A Pilot Study of
Four-Dimensional Conformal IMAGE GUIDED Accelerated Partial Breast Irradiation
IN THE TREATMENT OF
STAGE 0 and I BREAST CARCINOMA

Principal Investigator	Suzanne Evans, M.D., M.P.H.
Radiation Therapy	Susan Higgins, M.D. Lynn Wilson, M.D., M.P.H.
Surgery	Don Lannin, M.D. Nina Horowitz, M.D. Anees Chagpar, M.D. MSc, MA, MPH, FRCS(C), FACS Brigid Killelea, M.D.
Physics	Jay Chen, Ph.D. John Kim, C.M.D.
Statistics	Daniel Zelterman, Ph.D.
Clinical Research Nurse	Jeannie Kluytenaar, R.N., B.S.N.
Clinical Research Assistant	Kira Pavlik

Version	9
Version Date	September 5, 2014

A Pilot Study OF
Four-Dimensional Conformal IMAGE GUIDED Accelerated Partial Breast Irradiation
IN THE TREATMENT OF
STAGE 0 and I BREAST CARCINOMA
SCHEMA

Patients with Stage 0, or I Breast Cancer Resected by Lumpectomy
Tumor Size ≤ 2.0 cm
No Histologically Positive Nodes
Cavity and cavity to breast ratio suitable to 4D CRTAPBI

↓

Enrollment into Study

↓

4D treatment planning CT scan
Generation of Four-Dimensional Conformal Partial Breast Plan
Treatment with 4DCRT to 38.5 Gy in 3.85 Gy fractions delivered BID with daily image guidance and a minimum six hours between fractions

↓

Follow up evaluation of side effects and cosmesis ongoing for three years from completion of treatment

Chemotherapy or Hormonal Therapy

Chemotherapy or Hormonal Therapy may be given at the discretion of the treating physician, but cytotoxic chemotherapy is not to be started until at least 2 weeks post radiation. Hormonal therapy can be started at once.

ELIGIBILITY:

-Stage 0 or I breast cancer; if stage I tumor must be ≤ 2cm and node negative (E.G. T0 tumors not allowed)
-The tumor can be histologically DCIS (also held to <2cm in size), or invasive ductal or lobular carcinoma of the breast. In patients with both invasive and in situ carcinoma, they should be <2cm individually, but may be more than 2cm in aggregate (i.e. a patient with a 1.5 cm infiltrating ductal carcinoma in a background of 1 cm of dcis would be eligible).
-Patients with invasive cancer must have axillary staging by a) SNB alone (if SN is negative).
-Unifocal breast cancer (single focus which can be encompassed by one lumpectomy).
-Negative surgical margins greater than or equal to 2mm
-No collagen vascular disease
-No known unresected residual carcinoma; no suspicious microcalcifications.
-No prior malignancy (≤ 2 years prior to enrollment in study) except nonmelanoma skin cancer, in situ melanomatic skin cancer, or CIS of the cervix or colon.
-Negative pregnancy test for women of childbearing age.
-Time interval from last breast surgical procedure to simulation is ≤ 8 weeks.
-Signed study-specific consent form.
-Patients who have undergone any oncoplastic resection involving significant manipulation of the tumor bed are not eligible.
-Patient must have a well-defined seroma cavity (see Appendix VIII) with Cavity visualization score (CVS) of ≥3 or at least 4 surgical clips geometrically defining the cavity in order to be eligible. NOTE: surgical clips are to be used to delineate the cavity as a primary function, whereas the gold fiducial markers can be used for cavity demarcation and also for daily set up with kilovoltage imaging.
-Patient must not have received radiation to the same breast or in the thorax overlapping the treatment field.
-Patients must be 50 years of age or older.
-Patients must not have had neoadjuvant chemotherapy or hormonal therapy prior to surgery.
-Patients must not have a post-operative seroma which, in the opinion of the treating radiation oncologist, is changing volume in a dynamic fashion as this will prevent accurate targeting.
-Patients who are tested BRCA1/2 positive are ineligible due to the association with multifocality.

INDEX

and patient satisfaction with radiation treatment has been added to the protocol.

2.0 STUDY AIMS

A. Primary Aim

The purpose of this study is to evaluate the feasibility of using image guidance and four-dimensional computed tomography to reduce the volume of non target breast tissue that is treated with accelerated partial breast irradiation via the external beam technique.

This is a pilot study to evaluate the feasibility of using 4DCT and daily image guidance in APBI to decrease set up error and individualize planning target volumes to limit the non-target breast tissue dose. The two specific breast constraints which shall be decreased are the V50 (percent volume of breast receiving 50% of the prescribed dose) and the V100 (percent volume of breast receiving 100% of the prescribed dose). The goal will be to decrease these to 45% and 23.5%, respectively, which is down 33% from the NSABP B39 standard of 60% and 35%. These are similar to the constraints which will be suggested by Dr. Jaroslaw Hepel (V50<40%, V100 <20%, to be presented at

ASTRO 2011, Miami Beach, oral presentation-- via personal communication). Patients in his series that followed these constraints have no grade 3 or higher subcutaneous toxicity.

This study will be considered a success if >50% of patients enrolled are able to meet the dosimetric constraints on the breast (V50 <45% and V100 <23.5%). If this occurs, a phase II study approval will be sought.

B. Secondary Aims

To track MD rated cosmesis and toxicity and patient rated cosmesis over time, with an expectation that less than 15% of patients starting at a good or excellent baseline will deteriorate to a poor cosmetic outcome. Individual dosimetric parameters will be correlated with cosmetic outcomes and any other toxicity outcome.

To track patient reported breast pain and patient satisfaction with the radiation treatment delivered.

3.0 ENDPOINTS

A. To achieve more rigid dose constraints on normal non-target breast tissue by using 4D CT and daily image guidance.

B. Measure subcutaneous fibrosis toxicity, cosmesis, breast pain, and patient satisfaction the first 3 years following treatment with 4D conformal accelerated partial breast radiation with more rigid dose constraints.

C. Collection of information of treatment parameters in order to define parameters most predictive of cosmesis, skin, subcutaneous, breast pain, or other toxicity.

D. Duration of Study: Until accrual and treatment of 60 patients is complete with three years follow-up after treatment completion, which is expected to take 4 to 7 years.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

Women who satisfy all of the following conditions are the only patients who will be eligible for this study.

1. The patient must consent to be in the study and must have a signed an approved consent form conforming with institutional guidelines.

2. Patient must be ≥ 50 years old.

3. The patient should have a life expectancy of at least two years with a karnofsky performance status ≥70.

4. The patient must have stage 0 or I breast cancer.

5. On histological examination, the tumor must be DCIS or invasive adenocarcinoma of the breast.

6. Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (≥2mm, DCIS and invasive). Re-excision of surgical margins is permitted.

7. Gross disease must be unifocal with pathologic (invasive and/or DCIS) tumor size 2 cm or less. (Patients with microscopic multifocality are eligible as long as total pathologic tumor size is 2 cm or less.) Patients with both DCIS and invasive cancer may have more than 2 cm of disease in aggregate, provided they are both individually < 2cm.

8. Patients with invasive breast cancer are required to have axillary staging which can include sentinel node biopsy alone (if negative), sentinel node biopsy followed by axillary dissection or sampling with a minimum total of 6 axillary nodes or axillary dissection alone (with a minimum of 6 axillary nodes). Axillary staging is NOT required for patients with DCIS.

9. The patient must have simulation within 8 weeks/56 days of the final surgery for their breast cancer (lumpectomy, re-excision of margins, or axillary staging procedure).

10. Patients with a history of non-ipsilateral breast malignancies are eligible if they have been disease-free for 2 or more years prior to enrollment. Patients with the following cancers are eligible even if diagnosed and treated within the past 2 years: carcinoma in situ of the cervix, colon, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.

11. Chemotherapy is permitted if planned for ≥ 2 weeks after radiation.

12. Urine pregnancy test must be performed and be negative on all women younger than 60 who have not had a tubal ligation, oophorectomy, or hysterectomy.

13. Separate incisions for the lumpectomy and sentinel node biopsy should be present. Use of only one incision will typically result in a contiguous cavity with the tumor bed and the sentinel node sampling, and inability of the radiation oncologist to delineate the tumor bed from the sentinel node bed.

14. The patient must have a cavity which is able to be targeted with external beam APBI, either through surgical clip placement, or CVS 3 or higher. The cavity to whole breast ratio must be 30% or less.

15. Eligible patients have not received prior thoracic radiation.

16. Eligible patients have not received pre-operative hormonal or chemotherapy.

4.2 Exclusion Criteria

1. Men are not eligible for this study as men are not breast conservation candidates.

2. T0, T2 (>2.0 cm), T3, node positive, stage III or IV breast cancer.

3. Any positive axillary nodes.

4. Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular or internal mammary nodes, unless biopsy proven to be negative for tumor.

5. Suspicious microcalcifications, densities or palpable abnormalities in either breast unless biopsy proven to be benign.

6. Non-epithelial breast malignancies such as sarcoma or lymphoma.

7. Proven multicentric carcinoma in more than one quadrant or separated by more than 2 centimeters.

8. Paget's disease of the nipple.

9. History of invasive breast cancer or DCIS in the same breast.

10. Surgical margins that cannot be microscopically assessed or are less than 2 mm.

11. Collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis or scleroderma.

12. Pregnancy or lactation at the time of proposed radiation. Women of reproductive potential must agree to use an effective non-hormonal method of contraception during therapy.

13. Psychiatric or addictive disorders or other conditions that, in the opinion of the treating physician, would preclude the patient from meeting the study requirements.

