rates of recurrence in properly selected patients with DCIS treated with APBI.[30-34]

1.3.2 Dose and Fractionation

The linear-quadratic formula model has emerged as 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.[35] 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.[36]

Several lines of evidence suggest that the α/β ratio of breast cancer may be more in line with those of late responding tissues.[37,38] Indeed, the most robust data to date suggesting this relationship has come from the UK Standardization of Breast Radiotherapy (START) trials, two modern 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).[39] 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. 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.

In START-B, 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.[39,40] 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 is the case with APBI.[41,42]

The overlying hypothesis of this study is that the low α/β for breast cancer can be further exploited by compressing treatment into a 3 fraction daily regimen, provided that care is taken not to exceed the tolerance of normal tissues. Previous fractionation schemes for APBI have largely been devised empirically. The most common brachytherapy regimen in North America has been 3.4Gy delivered in 10 fractions given twice daily, the regimen adopted in NSABP B-39/RTOG 0413. This regimen has been reported to result in acceptable local control and cosmesis in numerous studies reported to date although retrospective population based analyses have suggested brachytherapy may be associated with increased frequency of infectious and noninfectious complications, compared with whole breast irradiation.[18,43-46] Using an α/β ratio of 3.5 for tumor control and late effects, this regimen translates into a dose of 43Gy in 2Gy fractions.

For external beam partial breast irradiation, the most common regimen used to date has been 38.5Gy delivered in two fractions per day for 10 fractions. This is also the dose

prescribed in NSABP B-39/RTOG 0413 as well as the Canadian Accelerated Partial Breast Irradiation Using Three-Dimensional Conformal External Beam Radiation Therapy (RAPID) randomized trials. Olivotto et al. recently reported the interim cosmetic and toxicity results from the latter study which compared 3D-conformal APBI to whole breast irradiation (WBI). 82% of patients in the WBI arm received 42.5Gy in 16 fractions, and just 21% of patients received a boost. At 3 years, 29% of patients in the APBI arm had fair or poor cosmesis compared to 19% at baseline, an absolute difference of 10%. In the WBI arm, the rate of fair or poor cosmesis at 3 years was 17%, the same rate as at baseline. Telangiectasia and breast induration were also significantly more common with external beam APBI ($p<0.001$), as was fat necrosis ($p=0.01$).[47] Other institutions have also noted adverse toxicity with similar regimens.[22,48]

There are likely several reasons for the higher than expected adverse cosmesis seen in the RAPID trial that may be also relevant to the increased complications seen with brachytherapy in population based analyses. These considerations have been taken into account in the development of the brachytherapy, external beam photon and proton fractionation regimens of this study. First, the dose of 38.5Gy in 10 fractions given twice daily was too high. The RAPID trial investigators recognized that this prescription had a higher biologic equivalence than the whole breast regimens used in the study, but they hypothesized that the reduced volume of APBI would make up for this difference. Indeed, using an α/β ratio of 3.5 for late effects, the 3.85Gy x 10 fraction regimen translates into 51.5Gy in 2 Gy fractions, higher than the 2Gy fraction equivalent dose of 42.5Gy delivered in16 fractions ($47.7Gy_2$) which was received by the majority of patients in the WBI control arm of the study.

Perhaps more importantly, the 6 hour interval between fractions may not have been long enough to complete sublethal damage repair of late responding breast tissue following 3.85Gy fractions, resulting in a much more biologically potent dose to the tissues.[49] Indeed, data from the head and neck cancer CHART study suggested that normal tissue recovery halftimes for skin telangiectasia and subcutaneous fibrosis were 3.8h (95% CI 2.5, 4.6) and 4.9h (95% CI 3.2, 6.4), respectively.[50] Therefore, with inter fraction intervals of just 6 hours, incomplete repair could have a marked effect on the response of normal tissues, particularly in the context of fractions larger than 2Gy. In support of the importance of taking into account sublethal damage repair in APBI, cosmesis was rated as good/excellent in 89% of patients with at least 36 months follow-up in a prospective trial of 3D-CRT APBI of 100 patients treated in the prone position to a total dose of 30Gy in 6Gy fractions, but delivered over 10 days. This regimen is equal to $51.82Gy_2$ with an α/β ratio of 3.5 for tumor control which is comparable, under linear quadratic modeling, to the regimen used in the RAPID study but with greater interval between fractions for repair of sublethal damage.[23] Finally, the volume of breast treated by physicians in RAPID, which included a 1.0cm PTV expansion, may have been too high.[22]

Given this background, this study will explore treating patients with 3 fractions of 7.3Gy delivered once daily with 3DCRT and protons and 3 fractions of 7 Gy for brachytherapy. Using an α/β ratio of 3.5 for tumor control and late effects, these regimens is approximately equivalent to the 3.4Gy x 10 fraction regimen that has been the most widely used with promising results to date. We believe late toxicity will be reduced because of more complete sublethal damage repair with daily, as opposed to twice daily fractionation. Of note, similar 3 fraction regimens have been utilized in other disease sites and have been well tolerated with high rates of disease control.[51]

It is understood that the linear quadratic model has been questioned for large doses per fraction and alternative models have been proposed.[52,53] A simple linear quadratic model was implemented here because it has decades of use in the radiotherapy treatment field, it is mathematically simple, and biological parameters other than alpha/beta are not well established. It has also been suggested that cell damage from radiotherapy with high dose gradients (brachytherapy) may be greater than for a more homogenous dose distribution (external beam radiotherapy).[54] In the brachytherapy arm, a small volume of tissue may receive a higher biologically equivalent dose by linear quadratic modeling due to treatment inhomogeneities, compared to 3.4Gy x 10. We expect this to be offset by more complete inter-fraction recovery than the commonly used twice daily regimen. The dose will also be slightly reduced in this arm (21 Gy in 3 fractions) compared to the 3DCRT and proton arms (21.9Gy in 3 fractions).[49] V400 and V300 for the brachytherapy arm will be minimized to the degree possible, and monitored, although a constraint is not specified. Daily image guidance, as described in the radiation therapy section below, is used to safely reduce the planning target volume and subsequent normal tissue volume treated in photon and proton APBI.

1.4 Rationale for allowing 3 different APBI techniques

Prospectively conducted clinical trials have demonstrated the safety and efficacy of each of the APBI techniques that will be allowed on this study. On the recently closed NSABP B-39/RTOG 0413 protocol, A Randomized Phase III study of Conventional Whole Breast Irradiation Versus Partial Breast Irradiation for Women with Stage 0, I, or II Breast Cancer, APBI could be administered with brachytherapy or 3D-CRT at the physician's discretion, highlighting the equipoise that exists between the techniques and justifying pooling outcomes of patients treated with either technique on this study to assess the primary and secondary endpoints. Given the conformal and homogeneous dose distribution of protons as well as the favorable outcomes reported to date, proton APBI will also be allowed at centers where this modality is available. At least one of the three APBI techniques allowed in this study is available at all participating centers. Similar to NSABP-B-39/RTOG 0413, the APBI technique to be 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. In addition, after reduction mammoplasty patients will only be allowed if they undergo brachytherapy as the extensive manipulation of breast tissue at the time of surgery is felt to preclude reliable targeting with external beam photon or proton techniques.

