A UW Phase II Trial of Multicatheter HDR Brachytherapy Following Lumpectomy for Early Stage Breast Cancer

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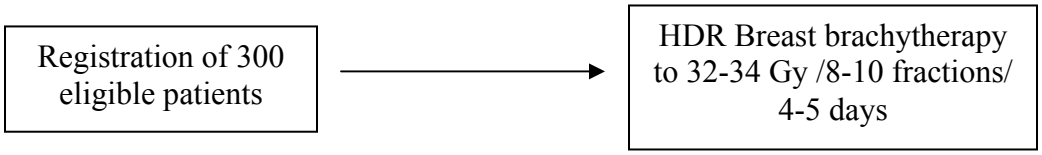
SCHEMA



Systemic Therapy

Cytotoxic chemotherapy should not start until at least two-weeks post-brachytherapy to allow adequate time for healing. Chemotherapy prior to brachytherapy is not permitted. Hormonal therapy may be utilized in any clinically appropriate sequence but will be discontinued during the one-week brachytherapy treatment course.

ELIGIBILITY:

- Invasive ductal, medullary, papillary, colloid *(mucinous)*, tubular histologies *or* Ductal carcinoma in situ (DCIS)
- Tumor Stage: Tis, T1, T2 if lesion ≤ 3 cm
- Nodal Stage: N0 (*negative sentinel node mapping is acceptable*) (subjects with DCIS are exempt from nodal staging)
  or N1(*1-3 nodes positive* ***and*** *no extracapsular extension)*. This represents a cohort of patients that would not ordinarily receive axillary irradiation.
- Clearly visible target as defined by ultrasound, surgical clips, or mammography
- Unifocal breast cancer *(single focus which can be encompassed by one lumpectomy)*
- Negative surgical margins
- Negative post-lumpectomy mammogram if cancer presented with malignancy-associated microcalcifications
- No Paget's disease of the nipple or extensive intraductal component (EIC by Harvard definition: 1) more than 25% of the tumor is DCIS and there is DCIS in adjacent breast tissue, or 2) an intraductal carcinoma with microinvasion).
- No previous radiation or chemotherapy for current breast cancer
- No collagen vascular disease (systemic lupus erythematosis, scleroderma, or dermatomyositis)
- No co-existing medical conditions with life expectancy < 2 years.
- Age > 18 years old
- No pregnant or lactating women.
- No psychiatric or addictive disorders which would preclude obtaining informed consent
- Signed study-specific consent form

ELIGIBILITY CHECK

The following questions will be asked at registration:

_____(Y) 1. Does the patient have histologically confirmed invasive ductal, medullary, papillary, colloid *(mucinous)*, tubular cancer of the breast, or DCIS

_____(Y) 2. Is the AJCC T classification Tis,T1-2, N0-1, M0?

_____(Y) 3. Is the tumor size ≤ 3 cm.

_____(Y) 4. Are there ≤ 3 nodes positive without extracapsular extension?

_____(Y) 5. Does the patient have a well-defined target (ultrasound-defined seroma, surgical clips, or mammography)?

_____(N) 6. Has the patient undergone lumpectomy resulting in negative tumor margins? *(if yes, skip to Q8)*

_____(Y) 7. If no, is re-excision planned prior to introduction of radiation sources? *(failure to meet all criteria subsequent to re-excision will result in ineligibility)*

_____(Y/N) 8. Any evidence of pre-excision breast microcalcifications in the initial mammogram?

_____(Y) If yes, was a postoperative mammogram done and found negative for residual suspicious microcalcifications?

_____(N) 9. Any evidence of multicentric breast tumor, or unresolved suspicious synchronous tumors/calcifications

_____(N) 10. Any evidence of Paget's disease of the nipple, tumor involving skin, internal mammary or supraclavicular lymph nodes or distant metastasis?

_____(N) 11. Any evidence of collagen vascular disease or shortened life expectancy from coexisting medical conditions *(< 2 yrs)?*

_____(N) 12. Any prior radiotherapy, chemotherapy or non-hormonal therapy for the present breast cancer?

_____(N) 13. Is the patient pregnant or lactating?

_____(Y) 14. Is the patient ≥ 18 years old?

1.0 BACKGROUND

Breast Conservation Therapy (BCT)