14. Patients with coexisting medical conditions in whom life expectancy is < 2 years.

15. Patients with skin involvement, regardless of tumor size.

16. Patients with a prior diagnosis of ipsilateral breast cancer are ineligible.

17. Patients who are tested BRCA1/2 positive are ineligible due to the association with multifocality.

5.0 PRETREATMENT EVALUATIONS

1. History including family history of breast carcinoma and method of detection of the breast tumor (clinical, mammographic, or both).

2. Physical examination with the location and palpable size of the tumor in cm.

3. Mammogram of both breasts.

4. CBC, platelets, alkaline phosphatase, SGOT, serum calcium within the past 6 months.

5. Bone scan if the alkaline phosphatase is elevated 1.5 times the upper limit of normal (ULN) and/or the patient complains of bone pain or has other symptoms possibly associated with skeletal metastasis.

6. Evaluation of liver by CT if the liver function blood tests are elevated 1.5 times the ULN.

7. Chest X ray if new or concerning pulmonary symptoms are present.

8. An excision cavity amenable for 4D CRT PBI, defined as a CVS greater than or equal to 3 **OR** the presence of 4 or more surgical clips marking the cavity. At the discretion of the treating physician, a pre-enrollment CT scan may be taken to determine the ability to visualize the cavity, as well as to calculate the cavity to whole breast ratio (≤30%). This may be omitted in patients with surgical clip placement documented in the operative note or through personal communication with the surgeon, or in women who clinically have ample breast tissue.

9. 4 dimensional CT scan for treatment planning.

6.0 4D CONFORMAL EXTERNAL BEAM PBI

Please note:
• Boosts are not permitted with delivery of PBI.
• Electrons are not allowed.

A. 4D-CRT Treatment Planning

The pre-enrollment CT data set (used to determine cavity visualization score for protocol eligibility, IF PERFORMED) cannot be used for 4D-CRT treatment planning. A separate 4D CT scan is to be obtained. Treatment will be delivered only to the planning target volume (PTV) using 3-dimensional conformal fields. Field within a field technique to improve dosimetric coverage can be utilized; however, the use of dynamic multi-leaf collimator (MLC) to facilitate the delivery of intensity-modulated distributions derived from constraints-based computer optimization (i.e., inverse planning) is excluded. Field arrangements are at the discretion of the physician and will be determined by 4D-CRT treatment planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the planning target volume for evaluation (PTV_EVAL) and critical normal tissues. **Dose calculations with tissue inhomogeneity correction must be used**.

B. Imaging

A treatment planning 4D CT scan with the patient in a supine position will be required. The CT should start at or above the mandible and extend several cm below the inframammary fold (including the entire lung). A CT scan thickness of ≤ 0.5 cm should be employed. Cases will only be acceptable if the following structures are contoured: excision cavity, clinical target volume (CTV), ITV, PTV, PTV_EVAL, skin, ipsilateral and contralateral breast reference volumes, thyroid, ipsilateral and contralateral lung, and heart. The chin, shoulders and contralateral breast should be included in the scan. The target structures and normal tissue structures must be outlined on all CT slices. The extent of normal tissue contouring is necessary with 4D-CRT to guide beam arrangement and normal tissue avoidance.

C. Target Volumes

The excision cavity will be outlined based either on clear visualization on CT (defined as a CVS greater than or equal to 3) or, if placed, with the help of surgical clips. If the excision cavity cannot be clearly delineated, the patient is not eligible for study participation. This score will be determined by the treating physician at the time of simulation. A four dimensional CT will be used to capture the excision cavity throughout its full respiratory excursion, and this volume will be called the internal target volume (ITV). The clinical target volume (CTV) will be defined by uniformly expanding the ITV by 15 mm. However, the CTV 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 CTV should never be smaller than the ITV ("Boolean operator" CTV OR ITV may be necessary). Questions about the CTV should be addressed to Dr. Suzanne Evans. Treatment set up variation will be all but eliminated with cone beam CT/kv imaging, and as such, only 2mm additional margin is placed upon the CTV to form the planning target volume (PTV). The PTV is saved and is used to generate the beam aperture with an additional margin to take penumbra into account.

****In patients with a very posterior or very anterior cavity, it might be possible that the CTV is shaved off the pectoralis or skin such that the ptv becomes very close (2mm) to the ITV. In all cases, the PTV should be no closer to the ITV than 5mm. In eclipse, this can be achieved by creating a structure of ITV + 5mm margin, and performing a Boolean operator to PTV ("itv + 5mm or PTV"). The PTV should never be less than 5mm from the ITV.*****

Since a substantial part of the PTV often extends outside the patient (especially for superficial cavities), the PTV is then copied to a PTV_EVAL, which is edited. This PTV_EVAL is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding (if applicable) the PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung). This PTV_EVAL is the structure used for DVH constraints and analysis. **This PTV_EVAL CANNOT be used for beam aperture generation.**

D. Beam Angles/Treatment Position

The radiation oncologist may choose whatever beam arrangement and number of beams they desire, as long as the necessary dose volume constraints mentioned below can be met. Typically, a 3, 4, or 5-field non-coplanar beam arrangement utilizing high-energy photons can be used. No plan will be considered acceptable if any of the beams are directed towards critical normal structures: heart, lung, contralateral breast. Patients should be treated in the supine position in most cases, although prone positioning is allowed at the discretion of the treating physician with the assent of Dr. Suzanne Evans. **Bolus to improve anterior target coverage should not be used.**

E. Design of Beam Arrangements

Suggested beam arrangements include noncoplanar 3-, 4- and 5-field beam arrangements using 6-MV photons. These arrangements use fields that approximate breast tangents within a 10°-20° steeper gantry angle for the medial beams to maximally spare breast tissue and couch angles of 15°-70°. The beam arrangement is arrived at in a similar manner for both. First, the isocenter is placed in the center of the PTV. The procedure used to set up the 4-field technique, consisting of a left anterior superior-to-inferior oblique (Lt ASIO), left anterior inferior-to-superior oblique (Lt AISO), right anterior inferior-to-superior oblique (Rt AISO), and right posterior superior-to-

inferior oblique (Rt PSIO) for a right breast lesion is described. First, 3 medial tangents (couch angle of 0° for 2 beams and 180° for 1 beam) and 1 lateral tangent (couch angle of 0°) are constructed. Typically, the medial tangents have a 10°-20° steeper gantry angle than whole breast tangents to spare more breast tissue. The lateral tangent may also have a slightly shallower gantry angle to spare breast tissue, provided that it does not exit through the contralateral breast. Next, couch angles are applied to each beam. Typical couch angles for the 3 anterior oblique fields are 35°-45° from a transverse plane. However, for the Rt AISO beam, particular care should be taken to ensure that the field exited superior to the heart. The couch angle used for the posterior oblique field is usually only 10°-20° to avoid entering through the ipsilateral arm, as well as collision problems with the gantry head and treatment couch. The 5-field technique is usually used for left-sided lesions and consists of Rt ASIO, Rt lateral, Rt AISO, Lt PSIO, and Lt PISO beams. The primary difference that makes this technique better suited for left-sided lesions is the elimination of the Lt AISO beam that would exit through the heart. The tradeoff is a larger volume of normal breast tissue irradiated. Each field typically has a universal 60° wedge in place for part of the treatment time. The heel of the wedge was directed anteriorly for all fields. The field edge is 5 mm beyond the PTV to account for penumbra. (Baglan KL, Sharpe SB, Jaffray D, et al. Accelerated partial breast irradiation using 3D conformal radiation therapy [3D-CRT]. Int J Radiat Oncol Biol Phys. 55:302-311, 2003.)

F. Dose Prescription and Delivery

• 4D-CRT will begin within 56 days of lumpectomy or re-excision of margins and within 6 weeks of study entry.
• A total of 38.5 Gy will be prescribed to the ICRU 50 reference point dose (usually isocenter). Two fractions per day, each of 3.85 Gy, separated by at least 6 hours, given on 5 treatment days (over a period of 5 to 10 days), will sum to 10 fractions and 38.5 Gy.

G. Dose Limitations for Normal Tissues

• **Uninvolved normal breast**: Ideally, < 45% of the whole breast reference volume should receive ≥ 50% of the prescribed dose and < 23.5% of the whole breast reference volume should receive the prescribed dose. However, a treatment plan will be considered acceptable if <60% of the whole breast reference volume receives ≥ 50% of the prescribed dose and <35% of the whole breast reference volume receives the prescribed dose (as done in in NSABP B39). Plans which exceed these parameters (V50 >60% or V100 >35%) must be evaluated by Dr. Suzanne Evans prior to approval by the treating physician. For these calculations, the whole breast reference volume is defined as per Appendix VIII.

• **Contralateral breast:** The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive < 3% of the prescribed dose to any point.

• **Ipsilateral lung:** < 15% of the lung can receive 30% of the prescribed dose.

• **Contralateral lung**: < 15% of the lung can receive 5% of the prescribed dose.

• **Heart (right-sided lesions):** < 5% of the heart should receive 5% of the prescribed dose.

• **Heart (left-sided lesions):** The volume of the heart receiving 5% of the prescribed dose (V5) should be less than 40%.

Thyroid: maximum point dose of 3% of the prescribed dose.

H. Treatment Verification

Imaging dose for cone beam CT and kv imaging will be measured for the first 5 patients, and reported to the clinical PI.

• Before first treatment

− For patients with fiducial markers placed:

Portal images of each beam and a KV orthogonal pair (typically AP and lateral) must be obtained prior to initiation of treatment. Shifts will be made based on the KV orthogonal pair. Cone Beam CT matching and kilovoltage imaging should plan to align seroma cavity and clips rather than bony structures if there is a conflict. All shifts greater than 1 mm will be made. Any concerns about what structure is to be matched will be addressed to the supervising physician. Cone beam CT will be performed at the first fraction to ensure stable clip geometry and seroma volume, and may be performed at the discretion of the supervising physician.