2.0 Goals

2.1 Primary:

2.11 To evaluate the rate of adverse cosmesis (defined as fair or poor cosmesis) with accelerated 3 fraction APBI at 3 years, compared to baseline.

2.2 Secondary:

2.21 To evaluate the acute and late toxicities of accelerated 3 fraction APBI

2.22 To evaluate local disease control of accelerated 3 fraction APBI.

2.23 To assess the rate of patient reported adverse cosmesis at 2 years, compared to baseline

2.23 To assess quality of life and other patient reported outcomes following accelerated 3 fraction APBI

2.24 To compare the local control, acute and late toxicities, cosmesis, quality of life and other patient reported outcomes between the three radiation therapy techniques (3D-CRT, proton, brachytherapy).

2.24 To evaluate clinical features, dose-volume parameters, and genetic variants associated with fair and poor cosmetic outcome

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Female

3.12 Age ≥ 50 years at diagnosis

3.13 Grade 1-3 invasive ductal, mammary, mucinous, tubular, colloidal, or pure ductal carcinoma in situ (DCIS) measuring ≤ 2.5 cm on final pathology (the tumor should be clinical stage T1N0M0 in patients electing brachytherapy in whom the catheter will be placed intraoperatively).

3.14 Estrogen Receptor (ER)+ (ER- DCIS meeting other eligibility criteria are eligible)

3.15 Unicentric: Patients with microscopic multifocality are eligible as long as the total pathologic tumor size is ≤2.5cm

3.16 Surgical treatment of the breast must have been lumpectomy.

3.17 The final margins of the resected specimen must be histologically free of tumor.

3.18 Patients with DCIS do not require an axillary staging procedure. For patients with invasive breast cancer (except T1mi), an axillary staging procedure should be performed (either sentinel lymph node biopsy alone or axillary dissection and the axillary node must be pathologically negative) and they should be pathologically node negative.

Note: Patients with N0 (i+) tumors on sentinel lymph node mapping or dissection (i.e., if the tumor deposit is 0.2mm or less as determined by immunohistochemistry or hematoxylin and eosin staining) will also be eligible.

3.19 ECOG Performance Status of 0 or 1

3.20 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.21 Ability to complete questionnaire(s) by themselves or with assistance.

3.22 Ability to elect radiotherapy care in conjunction with their physician

3.23 Able and willing to provide written informed consent

3.24 Willingness to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.25 Willing to provide tissue and blood samples for correlative research purposes

3.26 Rochester and Arizona patients: Willing to sign consent onto the Mayo Clinic Radiotherapy Patient Outcomes Registry and Biobanking study and collect involved blood specimen prior to the start of radiation therapy, IRB number 15-000136.

3.3 Exclusion Criteria

3.31 Any of the following because this study involves therapy that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception

3.32 Neoadjuvant chemotherapy

3.33 Prior history of ipsilateral breast cancer

3.34 Prior radiation therapy to the ipsilateral breast or thorax

3.35 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.

3.36 Active collagen-vascular disease that, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

3.37 Paget's disease of the breast

3.38 Proven multicentric carcinoma (DCIS or invasive) in more than one quadrant or separated by 4 or more centimeters or diffuse (>1 quadrant) suspicious calcifications

3.39 Histologic evidence of angiolympatic invasion (ALI).
Note: Cases termed focally suspicious for ALI but where no definitive ALI is found are eligible.

3.40 Surgical margins that cannot be microscopically assessed or that are positive

3.41 Pathologic tumor >2.5cm in size

3.42 Metastatic disease

3.43 Patients for whom the delivery of APBI is not feasible or any of the dosimetric treatment criteria in section 9.7 have not been met.

3.44 BRCA 1/2 mutation
Note: Patients are not required to undergo BRCA1 and BRCA2 or other genetic mutation tests in order to enroll on the study. However, in the event a patient is tested and is found to be a mutation carrier, she would be excluded from the study.

3.45 Breast implants (patients who have had implants removed are eligible).

3.46 Extensive intraductal component

3.47 Active connective tissue disease

3.48 Reduction mammoplasty if 3DCRT or proton APBI are planned

3.49 Last surgery >10 weeks from enrollment

4.0 Test Schedule

Assessments, tests and procedures	Active Monitoring Phase				
	Treatment				Observation
	Baseline[2]	Radiation Treatment	Last day of radiation treatment (+/-2 days)	12 weeks (+/- 8 weeks) post-radiation	12 months (+/- 3 months) post completion of radiotherapy, annually for up to 5 years (+/- 3 months)[7]
History and Physical exam (including breast assessment/exam)[1]	X		X	X	X
Mammogram	X[11]				X[8]
Consent	X				
Cosmetic and QOL Outcome Assessment (see section 11.3 and Appendix)	X		X	X	X
Digital Photograph	X[10]		X	X	X
Histologic Assessment	X[3]				
Radiation toxicity assessment (see section 10.4)	X		X	X	X
Serum pregnancy test	X[4]				
Blood specimen[5,R]	X[12]		X		
Clinically indicated treatment		X			

Surgical tumor specimen[6,R]	X[9]				

1. A general clinical history & physical must be done ≤ 8 weeks prior to registration. This should include assessment of ECOG performance status (see Appendix I).
2. Procedures done prior to radiation therapy.
3. Outside pathology must be reviewed at the treating institution.
4. For women of childbearing potential only
5. See section 14 for collection time and preparation of samples
6. See section 17 for collection time and preparation of samples
7. Patients that cannot come back to Mayo Rochester within the time constraints of the follow-up schedule; efforts to obtain outside records and send QOL's to be completed will occur however the specifics of the test schedule may not be captured. Observation will occur for a total of 5 years unless the patient goes off study.
8. As clinically indicated
9. Collect post-surgery
10. Ideally prior to surgery but can be done prior to radiation
11. Completed ≤ 6 months prior to study entry
12. Radiation Oncology Registry and Biobank (IRB: 15-000136): Blood specimen is required to be collected prior to the start of radiation therapy.

R. Research required testing

5.0 Stratification Factors

- None – Patients, along with their physicians, will determine which treatment arm is appropriate for their needs. The APBI technique to be utilized will be based on technical considerations, availability at the radiation oncology facility, insurance coverage considerations, and patient preference. In addition, after reduction mammoplasty patients will only be allowed if they undergo brachytherapy as the extensive manipulation of breast tissue at the time of surgery is felt to preclude reliable targeting with external beam photon or proton techniques.

6.0 Randomization/Registration Procedures

6.1 Randomization-none

6.2 Registration Procedures

Registration will entail confirming patient eligibility and signing the informed consent

6.21 Pretreatment tests/procedures, (see Section 4.0) will be completed within the guidelines specified on the assessment schedule.