BCT is now widely accepted as a treatment option for most women with Stage I and II invasive breast cancer and most patients with ductal carcinoma in situ (DCIS). Six prospective randomized trials have clearly demonstrated similar overall and distant disease-free survival for patients receiving breast-conserving therapy, compared with patients treated by conventional mastectomy.[1-6] Despite superior cosmetic outcome, BCT is more complex and requires a protracted treatment regimen comprised of 6 weeks of daily external beam radiation therapy to the whole breast. This often proves prohibitive for the working woman, elderly patients, and those who live at a significant distance from a radiation treatment center. In addition, with the more frequent use of adjuvant chemotherapy in both node-negative and node-positive patients, substantial delays can be incurred prior to the initiation of systemic chemotherapy if a conventional fractionated course of irradiation (XRT) is given first or in delivery of loco-regional XRT if chemotherapy is delivered beforehand. Thus, despite the potential benefits, only 30-50% of patients who are candidates for breast conservation actually receive it.[7]

A Paradigm Shift from Whole Breast to Partial Breast Irradiation

Most of the logistical problems associated with BCT relate to the protracted course of external beam XRT delivered to the whole breast. Standard therapy after tumor excision generally includes five weeks of external beam XRT to the whole breast (45-50 Gy) followed by an additional 10-15 Gy boost to the tumor bed. The rationale for this approach is based upon two principles. First, higher doses of XRT are given to the 'tumor bed' in an attempt to control residual small foci of cancer that may be left behind after excision alone. Second, whole breast XRT is used to eliminate possible areas of occult multicentric in situ or infiltrating cancer in remote areas of the breast. That such remote, multicentric areas of cancer exist has long been established. However, the biological significance of these areas of occult cancer is unknown and the necessity to prophylactically treat the entire breast has recently been questioned.

There are at least six prospective randomized trials that have been conducted comparing the outcome of patients treated with lumpectomy alone or followed by whole breast XRT.[5,8-12] Across these studies, there is a similar 3-fold reduction in the ipsilateral breast failure rate with the addition of radiotherapy. For instance, in the NSABP B-06 randomized prospective trial, which included patients with invasive cancers up to 4 cm in size with negative surgical margins, the breast recurrence rate of 43% with lumpectomy alone is considerably higher than the 10% breast failure rate of the lumpectomy and whole breast irradiation arm.[5] In these studies, the percentage of patients receiving whole breast irradiation who recur in a remote location of the breast potentially not covered by partial breast irradiation was low (< 3.5%). Is this absence of the expected number of remote breast recurrences due to sterilization of other quadrants by the whole breast radiation therapy employed in these series or to the biological insignificance of occult cancer foci in remote quadrants of the breast? If the former is true, then one would expect increased remote relapses in the conservative surgery alone patients.

To address this question, one must examine patients treated with surgery only and evaluate the number of remote recurrences. In fact, the proportion of patients who recur in a portion of the breast that would not be covered by partial breast irradiation is the same as patients receiving whole breast irradiation. This observation is validated by studies such as those conducted by Liljegren[8] and Crile[13] also demonstrated that 85% and 84% of local recurrences were in the immediate vicinity of the lumpectomy site defined as the surgical scar and the skin directly over the surgical field translating to an absolute risk of remote recurrence of 3.0% and 1.7%, respectively. From these data, one can infer that radiation therapy following lumpectomy has as its maximal effect on the reduction of breast cancer recurrence at or very near the lumpectomy site casting doubt on the belief that remote recurrences originate from multicentric disease at the time of the index lesion demonstrated on histopathology. If the above observations are valid, radiation therapy can be confidently directed to the tissue surrounding the excision cavity of the breast.

Clinical Experience:

There are currently several groups studying the efficacy of lumpectomy bed irradiation alone in the management of early stage breast cancer patients treated with BCT. Both interstitial brachytherapy techniques as well as external beam irradiation protocols have been implemented. Preliminary results from these trials are very encouraging and the techniques have been shown to be safe, tolerable, and highly reproducible (Data outlined in table below).[14]

Partial breast irradiation experience with >2-year follow-up series with patient selection criteria and quality assurance for brachytherapy