− For patients without fiducial markers placed:

Portal images of each beam and an orthogonal pair (typically AP and lateral) must be obtained prior to initiation of treatment. Shifts can be made based on the orthogonal pair. Following these films, cone Beam CT will be performed at the start of each treatment. Cone Beam CT matching should plan to align seroma cavity and/or clips rather than bony structures if there is a conflict. All shifts greater than 1 mm will be made. Any concerns about what structure is to be matched will be addressed to the supervising physician. **Cone beam CT imaging is to be performed on the low dose setting whenever permitted by imaging quality, and the scan should encompass the breast region only with little to no additional scan performed superior or inferior to breast tissue. Therapists are encouraged to clinically place radioopaque wires at the superior and inferior extent of breast to help plan the cone beam scan as breast tissue can be difficult to visualize on scout films**.

• Subsequent images or films

− Cone beam CT will be performed prior to each fraction in patients who do not have gold fiducial markers placed. Those patients with gold fiducials may have kilovoltage imaging with fiducial alignment or cone beam CT. Additional images may be obtained at the supervising physician's discretion. As is standard policy for all IGRT, therapists should notify the treating physician immediately with any difficulty in locating the target area.

7.0 Quality Assurance of Dose Distribution

DVHs for the PTV_EVAL, designated critical structures, and unspecified tissues will be submitted. Each treatment plan shall be judged as:

• **Acceptable:**
− Dose volume histogram analysis of the target volume confirms 90% of the prescribed dose covers ≥ 90% of the PTV_EVAL.
− Critical normal tissue DVHs within 5% specified value.
− Maximum dose does not exceed 120% of prescribed dose.
− Dose delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.

• **Unacceptable:**
− Dose volume histogram analysis of the target volume will confirm < 90% of the prescribed dose covers < 90% of the PTV_EVAL.
− Critical normal structure DVH exceeds 5% of the specified value
− Maximum dose exceeds 120% of prescribed dose.
− Dose delivered over a period of time extending greater than 10 days.

8.0 ASSESSMENT OF TOXICITY, COSMESIS, BREAST PAIN, AND SATISFACTION

The purpose of this study is to evaluate the feasibility of using image guidance and four-dimensional computed tomography to reduce the volumes of non target breast tissue that is treated with accelerated partial breast irradiation via the external beam technique. However, toxicity will be assessed and a larger trial will be planned to formally assess the presence or absence of improved cosmesis with this technique. Some patients who were originally referred to Yale-New Haven Smilow from Lawrence & Memorial (L&M) Hospital for this trial will be followed beginning 1 month after treatment at L&M because it is closer to home for them. Dr. Evans also works at Lawrence & Memorial. In these cases, Dr. Evans will be meeting with the patients for standard radiation therapy follow up and assessment of cosmesis. No treatment procedures will occur there.

A. The Breast Cancer Treatment Outcome Scale (BCTOS) will be used to assess cosmetic results using patient self-report. This brief self-report instrument has high reliability and validity, and has been used in a variety of previous studies on recovery from breast cancer treatment. The first patient-rated cosmetic evaluation will occur after informed consent but prior to completion of treatment (baseline). The BCTOS will be used to assess cosmesis at baseline, 1-year, and 3 year follow-up.

B. Treating radiation oncologist cosmesis assessment will occur at baseline, and 1 year, and 3 years post Radiation Therapy, and will be graded according to the Harvard Cosmesis Scale (Appendix V). Toxicity assessment will occur at 1 month, 3 months, 6 months, 1 year, and 3 years post Radiation Therapy, and will be graded according to RTOG.

C. Digital images (photographs) will be taken of the treated and untreated breasts, again using RTOG established protocol. For practical reasons, these digital images will only be taken at two points in time, at the 1-year and 3-year (final) assessment points. Two digital images will be taken at each of these assessment points. One will be a close up of the treated breast alone, in order to provide detailed information regarding the treatment effects, and should be taken at a 45° oblique with arms elevated over the patient's head. The second digital image will be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face, jewelry, or tattoos and framing or focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry. These digital images will then be blinded and evaluated for cosmetic results by 2 separate investigators of a different specialty (IE medical oncology, surgery, radiation oncology) for cosmetic result according to the Harvard Cosmesis scale (Appendix V). A placard with the first initial and the last 4 numbers of the medical record number and timepoint will be included in the photo (Example “A3456_1 year”).

For patients who have already passed the year 1 time point, cosmetic photos will be taken at year 3 only.

Patients enrolled prior to version 7 who decline photographs will still be followed on protocol. Patients enrolled after the implementation of version 7 will also have the option to opt out of the photographs.

D. Patients will be asked to complete a short questionnaire about breast pain and satisfaction with treatment at the 1-year and 3-year assessment points. All patients who have passed the 1-year assessment point will be mailed two copies of a consent addendum about the questionnaire as well as a copy of the questionnaire and be asked to return both documents via a pre-stamped envelope. Patients will be able to opt out of completing the questionnaire. Those who decline to complete the pain questionnaire will still be followed on protocol. Because this questionnaire is being added after some patients have already passed the 1-year assessment point, those patients will be asked to complete the survey as soon as possible after receiving it. Results will be compared to results of other studies which assessed pain in patients who had partial breast radiation. Findings will also be correlated to differences across patients in terms of radiation treatment plans and use of hormonal therapy.

9.0 SURGERY

A. In the majority of instances, it is recommended that the incision for the lumpectomy and that for the SLNB be separate. A single continuous incision for both the lumpectomy and the axillary sampling is to be avoided and will preclude inclusion on the protocol. This is likely to allow lumpectomy and axillary node sampling cavities to communicate, prohibiting targeting of lumpectomy cavity alone.

B. The cavity must be visible by CT . Placement of 4-6 surgical clips is strongly encouraged. The clips, if placed, are to be attached to the medial, lateral, anterior, posterior, superior and inferior walls of the resection cavity. ***Shaikh T, Chen T, Khan A, et al. Improvement in interobserver accuracy in delineation of the lumpectomy cavity using fiducial markers. Int J Radiat Oncol Biol Phys. 2010 Nov 15;78(4):1127-34. Epub 2010 Mar 19.).*** Closure of the resection cavity is encouraged to minimize the formation of large seromas which may make limiting non-target tissue exposure difficult.

NOTE: gold fiducial markers may be used for both cavity delineation and daily kv imaging and image guidance, whereas surgical clips serve to delineate the cavity only. Gold fiducial markers may be placed post-operatively or intraoperatively for use in image guidance. Closure of the resection cavity should be performed to limit seroma fluid accumulation and therefore minimize the target volume.

C. Oncoplastic reconstruction is not allowed.

D. If margins are positive, close (<2mm) or unknown, a re-excision is required prior to study entry.

10.0 OTHER THERAPIES

A. Hormonal therapy is allowed at any time after biopsy or lumpectomy, prior to, during or immediately after radiation, at the discretion of the patient's medical oncologist or other physicians.

B. The use of chemotherapeutic agents prior to or during radiation is not allowed.

C. Chemotherapy regimens should be started no earlier than 2 weeks after the completion of radiation.

11.0 PATHOLOGY

A. Pathology review at Yale of any specimen obtained from referring surgeons from outside institutions will be required for the purposes of this study.

B. Otherwise standard pathologic assessment from Yale will be required.

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

12.0 PRE AND POST ENROLLMENT PATIENT CALENDAR

A. Study Parameters

Assessment	Pre Rx	During Radiation Therapy	Post RX 4 weeks (+/- 2 weeks)	Post RX 3 mos. (+/- 2 weeks)	Post RX 6 mos. (+/- 2 weeks)	Post RX 1 year (+/- 6 weeks)	Post RX 3 years (+/- 6 weeks)
H&P	X		X	X	X	X[b]	X[b]
Breast exam	X		X	X	X	X[b]	X[b]
Weight	X				X	X[b]	X[b]
Height	X						
Disease status	X					X[b]	X[b]
Toxicity Assessment	X	X	X	X	X	X[b]	X[b]
Bilateral Mammogram	X					X[c]	X[c]
Chest x-ray	X[a]					X[a]	X[a]
CBC, platelets	X						
SGOT, Alk Phos	X						
Serum calcium	X						
Bone scan, Abd. CT.	X[a]						
Patient Reported Cosmesis (BCTOS)	X					X	X
MD Reported Cosmesis	X					X	X
Digital images taken of treated and untreated breasts						X[d]	X[d]
4D CT scan for planning	X						
Urine Pregnancy Test (ages 10-60, and of childbearing potential)	X						
Breast Pain Questionnaire						X[d,e]	X[d]

X to be performed routinely
X[a] if clinical symptoms or lab values warrant
X[b] as per standard practice
X[c] Bilateral mammograms will occur at least annually (+/- 6 weeks following the preceding bilateral mammogram), or as clinically indicated.

[d] If patient consents
[e] Patients who have passed the 1-year assessment point will be asked to complete the questionnaire as soon as possible.

As is standard for evaluation of radiation toxicity, patients will be followed for three years. For the first 90 days post-treatment, the RTOG acute toxicity scale will be used, and for up to three years the RTOG/EORTC late toxicity scale will be used. Any additional toxicities that do not meet the criteria for RTOG scoring will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines.

B. Patient Enrollment Sheet

C. Complete History and Physical Examination

D. Mammographic Report(s)

E. Pathology Reports

F. Initial Radiation Therapy Consult Note

G. Patient Treatment Data

H. Toxicity Reports

Skin reaction(s) to radiation, including erythema, desquamation, etc. and any radiation complications or unusual or severe side effects of treatment will be recorded using RTOG acute and RTOG/ECOG late toxicity scoring. All toxicity from radiation is described in both acute and late terms, and this is often grouped together, because radiation delivery can lead to either side effect for normal tissue. Specifically, RTOG acute and RTOG/ECOG late radiation toxicity scoring parameters were originally described for breast conservation treatment, and will be used in this study.[33] Acute toxicity includes any side-effects during treatment or within three months following treatment and late toxicity includes side-effects from three months up to three years in this study (see Appendix III and IV). Both acute and late toxicity use scores from 0-5. Toxicity is not expected for other tissues but will be documented. Excess toxicity will be reported as detailed below (Section 14 and Section 15).