6.22 All required baseline symptoms (see Section 10.0) must be documented and graded.

7.0 Clinical Protocol Treatment

7.1 Radiation Therapy

7.11 3D-CRT (photon) APBI

In situations where patients present to a radiation oncologist pre-operatively, if they meet study eligibility criteria they may be consented at that time for 3D-CRT APBI. After lumpectomy and axillary staging, at their postoperative visit in the radiation oncology department (generally 1-6 weeks following surgery) final pathology and eligibility will be confirmed. Consent may also be obtained for photon APBI at that time if it was not provided preoperatively or if the patient is consulting with the treating radiation oncologist for the first time. Patient must begin treatment $\leq$ 10 weeks after their last surgery.

Radiation Details:

Localization, Simulation, Immobilization: Prior to the treatment planning CT scan patients must be immobilized in the supine position in an arm up or down position at the discretion of the treating radiation oncologist. The CT should start at or above the mandible and extend several cm below the inframmamary fold (including the entire lung). Slice thickness should be 0.3 cm or less.

Treatment Planning/Delivery: Any combination of photon beams of energy 6MV or higher, with or without the addition of electrons of any energy, may be used provided that the dosimetric requirements of the planning target volume (PTV) and homogeneity are met. 3D-CRT should begin within 10 weeks of lumpectomy or re-excision of margins.

Image Guidance for IGRT: Cone-beam CT (CBCT) matched to soft tissue and or fiducial markers/clips placed at the time of lumpectomy or orthogonal kilovoltage (KV) images matched to fiducial markers/clips should be performed to ensure reproducibility of setup prior to initiation of each treatment. A manual registration can also be used to optimize the match prior to treatment.

Definition of Target Volumes: The radiation oncologist will identify and outline the tumor bed by noting contrasting areas of density and architectural distortion as well as the presence of clips or fiducials in the breast. Information from the surgical report, mammography, MRI and other available imaging should be taken into account when available. A margin of 1cm will then be added to the tumor bed in order to create the CTV. The CTV will be limited, however, to 5mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). The PTV is defined as a uniform 3mm expansion of the CTV to compensate for variability of set-up and any motion of the breast during treatment. The PTV is saved and is used to generate the beam aperture with an additional margin to take penumbra into account. Since a substantial part of the PTV often extends outside other patient (especially for superficial cavities), the PTV is then copied to a PTV_EVAL, which is edited. The PTV_EVAL is limited to exclude the part outside the ipsilateral breast and the first 5mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis). Bolus to improve anterior target coverage should not be used. It is preferred that the PTV does not exceed 25% of the breast volume. If it does, a delay of 1-3 weeks until the seroma decreases in size and another planning session is performed should be considered.

Dose Prescription to PTV: The prescribed radiotherapy dose will be 21.9 Gy in 7.3 daily fractions (total of 3 fractions). Radiotherapy should aim to be delivered on three consecutive work days. Per protocol ≥95% of the target volume PTV should be covered by ≥95% of the prescribed dose of 21.9Gy. Variation Acceptable ≥90% of the target volume PTV should be covered by ≥90% of the prescribed dose of 21.9Gy. The maximum dose should not exceed 115% of the prescribed dose.

Definition and Dose Limitations of Normal Tissues/Organs at Risk (OARs): The following normal tissue structures should be contoured for all patients by the physician: uninvolved normal breast, ipsilateral lung, contralateral lung, and heart.

Uninvolved ipsilateral normal breast: Includes the glandular breast tissue visualized by CT and the consensus definitions regarding “breast” from the RTOG breast atlas. The structure should be limited to 5mm from the skin surface to minimize inaccuracy of dose calculation at the skin surface. Per protocol <35% (variation acceptable <50%) of the whole breast reference volume should receive ≥ 50% of the prescribed dose and <20% (variation acceptable <30%) of the whole breast reference volume should receive the prescribed dose.

Ipsilateral lung: May be contoured with auto-segmentation with manual verification. The volume receiving 20Gy should not exceed 2%. The volume receiving 10Gy should not exceed 7%. The volume receiving 5Gy should not exceed 15%.

Contralateral lung: The volume receiving 20Gy should be 0. The volume receiving 10Gy should be <1%. The volume receiving 5Gy should be <2%.

Heart: 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) and extending to its most inferior extent near the diaphragm. Contouring along the pericardium itself, when visible, is appropriate. The esophagus, ascending and descending aorta, and inferior vena cava should be excluded. The volume of heart receiving 2.5Gy should be less than 40%.

7.12 Catheter-based Brachytherapy APBI

Patients that elect to undergo brachytherapy APBI will consult with a radiation oncologist preoperatively. If they meet study eligibility criteria they may be consented at that time for brachytherapy APBI. At surgery (day 1), metal vascular or marking clips should not be used during the lumpectomy procedure. Immediately following lumpectomy and axillary staging and during the same procedure, if the patient still meets eligibility criteria the brachytherapy catheter device (SAVI, Mammosite, or Contura) will be placed. Care should be taken to direct suture knots and tails away from the cavity and whenever possible position tissue between the potential balloon surface and the tails. Prophylactic antibiotics should be initiated prior to device placement and continued until the device is completely removed from the patient. On day 2-4, the patient will present to the radiation oncology department for brachytherapy treatment planning, with the first treatment generally administered the following business day but possibly as early as day 2.

Radiation Details:
Localization, Simulation, Immobilization: Prior to the treatment planning CT scan patients must be immobilized in the supine position, generally with the arms up and resting comfortably in a reproducible position stabilized by an immobilization device. A treatment planning CT scan with the patient in a supine position and in a deep inspiratory breath hold will be performed within 4 days of the lumpectomy and device placement. The CT should start at or above the mandible and extend several cm below the inframmamary fold (including the entire lung). Slice thickness should be 0.3 cm or less. Skin spacing, symmetry, and conformance of the applicator will be assessed at that time. An AP and lateral digitally reconstructed radiograph (DRR) should be constructed and the skin position of each catheter line should be marked on the skin for pre-treatment quality assurance. Finally, a photograph will be taken to document the orientation of the patient.

Treatment Planning/Delivery: Standard treatment planning guidelines for APBI will be employed and CT imaging is mandatory for treatment planning. Plans will be generated on Varian Eclipse Brachytherapy Treatment Planning software to produce the optimal conformal plan in accordance with volume definition and dose requirements. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV_EVAL and critical normal tissues. The treatment will be performed using the VariSource high dose rate (HDR) brachytherapy afterloader.

In general, brachytherapy should start between 1-5 days after device placement and treatment should be completed within 1 week of device placement. To confirm that the patient's setup is identical to the position of the initial planning CT, the applicator's position and integrity will be verified at the discretion of the treating physician with particular attention to applicator rotation and changes in soft tissue. This will be done by repeating the planning CT scan in the treatment position, assessing the position of the external catheter marker on the skin surface and by obtaining AP and Lateral planar radiographic images, CT scouts, or CT AP and Lateral views for verification of the balloon/strut size and shape. If a change in geometry is noted, this should be addressed prior to additional treatment and repeat planning should be considered at the discretion of the treating physician. The device should remain expanded throughout the treatment course.

Definition of Target Volumes: The following structures will be contoured: (a) the applicator surface (for example for the SAVI® device, the "device surface" is defined as a structure represented by a contour created by smooth contour connection of each strut), (b) planning target volume for evaluation (PTV_EVAL) – (see below), (c) trapped air and/or fluid, (d) skin (both a structure of 5mm of superficial tissue and a structure of the skin surface), (d) chest wall (including ribs), and (e) pectoralis major muscle. The target volumes and normal tissue structures should be outlined on all CT slices.