Author/institution	No. of cases	Follow-up interval (months)	Dose rate/(pt no.)	Scheme	Total dose (Gy)	% Breast recurrence	Good/excellent cosmesis
King *et al.*			LDR/(26)	>.4 Gy/hr	45		
Ochsner Clinic	52	75				2	75
New Orleans, Louisiana			HDR/(26)	4 Gy × 8	32		
Vicini *et al.*	196	65	LDR/(120)	.52 Gy/hr	50	1.2	91
William Beaumont Hospital			HDR/(79)	4 Gy × 8	32		
Royal Oak, Michigan				3.4 Gy × 10	34		98
Krishnan *et al.*							
University of Kansas	24	47	LDR 20–25 Gy	over 24–48 hr	20–25	0	100
Kansas City, Kansas							
Polgar *et al.*	45	60†	HDR/(8)	4.33 Gy × 7	30.3	4.4	97.8
National Institute of Oncology			HDR/(37)	5.2 Gy × 7	36.4		
Budapest, Hungary	89‡	30	HDR/(64)	5.2 Gy × 7	36.4	1.1	not stated
			Wide-volume electron (25)	2 Gy × 25	50		
Cionini *et al.*							
University of Florence							
Florence, Italy	90	27	LDR stated	not	50–60	4.4	not stated
Wazer *et al.*							
Tufts University							
Boston, Massachusetts	32	33	HDR	3.4 Gy × 10	34	3	88
Arthur *et al.*							
Virginia Commonwealth University			HDR/(31)	3.4 Gy × 10	34		
Richmond, Virginia	44	42	LDR/(13)	.50 Gy/hr	45	0	79.6
Lawenda *et al.*					50		
Massachusetts General Hospital	48	37	LDR 50 cGy/hr		55	0	92
Boston, Massachusetts					60		

Although these studies require longer follow-up, they have demonstrated that with appropriate patient selection, excellent local control and cosmetic outcome can be achieved with breast brachytherapy with minimal toxicity.

University of Wisconsin Hospital Experience

From 11/2000 to 4/2004, 240 pts have been treated with high-dose rate accelerated partial breast irradiation at our institution (211 interstitial multiple catheters). Selection criteria have included tumors < 3 cm pathologic size, 0-3 positive nodes with no extracapsular spread, negative margins and negative post-lumpectomy mammography. Two techniques, prone template with digital mammographic-guidance and supine with ultrasound or fluoroscopic guidance were used for catheter placement. Target volume has remained constant as the surgical cavity with 2 cm margin but at least 5-mm deep to the skin surface and no deeper than the pectoral fascia. In 5/2002, CT-based 3-D treatment planning was implemented allowing more accurate target delineation, improved geometric coverage of the target volume, and dosimetric verification. The volume of breast receiving 100% and 150% ($Vol_{100\%,}$ $Vol_{150\%}$) of the prescribed dose have been determined from dose volume histograms for each patient. The dose homogeneity index, and percent target volume receiving 100% of the prescription dose was determined for quality assurance. There has been excellent coverage of the target volume with fractionated HDR brachytherapy delivered in the supine position (32-34 Gy/8-10 bid fractions). Interstitial breast brachytherapy has been successfully delivered with high quality assurance and was well-tolerated in all patients. 98% of pts had good to excellent cosmesis at 12 months with minimal acute toxicity on formal review of digital photographs. All but one patient is without clinical or radiographic evidence of disease at a median follow-up of 19 months. There has been minimal significant late toxicity.[15]

Study Rationale

Can an acceptable outcome be achieved with radiation delivered only to the region of the tumor bed? If this were so, partial breast irradiation may lend itself to much shorter treatment times (one week) as the toxicities to adjacent normal structures (i.e., heart, lung, chest wall, skin, and contralateral breast) should be significantly reduced with this approach. This significantly shortened treatment time could potentially reduce health care costs, improve the quality of life of many patients undergoing BCT, and just as importantly, extend the conservation option to more women by reducing the inconvenience of radiation therapy. The implications of the presented clinical and pathologic data coupled with favorable early outcomes form the basis of the current study.

Patient selection criteria in this protocol have been chosen to minimize the risk of multicentricity and a remote breast recurrence. The key factors are the exclusion of patients with microscopic extension of tumor cells to the inked surgical margins, lobular histologies, tumors larger than 3 cm, and patients having an extensive intraductal component. Patients with involvement of 4 or more axillary lymph nodes have a significant risk for regional nodal relapse, and most radiation oncologists choose to include them in external beam portals. These patients would lose the logistical advantage of a shortened breast treatment regimen. Even with these strict selection criteria, approximately 71,000 women per year in the United States would be candidates for this protocol.

2.0 OBJECTIVES

This study will evaluate the local control rate of brachytherapy, cosmetic results, and complication rates when used as the sole method of radiation therapy for patients with

stage I and II *(≤ 3 cm)* carcinoma of the breast treated with lumpectomy, with histologically negative surgical margins.