I. Copies of Dosimetry Calculations (see Appendix VI).

J. Patient Follow Up

Patient follow up will occur 4 weeks, 3 months, 6 months, 1 year, and three years post Radiation Therapy. Some patients will be followed beginning 4 weeks after treatment at L&M because it is closer to home for them. In these cases, Dr. Evans will be meeting with the patients.

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

- Vital status. If patient has expired, a data form must be submitted.

- Disease status, classified local, elsewhere, contralateral, regional, or distant. A local failure is defined as an ipsilateral breast tumor recurrence within the same quadrant of the breast as the original lumpectomy. An elsewhere failure is defined as an ipsilateral breast tumor recurrence not inside the same quadrant as the original lumpectomy. A contralateral breast cancer is defined as a breast cancer in the opposite breast. A regional failure is a recurrence in the axilla, internal mammary nodal chain, or supraclavicular lymph node basins. A distant failure is any metastasis to distant organs (i.e. bone, lung, liver, brain).

- Toxicity evaluation.

- Follow-up physical examination and mammographic results.

13.0 STATISTICAL CONSIDERATIONS

A. Primary Endpoint

The purpose of this study is to evaluate the feasibility of using image guidance and four-dimensional computed tomography to reduce the volume of non target breast tissue that is treated with accelerated partial breast irradiation via the external beam technique.

Therefore, the primary focus will be to evaluate the utility of 4DCT and daily image guidance in APBI to decrease non target breast tissue constraints. The novelty of this protocol lies in the use of four dimensional CT and daily image guidance to minimize planning target volume, and thereby reduce incidental breast radiation (V50, V100 breast doses), which have been linked to poor cosmetic outcomes.[34,35]

This study will be considered a success if 50% or more of patients enrolled are able to meet the dosimetric constraints on the breast (V50 <45% and V100 <23.5%). If this occurs, a phase II study approval will be sought.

B. Secondary Endpoints

.

To study cosmesis rates and toxicity with improved dose constraints, and to assess whether this technique warrants further study in a larger trial designed to show improvement in cosmesis through this technique.

C. Patient Accrual

Patient accrual is expected to be 70 patients.

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

14.0 EXPECTED SIDE-EFFECTS AND ADVERSE EVENTS

A. Expected side effects

The side effects expected in this trial are not predicted to be significant, and should be similar to those experienced in the previously reported trials. Expected toxicities and relative incidences over time are given from Berrang et al. It is important to note that in addition to this list, Hepel et al reported 5/60 grade 3 toxicities, 4 of which were subcutaneous fibrosis, and one which was rib fracture and pericarditis. This group also reported one grade 4 subcutaneous toxicity, which was a patient who required wide local excision for severe breast pain at the site of APBI, and later underwent mastectomy for non-healing ulceration at the same site. This is the only toxicity higher than grade 3 reported in the literature (1 of a combined 3D CRT PBI PUBLISHED experience of 348, or 0.2%). If unexpected severe toxicities arise then we will follow early stopping and reporting guidelines as detailed in Section 15.

Table 3. Treatment-related toxicities

	Before RT (n = 104)			1 year after RT (n = 91-88)			3 years after RT (n = 87–85)		
Toxicity	Grade 0	Grade 1	Grade 2+	Grade 0	Grade 1	Grade 2+	Grade 0	Grade 1	Grade 2+
Breast pain	88%	11%	1%	74%	23%	3%	77%	23%	0%
Edema	68%	31%	1%	84%	11%	5%	94%	6%	0%
Dermatitis	90%	8%	2%	99%	1%	0%	100%	0%	0%
Fatigue	84%	13%	3%	96%	4%	0%	91%	8%	1%
Hyperpigmentation	90%	7%	3%	70%	26%	4%	88%	11%	1%
Hypopigmentation	97%	3%	0%	90%	10%	0%	94%	5%	1%
Induration	54%	40%	6%	64%	33%	3%	61%	31%	8%
Telangiectasia	91%	9%	0%	93%	5%	2%	80%	13%	7%

B. Assessing Adverse Events

All toxicities possibly, probably or definitely related to Radiation Therapy will be scored using RTOG acute and RTOG/EORTC late toxicity guidelines (see Appendix III and IV). Adverse events will be described and reported as described in Section 15.

Any additional toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines.

15.0 ADVERSE EVENTS REPORTING, SAFETY MONITORING, AND COMPLIANCE

A. Reporting Safety Information

An Adverse Experience or Event (AE) is any undesirable medical event occurring during the course of a clinical study, whether considered treatment-related or not, whether expected or not, whether it is serious or not. All AEs are to be reported.

B. Adverse Events

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

Following questioning and evaluation of the subject, all adverse clinical events, whether believed to be related or unrelated to the study treatment will be recorded and described. The subject will be followed until the AE has resolved or, if a chronic condition, stabilized.

Grading:

The maximum intensity of the AEs possibly, probably or definitely related to Radiation Therapy will be recorded using the current version of the RTOG acute and RTOG/EORTC late toxicity criteria (appendix III and IV). If a certain event or symptom is not described in the RTOG and EORTC toxicity criteria, it will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines.

Attribution:

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after the occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but is not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study treatment should be considered.

- Certain: An AE that occurred in a reasonable time after study treatment administration, and cannot be explained by concurrent disease or drugs.
- Probable: An AE that occurred in a reasonable time after study treatment administration is unlikely to be attributed to concurrent disease or drugs.
- Possible: An AE that occurred in a reasonable time after study treatment administration but could be related to concurrent disease or drugs.
- Unlikely: An AE where the clinical picture is highly consistent with a cause other than the study treatment, but attribution cannot be made with absolute certainty and a relationship between study treatment and AE cannot be excluded with complete confidence.
- Unrelated: An AE that is unrelated to the study treatment, for instance, one that is plausibly related to other drugs or the underlying disease. If the relationship is assessed as “Unrelated”, the cause is provided if known.
- Unassessable: Available information is insufficient, contradictory, and cannot be supplemented or verified at this point in time.

C. Unexpected Adverse Event

An unexpected AE may require expedited reporting if the nature and severity of the event is not consistent with information in the agent’s Toxicity List. The first occurrence of a previously unknown toxicity (regardless of RTOG/EORTC toxicity grade) is considered unexpected. A list of known toxicities, based on clinical events, will be updated and obtained from published outcomes of the treatment. Adverse events that are ‘expected’ based on toxicology or mechanism of action are still considered ‘unexpected’ if not previously observed (regardless of RTOG/EORTC Toxicity Grade

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

criteria) following the administration of the treatment in this trial. Expected adverse events are those that have been observed and attributed to the treatment in a clinical trial, and are listed on the agent's toxicity list.

D. Serious Adverse Events (SAEs)

A Serious Adverse Experience or Event (SAE) is any AE that occurring at any dose results in any of the following outcomes: death, life-threatening adverse toxicity experience, inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalization for elective procedures or transfusions), a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse treatment experience, when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. In general an important medical event is grade Grade 4-5 by the RTOG or RTOG/EORTC criteria.

The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical and scientific judgment should be exercised in deciding whether an important medical event is serious. Although the event may not be immediately life-threatening, fatal, or result in hospitalization, it should be considered serious when it jeopardizes the patient or requires intervention to prevent a serious outcome as defined above.

Examples of serious important medical events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

E. Expedited Reporting of Unexpected SAEs

AEs classified as "serious" and "unexpected" that are possibly, probably, or definitely attributed to treatment administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting to the Human Investigations Committee (HIC) to comply with regulatory requirements as well as to the FDA using the Medwatch form and the device maker. Deaths within 30 days of treatment administration will be reported to HIC, as well as any unexpected SAE that occurs more than 30 days after treatment administration but is possibly, probably, or definitely attributed to treatment administration.

All AEs meeting the criteria for expedited reporting will be reported to the Yale HIC within 48 hours of the PI`s initial receipt of the information. The PI will promptly investigate all safety information related to an adverse experience. Full written reports using the Yale Cancer Center Expedited SAE Report Form will be submitted to the HIC no later than 15 calendar days following the PI`s receipt of complete information on the

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

SAE. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

If the results of the PI`s investigation shows that an adverse treatment experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with treatment administration) is so reportable, the PI will report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

Results of the PI`s investigation of other safety information will be submitted, as appropriate, in an information amendment or annual report.

F. Yale Safety Monitoring and Reporting

The PI will monitor the clinical trial for safety. The PI will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events are followed which are in compliance with FDA 21 Code of Federal Regulations Part 312.32 and 312.33.

The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into a computerized database (OnCore) in a timely manner. The accuracy and completeness of the database, and compliance with the protocol, is assured by periodic auditing conducted by the Yale Cancer Center Office of Quality Assurance and Training, which reports to the Yale QUACS Committee. On a regular interval basis (approximately every 1-2 weeks), status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Weekly meetings are held to discuss ongoing patient treatment and adverse events. The Yale QUACS Committee also reviews safety data for the trial at least annually.

Possible actions taken by the PI or the Yale QUACS if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:

- Revise consent form
- Amend the protocol
- Suspend the protocol

All AEs found to be expected or non-serious, will be included in the Annual Report.

G. Stopping Rules

The trial will be discontinued if we experience 2 serious adverse events within the study cohort. Serious adverse events resulting in protocol discontinuation would include grade 3 pneumonitis, grade 3 pericarditis, or severe breast pain requiring excision of the area.