As the implanted device moves with the target, compensation for variability of treatment set-up and breathing motion is not needed; therefore planning target volume for evaluation (PTV_EVAL) = CTV = PTV. Therefore, within this protocol, only the PTV_EVAL will be referenced. The PTV_EVAL will be delineated as the breast tissue volume bounded by the uniform expansion of the applicator surface radius in all dimensions by 10 mm less the applicator volume and will be limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included).

The volume of trapped air/fluid that displaces the target beyond 1 cm from the balloon/applicator surface should be considered by the physician. The area of trapped air/fluid will be contoured at each level and a total volume obtained. The percentage of the PTV_EVAL that the air displaces may be calculated but this will not be considered in the PTV prescription constraints outlined below. If brachytherapy APBI is attempted but aborted prior to initiation because target coverage or normal tissue constraints (see below) cannot be met, then an alternative APBI technique (3DCRT photon or proton APBI) may be attempted on this protocol.

Dose Prescription to PTV_Eval: The prescribed radiotherapy dose will be 21 Gy in 7 Gy daily fractions (total of 3 fractions). Radiotherapy should aim to be delivered on three consecutive work days. Per protocol ≥95% of the target volume PTV should be covered by ≥95% of the prescribed dose of 21 Gy. High dose rate treatment delivery is required. Variation Acceptable ≥90% of the target volume PTV should be covered by ≥90% of the prescribed dose of 21 Gy. The volume receiving 150% and 200% (V150% and V200%) of the prescribed dose or more should be ≤35cc and ≤10cc, respectively. Variation Acceptable V150%

<50cc and V200% <15cc. The volume receiving 300% and 400% (V300% and V400%) of the prescribed dose should be reported.

Definition and Dose Limitations of Normal Tissues/Organs at Risk (OARs): The following normal tissue structures should be contoured for all patients: uninvolved normal breast, ipsilateral lung, contralateral lung, heart, skin, adjacent ribs.
Skin: The maximum dose at the skin surface should be reduced to as low as achievable while satisfying the other dose parameters but should not exceed 100% of prescription. If this constraint cannot be met than a different APBI technique can be considered on study. Ideally, the maximum dose of the first 5mm of superficial tissue from the body surface will also not exceed 125% of prescription and the maximum dose of the first 10mm of superficial tissue will not exceed 150% of prescription.

Chest wall (including ribs): Should be outlined on all CT slices when within 5mm of the PTV. The maximum dose and V0.1cc will be reduced to as low as achievable while satisfying all dose parameters but should not exceed 115% of the prescribed dose.

Uninvolved ipsilateral normal breast: Includes the glandular breast tissue visualized by CT and the consensus definitions regarding "breast" from the RTOG breast atlas. The structure should be limited to 5mm from the skin surface to minimize inaccuracy of dose calculation at the skin surface. Per protocol <35% (variation acceptable <50%) of the whole breast reference volume should receive ≥ 50% of the prescribed dose and <20% (variation acceptable <30%) of the whole breast reference volume should receive the prescribed dose.

Ipsilateral lung: May be contoured with auto-segmentation with manual verification. The volume receiving 20Gy should not exceed 2%. The volume receiving 10Gy should not exceed 7%. The volume receiving 5Gy should not exceed 15%.

Heart: 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) and extending to its most inferior extent near the diaphragm. Contouring along the pericardium itself, when visible, is appropriate. The esophagus, ascending and descending aorta, and inferior vena cava should be excluded. The volume of heart receiving 2.5 Gy should be less than 40%.

Applicator Removal: The applicator should be removed after completing the last fraction of treatment using standard technique. The applicator entrance/exit site should be dressed according to standard medical practice.

7.13 Proton APBI

In situations where patients present to a radiation oncologist pre-operatively, if they meet study eligibility criteria they may be consented at that time for proton APBI. After lumpectomy and axillary staging, at their postoperative visit in the radiation oncology department (generally 1-6 weeks following surgery) final pathology and eligibility will be confirmed. Consent may also be obtained for

proton APBI at that time if it was not provided preoperatively or if the patient is consulting with the treating radiation oncologist for the first time. Patient must begin treatment ≤ 10 weeks after their last surgery.

Radiation Details:
Localization, Simulation, Immobilization: Prior to the treatment planning CT scan patients must be immobilized in the supine position in an arm up or down position at the discretion of the treating radiation oncologist. Slice thickness should be 0.3 cm or less.

Treatment Planning/Delivery: Any combination of at least 2 proton beams may be used provided that the dosimetric requirements of the planning target volume (PTV) and homogeneity are met. Proton APBI should begin within 10 weeks of lumpectomy or re-excision of margins.

Image Guidance for IGRT: Orthogonal kilovoltage (KV) images matched to fiducial markers placed at the time of lumpectomy should be performed to ensure reproducibility of setup prior to initiation of each treatment.

Definition of Target Volumes: The radiation oncologist will identify and outline the tumor bed by noting contrasting areas of density and architectural distortion as well as the presence of clips or fiducials in the breast. Information from the surgical report, mammography, MRI and other available imaging should be taken into account when available. A margin of 1cm will then be added to the tumor bed in order to create the CTV. The CTV will be limited, however, to 5mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). The proton PTV expansion will be defined initially as a 5mm expansion of the CTV to compensate for variability of set-up and any motion of the breast during treatment but will be expanded or contracted as necessary to maintain a 3.0%/3mm robustness such that the CTV coverage of 95% of the volume gets at least 95% of the dose. The border of this proton PTV will be limited to within 5mm below the skin surface and posteriorly to the anterior surface of the ribs. It is preferred that the PTV does not exceed 30% of the breast volume. If it does, a patient could potentially wait for 1-3 weeks until the seroma decreases in size and another planning session is performed.

Dose Prescription to PTV: The prescribed radiotherapy dose will be 21.9 Gy in 7.3 daily fractions (total of 3 fractions). Radiotherapy should aim to be delivered on three consecutive work days. Per protocol ≥95% of the target volume CTV should be covered by ≥95% of the prescribed dose of 21.9Gy.

Definition and Dose Limitations of Normal Tissues/Organs at Risk (OARs): The following normal tissue structures should be contoured for all patients by the physician: uninvolved normal breast, ipsilateral lung, contralateral lung, heart and skin.

<u>Uninvolved ipsilateral normal breast:</u> Includes the glandular breast tissue visualized by CT and the consensus definitions regarding “breast” from the RTOG breast atlas. The structure should be limited to 5mm from the skin surface to minimize inaccuracy of dose calculation at the skin surface. Per

protocol <35% (variation acceptable <50%) of the whole breast reference volume should receive ≥ 50% of the prescribed dose and <20% (variation acceptable <30%) of the whole breast reference volume should receive the prescribed dose.

Ipsilateral lung: May be contoured with auto-segmentation with manual verification. The volume receiving 20Gy should not exceed 2%. The volume receiving 10Gy should not exceed 5%. The volume receiving 5Gy should not exceed 10%.