2.1 Primary Objective

To determine if for DCIS and stage I and II breast cancer (≤ 3 cm primary), brachytherapy will produce non-inferior local-regional control at 5 years compared to historical observed results with a conventional course of external beam radiotherapy (~94%)—(See 10.1.1)

2.2 Secondary Objectives

- To determine if brachytherapy will have non-inferior toxicity to external beam radiotherapy (5%) at 3 years. Grade 3 or higher toxicity will be scored.
- To evaluate cosmesis at each follow-up by utilizing a cosmesis score based on established Harvard criteria.
- To assess patient satisfaction with breast brachytherapy by a questionnaire pre-brachytherapy, at completion, and post-brachytherapy.
- To perform a dosimetric comparison with an external beam plan for each patient. The following parameters will be evaluated: skin dose, target coverage, dose homogeneity index, and NTDmeans from dose volume histograms for each individual patient for heart, lung, and contralateral breast.
- To assess the ability to interpret mammography after interstitial brachytherapy.
- To evaluate Disease-free, Mastectomy-free, and Overall Survival.

3.0 PATIENT SELECTION CRITERIA

3.1 Eligibility Criteria

- Diagnosis of invasive ductal, medullary, papillary, colloid *(mucinous)*, tubular histologies *or* Ductal carcinoma in situ (DCIS)
- Tumor stage: Tis, T1, T2 if lesion ≤ 3 cm
- Nodal Stage: N0 (*or a negative sentinel node mapping is acceptable*) *or* N1 (*1-3 nodes positive* ***and*** *no extracapsular extension*). This represents a cohort of patients that would not ordinarily receive axillary irradiation. (subjects with DCIS are exempt from nodal staging)
- Clearly visible target as defined by ultrasound, surgical clips, or mammography
- Unifocal breast cancer *(single focus which can be encompassed by one lumpectomy)*
- Negative microscopically-assessed surgical margins
- Negative post-lumpectomy mammogram if cancer presented with malignancy-associated microcalcifications
- No Paget's disease of the nipple or EIC by the Harvard definition, i.e. 1) more than 25% of the tumor is DCIS and there is DCIS in adjacent breast tissue, or 2) an intraductal carcinoma with microinvasion.
- No collagen vascular disease (systemic lupus erythematosis, scleroderma, or dermatomyositis)

- No previous radiation or chemotherapy for current breast cancer
- No co-existing medical conditions with life expectancy < 2 years
- Age > 18 years old
- No pregnant or lactating women.
- No psychiatric or addictive disorders which would preclude obtaining informed consent or completing the full series of brachytherapy treatments on an outpatient basis.
- Signed study-specific consent form

4.0 REGISTRATION PROCEDURE

Patients must meet all eligibility requirements and sign an informed consent form prior to study enrollment. All patients will be registered by the Radiation Oncology Research Coordinators at (608)263-8500 prior to treatment. The Research Coordinators will verify eligibility, and completion of pretreatment evaluations.

5.0 RADIATION THERAPY: 3-D Based Treatment Planning

5.1 Brachytherapy/Target Visualization

Patients will undergo an interstitial implant, either utilizing a prone stereotactic method or a supine, ultrasound-guided or CT-guided technique, both under local anesthesia. Multiple catheters must be placed either free-hand or with the template system. Single balloon intracavitary catheter (MammoSite) is not permitted.

5.2 Target Volume Definition

Radioactive implants following lumpectomy are intended to deliver a tumoricidal dose to the target volume. The delineation of this target volume is essential for prescribing a dose and dose distribution capable of sterilizing occult tumor foci in the breast tissue surrounding the excision cavity. The target can be defined either by surgical clips visualized on stereotactic digital mammography, ultrasound, or CT visualization of the post-surgical seroma with subsequent Omnipaque nonionic contrast injection. The target volume will be defined as the volume encompassed by an irregularly-shaped surface 1.5-2 cm outside the excision cavity in all dimensions unless limited by skin or chest wall.

5.3 Implant Geometry Design

- Peripheral coverage is obtained positioning at least one catheter on each side 1 cm or more beyond the target volume. The other dimension of peripheral coverage is determined by the length of the active sources within each catheter.
- The catheters must be parallel to each other and as straight as possible.
- The rigid template will be used for the prone stereotactic method. The advantage of templates is precise geometrical source distribution, but there may be a problem with coverage of a curved, irregularly-shaped target volume. This can be overcome by the addition of free-hand catheters in areas of potential cold spots, thereby improving geometric volume coverage. This free-hand technique will be used with ultrasound or CT guidance for the supine method.

5.4 3-D CT Based Treatment Planning

CT based planning will be used for dosimetric evaluation. Simulator-based planning is not permitted.