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

This trial will be discontinued if we are unable to achieve the more rigid dose constraints on breast reference volume (V50<45%, V100<23.5%) on 15 patients, as this would make the primary endpoint impossible.

16.0 PATIENT TERMINATION

Patients will be removed from the study at the patient's request. If a patient is unable to lie still for treatment or complete 4D CT, the patient may be removed from the trial. In the event that the patient does not tolerate treatment, at the discretion of the treating radiation oncologist, the patient will be removed from the trial. Patients will be removed from protocol therapy if the target area is not visible by cone beam CT scan or kilovoltage imaging at any point during the treatment.

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

17.0 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 347:1233-1241, 2002.

2. Veronesi U, Cascinelli N, Mariani L, Greco M, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J. Med 347:1227-1232, 2002.

3. Morrow M, White J, Moughan J, et al. Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. J Clin Oncol 19:2254-2262, 2001.

4. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 345:1378-1387, 2001.

5. Rosen PP, Fracchia AA, Urban JA, et al. "Residual" mammary carcinoma following simulated partial mastectomy.
Cancer 35:739747, 1975.

6. Veronesi U, Marubini, E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 12:997-1003, 2001.

7. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst 88:1659-1664, 1996.

8. Holli K, Saaristo R, Isola J, et al. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. Br J Cancer 84:164-169, 2001.

9. Lijegren G, Holmberg L, Bergh J, et al. 10-Year results after sector resection with or without postoperative radiotherapy for Stage I breast cancer: a randomized trial. J Clin Oncol 17:2326-2333, 1999.

10. Morrow M. Rational local therapy for breast cancer. N Engl J Med 347:1270-1271, 2002.

11. Smith TE, Lee D, Turner BC, et al. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Radiat Oncol Biol Phys 48:1281-1289, 2000.

12. Obedian E, Fischer DB, Haffty BG. Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. J Clin Oncol 18:2406-2012, 2000.

13. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 86:429-438, 1999.

14. Faverly DR, Burgers L, Bult P, Holland R. Three dimensional imaging of mammary ductal carcinoma in situ: clinical implications. Semin Diagn Pathol 11:193-198, 1994.

15. King TA, Bolton JS, Kuske RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. Am J Surg 180:299-304, 2000.

16. Park SS, Grills IS, Chen PY, et al. Accelerated Partial Breast Irradiation for Pure Ductal Carcinoma in Situ. Int J Radiat Oncol Biol Phys. 2010 Aug 26. [Epub ahead of print]

17. Vicini F, Baglan K, Kestin L, et al. The emerging role of brachytherapy in the management of patients with breast cancer. Semin Radiat Oncol 12:31-39, 2002.

18. Kuske RR Jr. Breast brachytherapy. Hematol Oncol Clin North Am 13:543-558, 1999.

19. Vicini F, Winter K, Wong J, et al. Initial Efficacy Results of RTOG 0319: Three-Dimensional Conformal Radiation Therapy (3D-CRT) Confined to the Region of the Lumpectomy Cavity for Stage I/ II Breast Carcinoma. Int J Radiat Oncol Biol Phys. 2010 Jul 15;77(4):1120-7. Epub 2009 Nov 10.

20. T.B. Julian, J. P. Costantino, F. A. Vicini, et al. Early toxicity results with 3D conformal external beam therapy (CEBT) from the NSABP B-39/RTOG 0413 accelerated partial-breast irradiation (APBI) trial. ASCO 2010 Breast Cancer Symposium, National Harbor, Maryland, October 1-3, 2010.

21. Keisch M, Vicini F, Kuske RR, et al. Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 55:289-293, 2003.

22. Clark. High dose rate brachytherapy for breast cancer. In: Nag S, editor. High dose rate brachytherapy: A textbook. Futura Publishing 321-329, 1994.

23. Polgar C, Sulyok Z, Fodor J, et al. Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-year results of a Phase I-II study and initial findings of a randomized Phase III Trial. J Surg Oncol 80:121-128, 2002.

24. Polgár C, Major T, Lövey K, et al. Hungarian experience on partial breast irradiation versus whole breast irradiation: 12-year results of a phase II trial and updated results of a randomized study. Brachytherapy 2008;7:91–2

25. Perera F, Engel J, Holliday R, et al. Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: a pilot study. J Surg Oncol 65:263-267, 1997.

26. Perera F, Chisela F, Engel J, et al. Method of localization and implantation of the lumpectomy site for high dose rate brachytherapy after conservative surgery for T1 and T2 breast cancer. Int J Radiat Oncol Biol Phys 31:959-965, 1995.

27. Vicini FA, Baglan KL, Kestin LL, et al. Accelerated treatment of breast cancer. J Clin Oncol 19:1993-2001, 2001.

28. Baglan KL, Martinez AA, Frazier RC, et al. The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast- conserving therapy. Int J Radiat Oncol Biol Phys 50:1003-1011, 2001.

29. Kuske RR, Martin B, Hanson W, et al. Quality assurance and reproducibility on RTOG 95-17: A Phase II trial of brachytherapy alone for select breast cancers. Personal Communication. 2001.

30. Benitez PR, Keisch ME, Vicini F, et al. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Am J Surg. 2007 Oct;194(4):456-62.

31. Wazer DE, Berle L, Graham R, et al. Preliminary results of a Phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer. Int J Radiat Oncol Biol Phys 53:889-897, 2002.

32. Chen PY, Wallace M, Mitchell C, et al. Four-year efficacy, cosmesis, and toxicity using three-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2010 Mar 15;76(4):991-7. Epub 2009 Jun 8.

33. Berrang TS, Olivotto I, Kim DH, et al. Three-Year Outcomes of a Canadian Multicenter Study of Accelerated Partial Breast Irradiation Using Conformal Radiation Therapy. Int J Radiat Oncol Biol Phys. 2010 Oct 23. [Epub ahead of print]

34. Hepel JT, Tokita M, MacAusland SG, Evans et al. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2009 Dec 1;75(5):1290-6. Epub 2009 Apr 22.

35. Jagsi R, Ben-David MA, Moran JM, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys. 2010 Jan 1;76(1):71-8.

36. Yue NJ, Goyal S, Zhou J, Khan AJ, Haffty BG. Intrafractional target motions and uncertainties of treatment setup reference systems in accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2011 Apr 1;79(5):1549-56. Epub 2010 Aug 26.

37. Leonard CE, Tallhamer M, Johnson T, et al. Clinical experience with image-guided radiotherapy in an accelerated partial breast intensity-modulated radiotherapy protocol. Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):528-34. Epub 2009 May 19.

38. Fatunase T, Wang Z, Yoo S, et al. Assessment of the residual error in soft tissue setup in patients undergoing partial breast irradiation: results of a prospective study using cone-beam computed tomography. Int J Radiat Oncol Biol Phys. 2008 Mar 15;70(4):1025-34. Epub 2007 Sep 24.

39. Liao ZW, Guan XX, Li FY, et al. Accelerated partial breast irradiation: Use of four-dimensional CT for target localization and assessment of intrafractional motion. Oncol Res. 2010;18(10):503-7.

40. Hasan Y, Kim L, Wloch J, Chi Y, Liang et al. Comparison of Planned Versus Actual Dose Delivered for External Beam Accelerated Partial Breast Irradiation Using Cone-Beam CT and Deformable Registration. Int J Radiat Oncol Biol Phys. 2010 Jul 23. [Epub ahead of print]

41. Ahunbay EE, Robbins J, Christian R, et al. Interfractional Target Variations for Partial Breast Irradiation. Int Radiat Oncol Biol Phys. 2011 May 11. [Epub ahead of print]

42. Kan MW, Leung LH, Wong W, Lam N. Radiation dose from cone beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 2008 Jan 1;70(1):272-9. Epub 2007 Nov 5.

43. Song WY, Kamath S, Ozawa S, Ani SA, Chvetsov A, Bhandare N, Palta JR, Liu C, Li JG. A dose comparison study between XVI and OBI CBCT systems. Med Phys. 2008 Feb;35(2):480-6.

44. Hyer DE, Serago CF, Kim S, Li JG, Hintenlang DE. An organ and effective dose study of XVI and OBI cone-beam CT systems. J Appl Clin Med Phys. 2010 Apr 17;11(2):3183

45. Lewin AA, Derhagopian R, Saigal K, et al. Accelerated Partial Breast Irradiation is Safe and Effective Using Intensity-Modulated Radiation Therapy in Selected Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2011 Jun 1. [Epub ahead of print]

46. Olivotto IA, Whelan TJ, Parpia S, et al. Interim Cosmetic and Toxicity Results From RAPID:A Randomized Trial of Accelerated Partial Breast Irradiation Using Three-Dimensional Conformal External Beam Radiation Therapy. J Clin Oncol. 2013 Jul 8. [Epub ahead of print]

47. Mak KS, Chen YH, Catalano PJ, Punglia RS, Wong JS, Truong L, Bellon JR. Dosimetric Inhomogeneity Predicts for Long-Term Breast Pain After Breast-Conserving Therapy. Int J Radiat Oncol Biol Phys. 2014 Jul 29. pii: S0360-3016(14)00621-X. doi: 10.1016/j.ijrobp.2014.05.021. [Epub ahead of print])

48. Galland-Girodet S, Pashtan I, MacDonald SM, Ancukiewicz M, Hirsch AE, Kachnic LA, Specht M, Gadd M, Smith BL, Powell SN1, Recht A, Taghian AG. Long-Term Cosmetic Outcomes and Toxicities of Proton Beam Therapy Compared With Photon-Based 3-Dimensional Conformal Accelerated Partial-Breast Irradiation: A Phase 1 Trial. Int J Radiat Oncol Biol Phys. 2014 May 28. pii: S0360-3016(14)00446-5. doi: 10.1016/j.ijrobp.2014.04.008. [Epub ahead of print]

APPENDIX I

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick, hospitalization necessary, active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX II

BREAST STAGING, AJCC 7th Edition

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic, are used, the examiner can use the telescoped subsets of T1.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor.
T1 Tumor 2 cm or less in greatest dimension
T1mic Microinvasion 0.1 cm or less in greatest dimension
Tla Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b More than 0.5 cm but not more than 1 cm in greatest dimension
T1c More than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any sizes with direct extension to chest wall or skin
T4a Extension to chest wall, not including pectoralis muscle
T4b Edema (including peau d' orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c Both (T4a and T4b)
T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)
N0 No regional lymph node metastasis
NI Metastasis to movable ipsilateral lymph node(s)
N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3 Metastasis to ipsilateral internal mammary lymph node(s)

Pathologic Classification(pN)

pNX Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
pN0 No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i−) No regional lymph node metastases histologically, negative IHC
pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or
IHC including ITC)
pN0(mol−) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+) Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
pN1 Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2 Metastases in 4–9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3 Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c Metastases in ipsilateral supraclavicular lymph nodes

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node[(s)])

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1	N1mi	M0
Stage IIA	T0	N1	M0
	T1	N1*	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0-2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

* Note: The prognosis of patients with N1a is similar to that of patients with pN0.