Contralateral lung: The volume receiving 20Gy should be 0. The volume receiving 10Gy should be <1%. The volume receiving 5Gy should be <2%.

Heart: 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) and extending to its most inferior extent near the diaphragm. Contouring along the pericardium itself, when visible, is appropriate. The esophagus, ascending and descending aorta, and inferior vena cava should be excluded. The volume of heart receiving 1.5Gy should be less than 40%.

Skin: The maximum dose at the skin surface, defined as the most superficial 3mm of the body surface, should be reduced to as low as achievable while satisfying the other dose parameters but should not exceed 100% of prescription. If this constraint cannot be met than a different APBI technique can be considered on study.

8.0 Radiotherapy Dose Modifications Based on Adverse Events

8.1 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Radiation breaks, if necessary, should not exceed one treatment day. Radiation breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons.

8.2 Radiation Therapy Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4. A copy of the CTCAE, v. 4 can be downloaded from the CTEP web site ([redacted]).

EVENTS EXPECTED

Erythema, dry desquamation, hyper or hypopigmentation are anticipated to occur commonly. Some patients may develop moist desquamation, which usually heals within 2-3 weeks. Mild swelling of the breast or mild breast pain are also likely side effects of treatment. It is not anticipated that treatment breaks should be needed, as severe acute toxicities are extremely rare.

Transient, persistent, and occasionally symptomatic seroma formation can occur and will be monitored for during treatment and at follow-up. Telangiectasia, and chronic changes in pigmentation can also commonly be seen, as can soft tissue fibrosis.

Infection is less likely, occurring in less than 10% of patients, generally following brachytherapy.

Skin or subcutaneous toxicity requiring surgery, pneumonitis, rib fractures, or any grade 3 or greater complications including pain are uncommon after ABPI, and are expected to occur in <10% of patients

Patients will also undergo venipuncture as part of the study. Risks of that procedure include hematoma, swelling, tenderness and inflammation at the site, persistent bleeding, vasovagal response, and rarely thrombosis and infection.

Method of detection, signs and symptoms, and method of treatment will be reported for all detected toxicities

9.0 Ancillary Treatment/Supportive Care

9.1 Skin creams/ointments for the treatment of dermatitis may be used at the discretion of the treating physicians as per standard practice.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1Definitions

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 - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- Death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.
All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

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

[redacted]

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

10.22 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug 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 investigator will evaluate the event and determine the necessary follow-up and reporting required.

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

10.31 Investigator Reporting: Notifying the Mayo IRB:

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

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

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

Consider the following information to collect when developing any forms for documentation of adverse events.

Example
Information collected on the adverse event worksheet (and entered in the research database):

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

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

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

			Each	Grading scale

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	evaluation	(if not CTCAE)
Skin and Subcutaneous tissue disorders	Dermatitis Radiation	X	X	CTCAE
	Telangiectasia	X	X	See 10.1
	Breast Edema = CTCAE Vascular Lymphedema	X	X	CTCAE, BCTOS
	Superficial soft tissue Fibrosis	X	X	CTCAE
	Seroma	X	X	CTCAE
	Skin hyperpigmentation	X	X	CTCAE
	Skin hypopigmentation	X	X	CTCAE
Infections and infestations	Breast infection	X	X	CTCAE
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X	CTCAE
General disorders and administration site conditions	Non-cardiac chest pain	X	X	CTCAE

BCTOS = Breast Cancer Treatment Outcomes Scale

10.41 Grading Scale for other toxicities

Telangiectasia: Grade 0 – None; Grade 1 – 1cm2; Grade 2 – 2-4cm2; Grade 3 - >4cm2

10.5 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, internal regulatory areas, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.51 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.5 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. "Any serious adverse events will be followed up by the sentinel event reporting procedure"

10.52 Internal Data and Safety Monitoring

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis dependent on random study selection to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation

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

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

11.21 No evidence of disease (NED).

11.22 Recurrence of disease (REC). Recurrence must be confirmed by biopsy.

11.221 The site of recurrence (or failure) will also be collected and classified as local vs. regional vs. distant recurrence. The specific site of failure will also be collected as well. Moreover, if there is an IBTR, the location of the IBTR relative to the initial cancer will be documented and the IBTR will be classified according to Recht et al. as a "true recurrence/marginal miss" failure if the recurrence of the treated cancer occurs within or immediately adjacent to the primary tumor site. An "Elsewhere Failure" will be defined as an IBTR several centimeters from the primary site.

11.222 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

11.31 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 and both lateral views. Recommended framing should go from the sternal notch to the umbilicus. If possible, patients should be photographed against a solid colored background.

11.32 The Harvard Cosmesis Scale will be used to score cosmesis according to the schedule outlined in section 4.0. The patients will be assessed as one of the following:

- Excellent: treated breast nearly identical to untreated breast
- Good: Treated breast slightly different than untreated (minimal but identifiable effects of the treated breast)

- Fair: Treated breast clearly different from untreated but not seriously distorted (significant radiation effects readily observable)

- Poor: Treated breast seriously distorted (severe sequelae of breast tissue secondary to radiation effects)

A modified version of the Harvard Cosmesis Scale will also be used for patient reported assessment of cosmesis.

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

11.34 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be used for patient self-reporting of toxicities in the CTCAE.

11.35 Other Patient Reported Outcome questions (fatigue, pain, arm function etc.) included in the appendix.

12.0 Descriptive Factors

- Breast Quadrant: upper inner, upper outer, lower inner, lower outer
- AJCC Stage
- Tumor Size
- Invasive vs non-invasive

13.0 Treatment/Follow-up Decision at Evaluation of Patient

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 that complete all adjuvant treatment will then be followed during the observation phase as outlined in section 4.0.

14.0 Body Fluid Biospecimens

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

Collection Tube	**Volume to Collect per Tube (Number of Tubes to Collect)**

Collection Tube	Volume to Collect per Tube (Number of Tubes to Collect)
EDTA tubes	10 mL (1)
No additive tubes (for Serum)	10 mL (1)

All patients will undergo a blood draw at baseline and following the final administered fraction of radiotherapy. Label specimen tube(s) with patient ID number, time and date blood is drawn.

14.2 BAP will process and store specimens per standard operating procedures.

14.3 Bloods will be collected prospectively and stored until funding sources have been secured to investigate exploratory analyses described in section 16.7

15.0 Drug Information

Not Applicable

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a single arm phase II study evaluating the rate of adverse cosmesis (defined as fair or poor cosmesis) at 3 years, compared to baseline, of 3 fraction accelerated APBI. For the analysis of the primary endpoint, patients will be pooled across the three treatment techniques (photon, proton, and brachytherapy) as was done in the the NSABP B-39/RTOG 0413 national multi-institutional randomized control trial comparing APBI with WBI. The three techniques utilized are recognized as standard options for the delivery of APBI, and there is no evidence that any technique is superior to any other with commonly used dose and fractionation regimens.[4] The primary endpoint is the difference from baseline in the percentage of patients with adverse cosmesis (fair or poor cosmesis) at 3 years. The intent is to determine whether the difference of adverse comesis rate is acceptable. Of interest is whether the 3 fraction accelerated APBI results in an unacceptable increase in the adverse cosmesis rate at the end of 3 years, compared to baseline. If it does not, then the 3 fraction accelerated APBI will be recommended for further study. If the change in adverse cosmesis rate is found to be unacceptable, then the recommendation would be to do no further studies of the 3 fraction accelerated APBI. In addition to adverse cosmesis, this study will assess many additional secondary endpoints including IBTR (both invasive and non-invasive IBTRs will be considered), acute and late toxicity profile, quality of life measures, and translational studies.