APPENDIX III

RTOG Acute Radiation Morbidity Scoring Criteria					
	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinous discharge. May experience moderate Pain requiring analgesia	Confluent fibrinous mucositis/may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	No change	Mild conjunctivitis with or without scleral injection/increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration/objective decrease in visual acuity or in visual fields/acute glaucoma/panophthalmitis	Loss of vision (unilateral or bilateral
EAR	No change over baseline	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/serous otitis medius/hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus, not drug related	Deafness

SALIVARY GLAND	No change over baseline	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/thick, sticky saliva/markedly altered taste		Acute salivary gland necrosis
PHARYNX & ESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/may require topical anesthetic or non-narcotic analgesics/may require soft diet	Moderate dysphagia or odynophagia/may require narcotic analgesics/may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/erythema of mucosa	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/confluent fibrinous exudate. Marked arytenoid edema.	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

UPPER G.I.	No change	Anorexia with <= 5% weight loss from pretreatment baseline/nausea not requiring antiemetics/abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <= 15% weight loss from pretreatment baseline/nausea &/or vomiting requiring antiemetics/abdominal pain requiring analgesics	Anorexia with >=15% wt loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/ hematemesis or melena/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion.
RTOG Acute Radiation Morbidity Scoring Criteria					
	[0]	[1]	[2]	[3]	[4]
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

LUNG	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest/clinical or radiologic evidence of acute pneumonitis. Intermittent oxygen or steroids may be required	Severe respiratory insufficiency/continuous oxygen or assisted ventilation
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic. Gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis
HEART	No change over baseline	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart diseases	Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease/no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures

CNS	No change	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home care/nursing assistance may be required/medications including steroids/anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures > 3 per week despite medication/hospitalization required
HEMATOLOGIC WBC (X 1000)	=> 4.0	3.0 -<4.0	2.0-<3.0	1.0-<2.0	<1.0
PLATELETS (X 1000)	>100	75-<100	50-<75	25-<50	<25 or spontaneous bleeding
NEUTROPHILS (X 1000)	=>1.9	1.5-<1.9	1.0-<1.5	0.5-<1.0	<0.5 or sepsis
HEMOGLOBIN (X 1000)	>11	11-9.5	<9.5-7.5	<7.5-5.0	
HEMATOCRIT (%)	=>32	28-32	<28	Packed cell transfusion required	

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.
The evaluator must attempt to discriminate between disease and treatment related signs and symptoms
An accurate baseline evaluation prior to commencement of therapy is necessary.
All toxicities Grade 3,4, or 5* must be verified by Dr. Suzanne Evans
* ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.

APPENDIX IV

RTOG / EORTC Late Radiation Morbidity Scoring Scheme						
	0	1	2	3	4	5
SKIN	NONE	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangectasia; Total hair loss	Marked atrophy; Gross telangectasia	Ulceration	
SUBCUTA-NEOUS TISSUE	NONE	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture>10 % linear measurement	Necrosis	DEATH DIRECTLY RELATED TO RAD
MUCOUS MEMBRAN E	NONE	Slight atrophy and dryness	Moderate atrophy and telangectasia; Little mucous	Marked atrophy with complete dryness Severe telangectasia	Ulceration	
SALIVARY GLANDS	NONE	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	
SPINAL CORD	NONE	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
BRAIN	NONE	Mild headache; Slight lethargy	Moderate headache Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	

APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

EYE	NONE	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal Ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	LATE EFFECTS
LARNYX	NONE	Hoarseness; Slight Arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	NONE	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous o2/Assisted ventilation	
HEART	NONE	Asymptomatic or mild symptoms; Transient T wave inversion & ST changes; Sinus tachycardia>110 (at rest)	Moderate angina on effort Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	
ESOPHAGUS	NONE	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain swallowing Dilation required	Necrosis/Perforation Fistula	

SMALL/LARGE INTESTINE	NONE	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
LIVER	NONE	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis /Hepatic coma or encephalopathy	
KIDNEY	NONE	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%; Creatinine 1.5-2.0 mg%; Creatinine clearance>75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of real function Urea>36-60mg% Creatinine clearance (50-74%)	Severe albuminaria; Severe hypertension Persistent anemia (<10g%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance<50%	Malignant hypertension Uremic coma/Urea > 100%	
BLADDER	NONE	Slight epithelial atrophy Minor telangectasia (microscopic hematuria)	Moderate frequency Generalized telangectasia Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized telangectasia (Often with petechiae); Frequent hematuria; Reduction in bladder capacity (<150cc)	Necrosis/Contracted bladder (capacity <100cc) Severe hemorrhagic cystitis	

BONE	NONE	Asymptomatic; No growth retardation; Reduced bone density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	NONE	Mild joint stiffness; Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

APPENDIX V

Rose MA, Olivotto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer: Long-term cosmetic results. Arch Surg 1989;124:153–157.

Harvard Cosmesis Scale	
Excellent	the treated breast looked essentially the same as the opposite breast.
Good	minimal but identifiable effects of radiation on the treated breast.
Fair	significant effects of radiation on the breast were noted.
Poor	severe normal tissue sequelae.

Appendix VI

Patient reported Breast Cancer Treatment Outcome Scale (Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer. 2001;91:2273–2281.)

We are interested in your evaluation of your physical appearance and functioning since your breast surgery and/or radiation.
Please rate the following items on this four-point scale, according to your evaluation at this time: 1) no difference between treated and untreated breast and area, 2) slight difference between treated and untreated breast and area, 3) moderate difference between treated and untreated breast and area, and 4) large difference between treated and untreated breast and area.

After rating all items, you are asked to place a check by any difference that was bothersome.

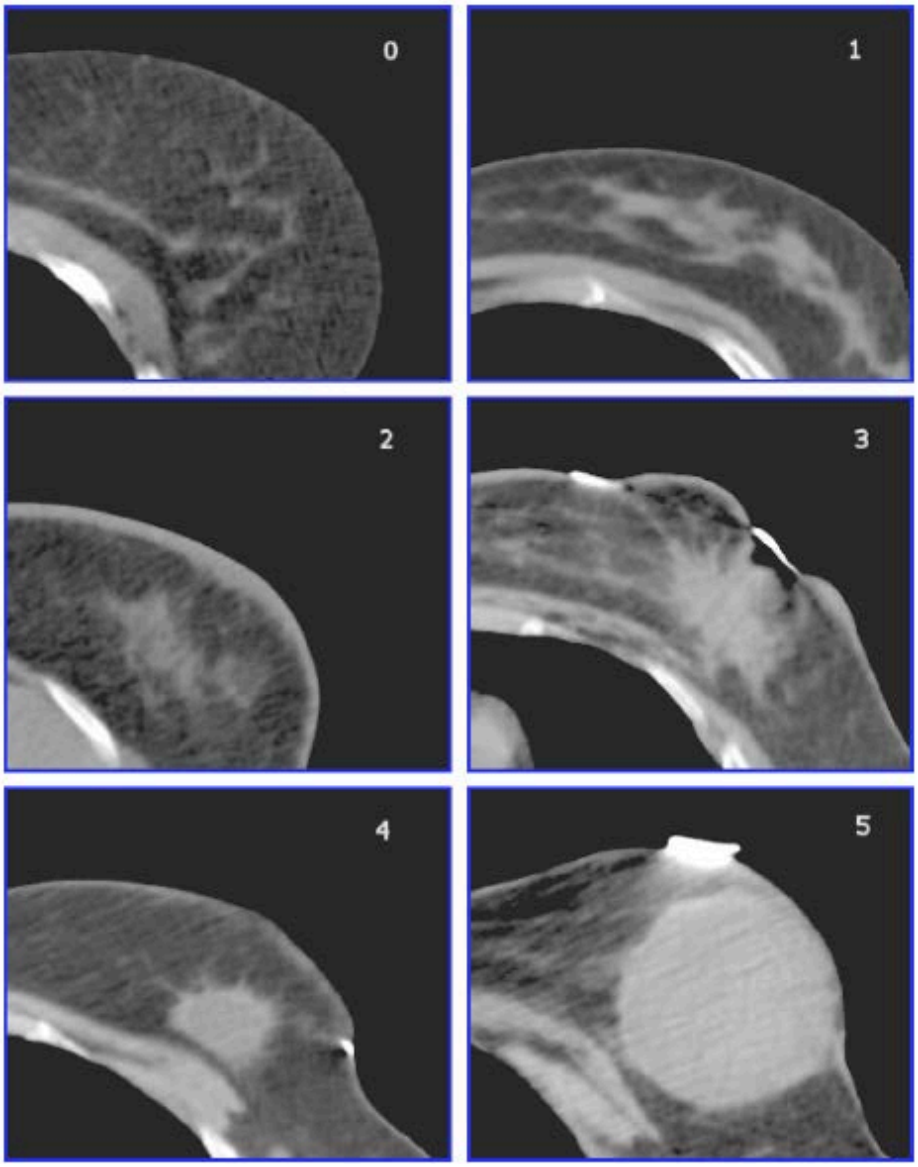
	1	2	3	4
Breast Size	No difference	Slight difference	Moderate difference	Large Difference
Breast texture/hardening	No difference	Slight difference	Moderate difference	Large Difference
Nipple appearance	No difference	Slight difference	Moderate difference	Large Difference
Breast Pain	No difference	Slight difference	Moderate difference	Large Difference
Breast Tenderness	No difference	Slight difference	Moderate difference	Large Difference
Breast Shape	No difference	Slight difference	Moderate difference	Large Difference
Breast Elevation (how high the breast is)	No difference	Slight difference	Moderate difference	Large Difference
Scar Tissue	No difference	Slight difference	Moderate difference	Large Difference
Fit of Bra	No difference	Slight difference	Moderate difference	Large Difference
Breast Sensitivity	No difference	Slight difference	Moderate difference	Large Difference
Fit of Clothing	No difference	Slight difference	Moderate difference	Large Difference