16.2 Primary Endpoint: The primary endpoint is the percentage difference in patients with adverse cosmesis (fair or poor cosmesis) at 3 years compared to baseline. Cosmesis will be assessed by a trained nurse provider using the Harvard Cosmesis Scale.

All patients meeting the eligibility criteria who have signed a consent form, and begun treatment will be considered evaluable for the primary endpoint.

16.3 Secondary Endpoints: The secondary aims of this study are to characterize acute and late adverse events, assess patient self-reported and panel-reported cosmesis, IBTR rate, and quality of life as well as exploratory comparisons of cosmesis, toxicity, and IBTR rate between the 3 techniques. In addition, regional recurrence rates, distant recurrence rates, invasive disease-free survival, and overall survival will be estimated for each patient group treated with APBI. Blood will be collected for future studies in order to examine molecular and genomic predictors of adverse cosmesis and late toxicity.

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

- *Acute adverse events* (up to 1 month post-RT): any adverse event, regardless of attribution, that occurs in the first month post-RT.
- *Late adverse events* (up to 3 years post XRT): any adverse event that occurred after the first month post-RT and up to 3 years post-RT.
- *Patient Reported Outcomes/Quality of life:* the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be used for patient self-reporting of toxicities in the CTCAE, along with other measures of fatigue, pain, and arm function listed in the appendix.
- *Patient self-reported cosmetic outcomes:* the patient self-reported outcome will be assessed using a modified Harvard Cosmesis Scale in the Breast Cancer Treatment Outcome Scale (BCTOS).
- *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. The Panel will be blinded to treatment allocation.
- *IBTR:* this is defined as local recurrence at 3 years from trial registration as a first event. 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.
- *Distant recurrence:* metastatic cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- *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, contralateral invasive breast cancer, and second primary non-breast invasive disease.
- *Overall survival:* is defined as the time from registration to death due to any cause.

16.4 Study Sample Size, Decision Rule, and Study Duration

16.41 *Sample size*: This study requires 153 evaluable women for the primary endpoint analysis. We anticipate accruing 15 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. The maximum projected accrual is therefore 168 women, and we expect a maximum of 60 and a minimum of 40 women within each cohort (photon, proton, and brachytherapy).

16.42 *Study Decision Rule and Operating Characteristics*: Olivotto et al. previously reported interim cosmetic and toxicity results from a randomized trial comparing APBI using 3D-CRT versus WBI. In this study, the same 3DCRT dose and fractionation was used as in the previously discussed NSABP B-39/RTOG 0413 randomized controlled trial comparing 3DCRT or brachytherapy APBI with WBI. At 3 years, the percentage difference in patients with adverse cosmesis in the APBI arm compared to baseline by trained nursing assessment was 10.6%. The proposed analysis is to compute the percentage difference in patients with adverse cosmesis (fair or poor cosmesis) at 3 years compared to baseline. A one-sided 95% confidence interval (with the upper bound of the interval) was computed, by assuming the difference in adverse cosmesis rate at 3 years compared to baseline is 10%, and the distance from 10% to the upper bound of the CI is 4%. The decision rule would be of the following:

- If the upper bound of the one-sided CI for the difference of adverse cosmesis rate lies above 14%, then recommend no further investigation and conclude that there is no sufficient evidence to accept the adverse cosmesis rate of 3 fraction accelerated APBI.
- If the upper bound of the one-sided CI for the difference of adverse comesis rate lies below 14%, then recommend further investigation and conclude the increase in 3-year adverse cosmesis rate of 3 fraction accelerated APBI is potentially acceptable.

The study operating characteristics is determined as the chance of declaring that APBI warrants further study, assuming a true value for the difference in adverse cosmesis rate at 3 years compared to baseline for APBI. The table below shows the operating characteristics of this trial with 153 patients and the decision rule given above.

True increase in adverse cosmesis rate at 3 years compared to baseline	**Probability of concluding PBI warrants further study**
5%	98.4%
10%	72.8%
15%	48.6%
20%	29.8%

If the increase in APBI adverse cosmesis rate from baseline is 5.0%, there is a 98.4% chance of concluding that the APBI adverse cosmesis increase from baseline is acceptable; this drops to 72.8% if the true rate is 10%, and further drops to 49.6% if the true rate is 15%. If the increase in APBI adverse cosmesis rate from baseline at 3 years is 20% or greater, we are most likely to recommend no further investigations, and conclude that the increase in APBI adverse cosmesis rate is unacceptably high.

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.

16.43 Preliminary Analysis: The preliminary analysis is to examine whether the data from the three methods (photon, proton and brachytherapy PBI) can be combined by assessing any difference in the safety profile and baseline patient and tumor characteristics. We will conclude that the variability in the three samples is acceptable and proceed to the primary analysis if all the following conditions are met:

- The difference in rate of grade 3 toxicity between the groups is ≤10%.
- There is not a significant difference in the rate of IBTR between the groups (using pair-wise chi-squared tests with Bonferroni correction for multiple comparisons).
- The distribution of African Americans and the percentage of cytotoxic chemotherapy use between the groups is not significantly different (using pair-wise chi-squared tests with Bonferroni correction for multiple comparisons).
- The distribution of age between the groups is not significantly different (p-value ≥ 0.05 using a Tukey's test). The difference in age in 10 increments (50-59, 60-69, and ≤ 70) will be reported.
- Tumor size will be dichotomized to two categories (≤ 1cm vs 1-2cm). The percentage of larger tumor (1-2cm) between the groups is not significantly different (using pair-wise chi-squared tests with Bonferroni correction).

If any of the above conditions are failed to be met, we will only report the safety and efficacy of each individual arm as secondary and exploratory endpoints.

16.44 *Accrual time and Study duration*: Since 10/1/2012 patients have been treated with brachytherapy APBI using an 8 or 10 fraction regimen and prospectively followed as part of a clinical registry at the Mayo Clinic in Rochester, MN. Patient interest in the procedure has steadily increased, and in the last 3 months, 13 patients have been treated (median 4.3 patients per month), all of whom would be eligible for this study. A similar to increased level of accrual ofbrachytherapy patients is anticipated during the course of this study as familiarity with this procedure amongst surgical and radiation oncology providers rises. With the addition of the photon APBI alternative for patients, we anticipate an accrual rate of 5 patients per month for the first year until the opening of

the Mayo proton facility, after which an accrual of 8 patients per month is anticipated. Therefore, the accrual period for this study is expected to be approximately 3 years. We plan to open this study at the Mayo Clinic in Scottsdale and Jacksonville which will further enhance accrual. Final analysis may begin approximately 5 years after the trial begins, i.e. as soon as the last patient registered has been observed for at least 24 months. A maximum of 60 patients and a minimum of 40 patients will be enrolled per treatment arm.

16.5 Primary Analysis: The primary analysis will be to estimate the percentage difference in patients with adverse cosmesis (fair or poor cosmesis) at 3 years compared to baseline. All patients meeting the eligibility criteria who have signed a consent form and started treatment will be in the primary analysis. The percentage difference in patients with adverse cosmesis will be estimated using a binomial estimator (number of women who had an adverse cosmesis event at 3 years minus number of women who had an adverse cosmesis event at baseline, and then divided by total number of women in the primary analysis) and a 95% exact binomial confidence interval. As mentioned above, the following decisions will be made based on the 95% CI:

- ***The upper bound of the 95% CI lies below 14%***: APBI adverse cosmesis is acceptable.
- ***The upper bound of the 95% CI lies above 14%***: No evidence to show that APBI adverse cosmesis is acceptable.

16.6 Secondary Analyses

16.61 *Acute adverse events (up to 90 days post-RT)*: All patients who were registered to the study and started treatment will be included in the acute adverse event analysis. An acute adverse event is an AE, regardless of attribution, that occurs up to 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. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.62 *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 occurs at least 90 days post-RT and up to 3 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. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Prior APBI reports have suggested rates of grade 3 or 4 toxicity to be $\leq$10%.[18,47,55,56]

16.63 *Quality of life*: The QOL measurements will be summarized at each time point as mean ± SD and median (minimum value, maximum value). Changes in the QOL measurements from baseline will be determined at each follow-up measurement. These will be displayed as spaghetti plots. The assessment of the changes at each time point will be done with a paired t-test or Wilcoxon signed rank test, whichever is appropriate.

16.64 *Cosmesis*: The values of the cosmesis instruments (patient self-reported and panel-assessed) will be summarized with the frequencies of fair or poor cosmesis events at baseline and 3 years, and the difference at 3 years, as well as their relative exact binomial confidence intervals.

16.65 *IBTR incidence*: The IBTR cumulative incidence will be estimated using a competing risks method (Gooley et al.). The competing risks will be regional/distant breast cancer recurrence and death.

16.66 *Regional recurrence incidence*: The regional breast cancer recurrence cumulative incidence will be estimated using a competing risks method (Gooley et al.). The competing risks will be local/distant breast cancer recurrence and death.

16.67 *Distant recurrence incidence*: The distant breast cancer recurrence cumulative incidence will be estimated using a competing risks method (Gooley et al.). The competing risks will be local/regional breast cancer recurrence and death.

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

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

16.7 Exploratory Analyses: Exploratory comparisons of the local control, acute and late adverse events, quality of life, and cosmesis among the three radiation regimens will be made. Comparisons of categorical variables will be done with a chi-square test or Fisher's exact test, whichever is appropriate. Comparisons of continuous variables will be done with an ANOVA or Kruskal-Wallis test, whichever is appropriate. Meaurements over time (i.e. QOL) will be summarized as area under the curve (AUC) and these values will be analyzed as continuous outcomes. All tests will be two-sided and a p-value less than 0.05 will be considered significant. No adjustments will be made for multiple comparisons.

Correlative Science: Adverse cosmesis has been reported to be significantly increased in prior studies of APBI, yet predictors of adverse cosmesis are poorly understood.[47,48] If a subset of patients at high risk of complications could be identified, their treatment could be personalized or they could be counseled to pursue other therapeutic options altogether. In the setting of WBI, factors previously reported to be associated with worsened cosmesis include inferior tumor location, large excision volume, the presence of postoperative breast complications, higher dose (including radiotherapy boost), inhomogeneity, and use of concurrent chemotherapy.[57-59] In order to begin identifying predictive factors for fair and poor cosmesis following 3 fraction APBI we will analyze clinical and dose volume parameters correlated with increased risk.

It is generally believed that clinical and dose-volume factors alone are not sufficient to explain the patient to patient variation in late toxicity following a course of radiation therapy.[60,61] Indeed, patient specific histologic and genomic features may also be of significant importance in determing variation in normal tissue radiation response and risk of adverse cosmesis. There is considerable variation in sensitivity to radiation across tissue type.[62] Therefore, as a preliminary step in considering biomarkers of risk of adverse cosmesis, we will analyze non-cancerous breast tissue from the lumpectomy specimen. In particular, we will determine whether the ratio of fat, connective tissue, and epithelium of the normal breast tissue away from the tumor is predictive of adverse cosmesis following APBI. A number of studies have correlated breast histopathological findings with mammography.[63-65] Mammographic density is largely determined by the relative amount of fat, connective tissue, and epithelium. If a correlation is made between histologic make-up of the normal breast parenchyma and adverse cosmesis, we will explore whether patients can also be stratificatied based on preoperative mammographic density, as determined by the qualitative Breast Imaging Reporting and Data System (BI-RADS) method for density assessment developed by the American College of Radiology.

Cytokines and growth factors are involved in the radiation response and tissue remodelling and may serve as predictive factors for normal tissue damage. For example, levels of transforming growth factor β1 (TGF- β1) vary substantially between individuals and has previously been associated with radiation fibrosis in early-stage breast cancer patients.[66] TGF- β1 is a multi-functional cytokine that attracts fibroblasts and stimulates collagen production.[67] Although basal levels may be important, expression levels of this protein are induced within an hour or less after exposure to ionizing radiation and therefore TGF- β1 induction following radiation may be a better functional marker of an elevated fibrotic response.[68,69] Therefore, blood will be drawn pre-treatment and on the last day of radiotherapy 1 hour following the final fraction. The pre and post radiotherapy levels of TGF- β1 and other proteins in the fibrotic response will be compared and association with adverse cosmesis following APBI will be determined.

Mounting evidence also suggests that genetic variation may play an important role in determining susceptibility to radiation toxicity.[70] Radiogenomics is an emerging field aimed at studying genetic differences associated with variability in the effectiveness and toxicity of radiation.[61] We plan to use a candidate gene approach[61] to investigate the association of single nucleotide polymorphisms (SNPs), previously correlated with radiation normal tissue toxicity, with adverse cosmesis following 3 fraction APBI. For example, in addition to TGF- β1, SNPs in the XRCC1 (codon 241) and XRCC1 (codon 399) genes, the protein products of which function in the DNA repair pathways of based excision repair and homologous recombination, respectively, have been correlated with increased risk of subcutaneous fibrosis following breast cancer radiotherapy. [redacted] laboratory at the Mayo Clinic has used a genome-wide association approach in human lymphoblastoid cell lines to identify radiation response biomarkers. C13orf34, MAD2L1, PLK4, TPD52, and DEPDC1B were identified and functionally validated as modifiers of radiation response. These promising findings, however, require further clinical validation.[61,71]

The final design of these future genomic and proteomic studies will depend on the event rate observed in the trial, cost and state of technology at the time of per protocol cosmetic evaluation of all patients enrolled. They may occur as part of a meta-analyses of patients treated with hypofractionated breast cancer radiotherapy from other institutions.