Appendix VII

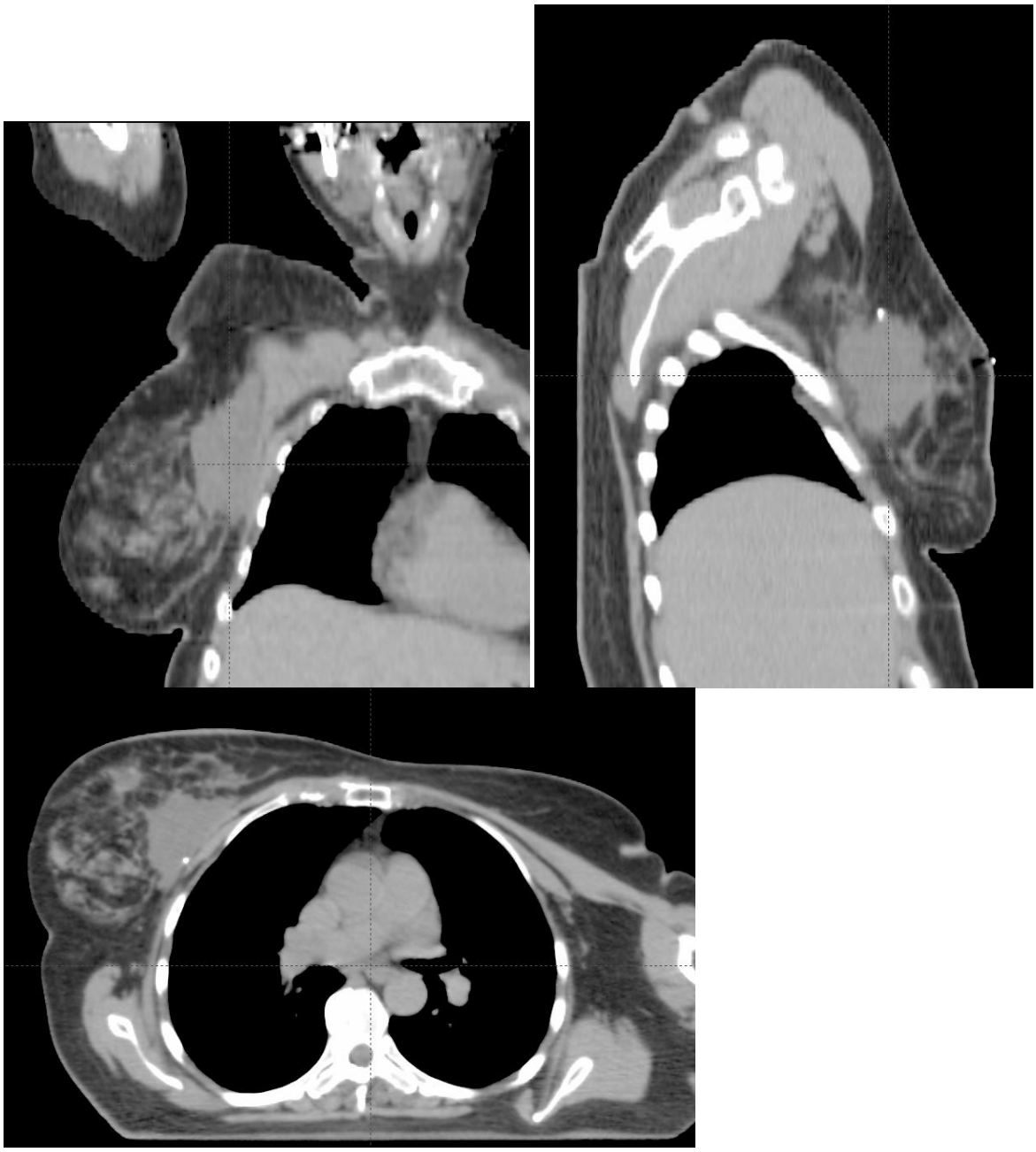
CAVITY VISUALIZATION SCORE

(Petersen RP, Truong PT, Kader HA, et al. Target volume delineation for partial breast radiotherapy planning: clinical characteristics associated with low interobserver concordance. Int J Radiat Oncol Biol Phys. 2007 Sep 1;69(1):41-8.)

0 = no visible seroma,
1 = scar/shadow
2 = seroma identifiable but with significant uncertainties
3 = seroma identifiable with minor uncertainties
4 = seroma easily identifiable, generally homogenous with slightly blurred margin
5 = seroma easily identifiable, homogenous with sharp boundaries.

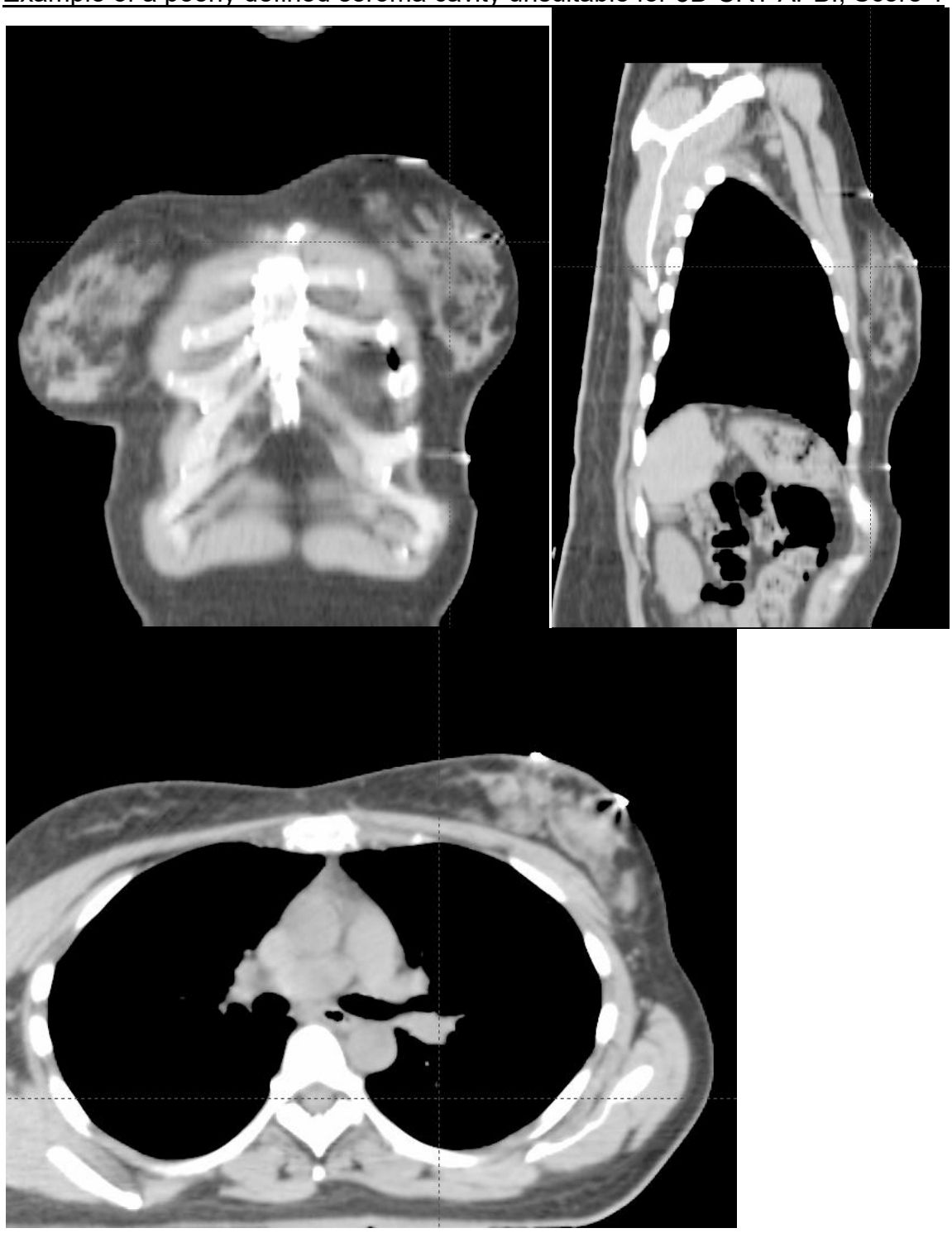


Example of Well-defined Seroma Cavity, 4



APPROVED BY THE YALE UNIVERSITY IRB 11/10/2017 VALID THROUGH 11/29/2018

Example of a poorly defined seroma cavity unsuitable for 3D CRT APBI, Score 1



APPENDIX VIII

CONTOURING GUIDELINES

1.0 Normal Structure And Target Contouring

The following structures will be contoured in all cases: the excision cavity throughout its respiratory motion (ITV), CTV, and planning target volume (PTV), the planning target for evaluation (PTV_EVAL), ipsilateral breast, contralateral breast, thyroid, ipsilateral and contralateral lung, and heart. Based on the 4D CT scan acquired during free breathing, the tumor bed will be segmented throughout its entire respiratory excursion to comprise the ITV. This will be expanded by 15 mm to comprise the CTV, although CTV will not include the pectoralis muscles, the chest wall, or within 5mm of skin. Questions about CTV are to be directed to Dr. Suzanne Evans. The CTV must never be smaller than the ITV, and a Boolean operator may be necessary (Boolean CTV "OR" ITV). The PTV will be a 2 mm expansion of the CTV. Treatment planning will be performed on the average scan with heterogeneity corrections. The chin, shoulders and contralateral breast should be included in the scan. The target structures and normal tissue structures must be outlined on all CT slices. The average scan may be used for contouring structures other than the ITV.

In patients who have a very posterior or anterior cavity where the CTV is trimmed down to the ITV off of skin or pectoral muscle, the PTV should be expanded such that the ptv is a minimum 5 mm away from the ITV. This is intended to make sure that ptv to itv distance is a minimum of 5 mm (normally 17 mm after 15 mm expansion for ptv, but can be less in very posterior or very anterior cavities.

A. Thyroid

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

B. Heart

The heart should be contoured beginning just below the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. All the mediastinal tissue below this level should be contoured, including the great vessels (ascending and descending aorta, inferior vena cava). The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. If one can identify the esophagus, this structure should be excluded. Contouring along the pericardium itself, when visible, is appropriate, as the coronary arteries lie between the percarium and the myocardium The left anterior descending artery may be contoured, although no specific dose constraints are applied to this structure.

C. Whole Breast Reference Volume Contouring

Delineation of breast tissue extent remains difficult and free-handed CT interpretation by each individual investigator will yield significant variability. For the purposes of this protocol, the whole breast volume will be referred to as the whole breast reference volume and defined as all tissue volume, excluding lung, within the boundaries of standard whole breast tangential fields. The whole breast reference volume should also exclude any non-breast structure deep to the lung-rib interface such as heart, pre-cardiac fat, and liver.

An acceptable method of autocontouring with Eclipse is to convert the 50% isodose line from a standard tangential plan to a structure, then Boolean operator "breast" and "Body" (to include nipple which may be excluded). Subsequently, the Boolean operator can be used to remove any "breast" volume extending inside lung.

This is meant to be only an approximation of the actual breast tissue volume, and it is recognized some degree of adjacent soft tissue will be included. However, with this definition it is anticipated that this volume will be reproducible and consistent from case to case and that the process can be automated within the 3D planning system for time conservation.
To facilitate, the patient should be positioned in standard whole breast external beam treatment position. It is recommended that external marker wires be placed to indicate the clinical expectations of the external beam tangential field borders as a guide. The CT should be obtained from the mandible to the base of the lungs with a slice thickness of ≤ 5 mm.

Free-handed contouring of the breast
Free handed contouring will not be performed.

Automated contouring of the breast
Each 3D planning system has available different contouring functions and the specific methods may vary from system to system. Institutions are encouraged to investigate the capabilities of their planning system in regards to these contouring functions.

With the Eclipse planning system, standard tangent fields should be set up as in whole breast radiation therapy. Beam weighting should be optimized as is typically done for tangential field planning and normalized so that the 100% isodose line satisfactorily covers the volume of interest as determined by the set field geometries. A new Structure should be created titled "Breast Reference" and the "convert isodose line to structure" tool should be used to convert the 50% isodose line to the breast reference structure. This should then be booleaned with the "patient" or "external" structure to include the nipple. The lung and heart should be subtracted, and the structure should be reviewed and edited to insure that no tissue deep to the ribs is included (i.e. pericardial fat, liver, bowel).

Within the Pinnacle 3D planning system, auto-contouring the whole breast reference volume, as defined above, is easily accomplished and can be completed in several ways. Outlined below is an example of one of these methods: The Pinnacle 3D planning system has within its contouring functions a Region of Interest (ROI) expansion/contraction tool, found under Options within the contouring window, which allows a selected contour to be altered/limited automatically by selected ROIs already entered in the patient's plan. At the start of each case, the skin and lung contours will be entered with automated functions and the virtual standard whole breast tangent fields designed. By way of the ROI expansion/contraction tool, the planning system will start with the skin contour and alter it by limiting this contour to within the boundaries of the tangential fields and lung/chest wall interface, thus creating a new contour that represents the whole breast volume as defined above. Since this ROI expansion/contraction tool only uses entered contours, ROI's representing the borders of the tangential fields must first be entered. To represent the superior and inferior field borders, a simple box contour that encompasses the entire body on each CT slice superior and inferior to the tangential field borders, are entered under a new ROI (i.e., field borders). This can be accomplished by entering manually on each appropriate CT slice or expediting by utilizing the interpolation tools. Added to the newly created ROI, named here field borders, is a contour that is entered on every CT slice within the tangent fields that represents the posterior tangent border. This contour is placed along the posterior field border, extending the contour beyond the CT slice and viewing window. This contour can be entered manually on each appropriate CT slice or, to save time, the interpolation tool can be used to automate. Once field boundary contouring is complete, each CT slice will have either a simple encompassing box contour (if superior or inferior to the tangent fields) or a posterior field boundary contour (if within the tangential field borders). At this time, the ROI expansion/contraction window is brought up. Designate the skin as the source ROI and designate the lung and field borders limiting ROI's. Highlight "contract" as the function and designate the destination of the newly created ROI (simply create a new ROI which will then be listed in the destination list). Click on Proceed with Contraction to complete the process.

D. Target Contouring

Target definitions are listed here:
• ITV: THIS WILL REPRESENT THE PHYSIOLOGIC MOVEMENT OF THE TUMOR. The ITV will be representative of the tumor bed throughout its entire respiratory excursion.

• CTV – 1.5 cm beyond excision cavity. Volume expansion limited to **exclude pectoralis muscles, chest wall, and the first 5 mm beneath the skin . This should not be smaller than the ITV.**

• PTV: this will be a 2mm expansion of the CTV to account for intrafractional motion.

• PTV_EVAL – the PTV excluding pectoralis muscles, chest wall and the first 5 mm

beneath the skin.

Appendix IX

QUALITY ASSURANCE OF DOSE DISTRIBUTION

Each treatment plan shall be judged as:

• Acceptable:

− Dose volume histogram analysis of the target volume confirms 90% of the prescribed dose covers ≥ 90% of the PTV_EVAL.
− Critical normal tissue DVHs within 5% specified value
− Maximum dose does not exceed 120% of prescribed dose.
- Dose delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.

• Unacceptable:

− Dose volume histogram analysis of the target volume will confirm < 90% of the prescribed dose covers < 90% of the PTV_EVAL.
− Critical normal structure DVH exceeds 5% of the specified value
− Maximum dose exceeds 120% of prescribed dose.
− Dose delivered over a period of time extending greater than 10 days.

APPENDIX X

DOSIMETRY WORKSHEET:

Indices of an approved treatment plan

Patient Name				Case #	
Target	Organ/Target Volume (cc)	Dosimetry Index	Value	Unit	Ideal Value**
Seroma/Excision Cavity=ITV		[redacted]			
CTV					
PTV					
PTV-Eval		V90 (34.65 Gy)		%	>90%
Whole Breast Reference Volume (V50 and V100 are only required constraints to be met, all other are reporting only)		V5 (1.92 Gy)		%	<75% suggested
		V10 (3.85 Gy)		%	<70% suggested
		V25 (9.625Gy)		%	<55% suggested
		V50 (19.25 Gy)		**%**	**< 45% IDEAL, <60% OK***
		V75 (28.875 Gy)		%	<30% suggested
		V100 (38.5 Gy)		**%**	**< 23.5% IDEAL, <35% OK***
Contralateral Breast		D_{max}		cGy	<115 cGy

Ipsilateral Lung		V30 (11.55 Gy)		%	<15%
Contralateral Lung		V30 (11.55 Gy)		%	<15%
Heart (right sided)		V5 (1.92 Gy)		%	<5%
Heart (left sided)		V5 (1.92 Gy)		%	<40%
Thyroid		D_{max}		cGy	<115cGy

* plans which exceed the V50 >60% or V100>35% will be reviewed by Dr. Suzanne Evans prior to approval. The definition and the method of collecting the above dosimetry quantities from an approved treatment plan for each patient are described as follows.

• Whole breast reference volume: Ideally, < 45% of the whole breast reference volume should receive ≥ 50% of the prescribed dose and < 23.5% of the whole breast reference volume should receive the prescribed dose. As was done in NSABP B39, < 60% of the whole breast reference volume receiving ≥ 50% of the prescribed dose and < 35% of the whole breast reference volume receiving the prescribed dose is acceptable, although not ideal.
• Contralateral breast: The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive <1.15 Gy (3% of prescribed dose) to any point.
• Ipsilateral lung: < 15% of the lung can receive 11.55 Gy (30% of the prescribed dose.)
• Contralateral lung: < 15% of the lung can receive 1.92 Gy (5% of the prescribed dose).
• Heart (right-sided lesions): < 5% of the heart should receive 1.92 Gy (5% of the prescribed dose).
• Heart (left-sided lesions): The volume of the heart receiving 1.92 Gy (5% of the prescribed dose) (V5) should be less than the 40%.
• Thyroid: maximum point dose of 1.15Gy (3% of the prescribed dose).