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

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 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 5 years 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 followed for at least 3 years.

16.9 Data & Safety Monitoring

16.91 The principal investigator(s) and the study statistician will review the study at least every quarter to identify accrual, adverse events, 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.

16.92 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. The following rule will be evaluated for each arm separately.

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 3 or more patients in the first 15 treated patients experience a grade 3 or higher adverse event, besides acute dermatitis, that is at least possibly related to treatment within 90 days post treatment..
- After the first 15 patients have been treated: if $\geq 20\%$ of all patients experience a grade 3 or higher adverse event, besides acute dermatitis, that is at least possibly related to treatment within 90 days post treatment.

Similarly, within each of the modalities (photon, proton, or brachytherapy APBI), accrual will be suspended for that modality:

- If 6 or more patients in the first 30 treated patients experience a grade 3 or higher adverse event at least possibly related to treatment at any time after 6 months following completion of the protocol treatment.
- After the first 30 patients have been treated: if $\geq 20\%$ of all patients experience a grade 3 or higher adverse event at least possibly related to

treatment at any time after 6 months following the completion of protocol 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.

16.10 Inclusion of Women and Minorities

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

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

16.13 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 100% of patients will be women.

17.0 Pathology Considerations/Tissue Biospecimens:

17.1 Summary Table of Research Tissue Specimens to be collected for this Protocol

	Mandatory or Optional	**Type of Tissue to Collect**	**Block, Slides, Core, etc. (# of each to submit)**	**Process at Site? (Yes or No)**	**Temperature Conditions for Storage/Shipping**
Diagnostic	Optional*	Formalin Fixed	2 H&E slides	Yes	Ambient
Lumpectomy	Mandatory	Formalin Fixed	2 H&E slides	Yes	Ambient

*If no tissue available from lumpectomy surgery, obtain diagnostic slides

17.2 Blocks from the diagnostic surgery (when applicable) and the clinical lumpectomy surgery, that have been identified by [redacted] lab, will be requested from Tissue Registry and slides cut (1 slide from the tumor/tumor vicinity and 1 slide distant from the tumor). Slides will be clearly labeled (see below for slide label) and forwarded to [redacted] office for quantification of the ratio of fat, connective tissue, and epithelium of the normal breast tissue away from the tumor. If the patient underwent surgical resection at an outside institution, slides and blocks will be viewed and cut the same manner as above and sent to [redacted]

Aperio imaging will be done on the H&E slide that is distant from the tumor and archived electronically.

Slide Label: Protocol Number

[redacted]

Send slides with study identifier to:

[redacted]

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 *6 months from accrual
Patient Eligibility	
Demographics	
On-Study	
Adverse Events- Baseline	
Specimen Submission: Blood (Baseline)	
Specimen Submission: Tissue (Baseline)*	
Patient Status: Baseline	
Patient Assessment	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	Post Radiation (cycle 2)	Observation[3] (subsequent cycles)
Radiation Treatment Form	X	
Patient Assessment	X	X
Specimen Submission: Blood (post rad tx)	X	

CRF	Post Radiation (cycle 2)	Observation[3] (subsequent cycles)
Adverse Events Solicited	X	X
Adverse Events Other	X[1]	X[1]
Off Treatment: Submit once per patient	X[1]	
Patient Status form	X	X
Adverse Events: Late		X[1]
Specimen Submission: Tissue (Recurrence)		X[1]
Consent Withdrawal form	X[1]	X[1]
Lost to Follow-up	X[1]	X[1]
Breast/Chest Wall Radiotherapy Questionnaire	X	X

1. When applicable
2. Survey will need to be entered manually if has not alternately been scanned or entered electronically
3. Observation (Active monitoring phase): 12 weeks (+/- 4 weeks), 12 months (+/- 30 days), annually for 5 years (+/-3 months). If a patient is still alive 5 years after registration, no further follow-up is required.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]	
	12 months	Annually for 5 years[2]
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X	X

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. If patient has a recurrence prior to being off radiation therapy for 5 years, continue to follow yearly.

18.2 Data Handling and Record Keeping

18.21 Confidentiality

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

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

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

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

The Medidata Rave database access model is role based and fully auditable at the study, form, and field levels. Data will be de-identified whenever possible and the ability to update will be limited to necessary staff. **Access will be managed by the Mayo CTMS Service and Solution Center, under a controlled and monitored access request system.** Medidata's platform specifically supports Electronic Record and Electronic Signature (ER/ES) requirements, including US 21 CFR part 11.

18.22 Source Documents

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

18.23 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction. CRF's will be built and managed in Rave data capture system.

18.24 Data Management

All data will be entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms will be automatically rolled out based on a predetermined, and visit based schedule to improve study staff workflow and data quality. Data will be exported nightly to a secure FTP for analysis and reporting.

18.26 Data Quality Assurance and Clarification Process

Each eCRF will contain edit checks and custom functions to ensure the highest possible data quality. Only necessary eCRF's will be available for data entry to reduce the

possibility of erroneous entry.

The edit checks and custom functions on the eCRF's will trigger queries requesting the attention of appropriate study staff. The fields will be marked in pink to allow study staff to quickly identify the data fields that require attention or actions. Additionally, secure email notifications will be sent for adverse event tracking and monitoring.

19.0 Study Finances

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.

21.0 References

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* Oct 17 2002;347(16):1233-1241.

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Appendices

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

Radiation Therapy Quality Control Guidelines

1. Tumor Volume Coverage
   a. No deviation -- coverage + $\leq$ 1 cm of specified.
   b. Minor deviation -- coverage + > 1 to 2 cm of specified or failure to cover tumor volume + $\geq$ 1/2 specified margin.
   c. Major deviation -- > 2 cm of specified or no CT and/or MRI scans available to assess treatment volume appropriateness (if not initially available should be requested) or failure to cover the target (tumor or tumor + edema) as defined in the protocol.

2. Isodoses - initial volume isodose plots are required on a minimum of three contours; one at central axis (CA), one superior to CA (2 cm below the superior field edge) and one inferior to CA (2 cm above the inferior field edge). Boost volume isodose plot required at CA.
   a. No deviation -- isodoses submitted as required, and inhomogeneity across the target volume shall be no greater than $\pm$ 5%.
   *b. Minor deviation -- isodose information incomplete or inhomogeneity across the target volume > 5 but $\leq$ 10%.
   *c. Major deviation -- no isodoses submitted or inhomogeneity across the target volume > 10%.

   * Deviations would occur only if isodose information is incomplete or not submitted after there has been a request to submit complete isodose information.

3. Normal Tissues
   Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity that would interfere with the scientific aims of the protocol. A major deviation will result when normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study.

4. Other parameters: (dose per fraction, total dose, overall treatment time and portal films).
   a. No deviation -- +/- < 5% of protocol specification.
   b. Minor deviation -- +/- > 5% to 10% of protocol specification.
   c. Major deviation -- +/- > 10% of protocol specification or incomplete data (i.e. no portal or sim films, etc.) available for review (after additional request has been made).

5. Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.