5.5 Dose Prescription

High dose-rate: Patients will receive either a total dose of 34 Gy given BID at 3.4 Gy per fraction (10 fractions), or 32 Gy given BID at 4.0 Gy per fraction (8 fractions) to be delivered with a high dose-rate Ir-192 source as an outpatient. Each fraction will be separated by a minimum of 6 hours.

5.6 Dosimetric Characteristics

- Dose optimization will be guided by dose homogeneity index (DHI) which is defined as DHI = $(V_{100}-V_{150})/V_{100}$, where V_{100} and V_{150} are the volumes covered by the 100% and 150% isodose lines, respectively. The DHI must be between 0.7-1.0.
- The dose must be prescribed to a depth of $\geq$ 5 mm from the skin surface.
- The following dosimetric parameters must be recorded on the dosimetry form: (1) target volume, (2) seroma volume, (3) percent target covered by chosen isodose line, (4) # of catheters, (5) volume of implant, and (6) V_{100} and V_{150}, (7) DHI, and (8) NTDmeans of heart, lung, and contralateral breast from DVH analysis.

5.7 Photography Documenting Implant Geometry

At least one digital image is required - a close-up encompassing the treated breast only in a position which optimally exhibits the implant geometry, taking care to exclude the patient's face.

5.8 Toxicity Reporting (Serious Adverse Effects):

University of Wisconsin Hospital and Clinics has created a data and safety monitoring plan, and a data and safety monitoring board to closely monitor the proposed study (Appendix). Modified RTOG toxicity scoring will be utilized (Appendix).

6.0 SYSTEMIC THERAPIES

- No prior chemotherapy. Subsequent systemic therapy will be at the discretion of the medical oncologist.
- Chemotherapy regimens should be started no earlier than 2 weeks after the removal of the brachytherapy catheters.
- Tamoxifen or other hormonal agents should not be given during brachytherapy.

7.0 PATHOLOGY

- All outside pathology slides should be reviewed at UW.
- Measurement of the resected breast specimen should be obtained in three dimensions and recorded if possible (gross or microscopic measurement is acceptable).
- If of adequate size, tumor should be harvested for estrogen and progesterone receptor determination. Immunohistochemical staining is an alternative.
- HER2/neu testing should be done in all patients if possible.
- Multiple blocks of the primary tumor and of breast tissue from the inked margins should be taken, the latter to confirm negative margins. Margins generally are **positive** if there is invasive or noninvasive tumor at the inked resection margin, **close but negative** if the tumor is within 2mm of the inked margin, and **negative** if the tumor is > 2mm from the inked margin. Extent of negative margin should be recorded as (≤ 2mm; 2-10mm; ≥10mm) if possible.

- Pathology report must include DCIS or invasive, LVI, lymph node status, histological subtype, grade, and EIC if present.

8.0 PATIENT ASSESSMENTS

8.1 Study Parameters

Assessment	Pre Rx	During/After Brachytherapy	Post RX 4-6 weeks	Post RX 6 mos.	Post RX 1 year
H & P (Initial Eval Form)	X				
Chest x-ray	X				
Lab studies[a]	X				
H & P (Follow-up Form)			X	X	Xc
Disease status	X		X	X	Xc
Toxicity Assessment		X	X	X	Xc
Mammograms	Xd			X	Xe
Cosmesis, Pt (Form)	X			X	Xb
Cosmesis, MD (Form)	X			X	Xb
Photographs	X	X	X	X	Xc
Questionnaire (QOL)	X	X	X	X	Xb

a. CBC, platelets, PTT, PT, BUN. creatinine, lytes
b. Yearly thereafter upto 5 years.
c. Clinical examination and disease status assessment at 6 month intervals for the first 5 years and yearly intervals thereafter. (Can be done via clinic visit notes from other physicians involved in patient's care or via telephone follow-up).
d pre and post lumpectomy (if applicable)
e Every 6 months for 3 years and then yearly for 5 years (for treated breast) and yearly for opposite breast

8.2 Response Criteria - Treatment failure

- The definition of a treatment failure is: histologic evidence of recurrent carcinoma, either invasive or non-invasive *(except LCIS)* in the ipsilateral breast at 5 years.
- Ipsilateral breast recurrences will be considered **local *(infield)*** if they occur within the prescription isodose volume, **peripheral** if between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume. Ipsilateral recurrences will be considered **non-contiguous or extrafield** if they are beyond the peripheral volume described above.
- Ipsilateral axillary, infraclavicular, internal mammary, or supraclavicular recurrence or distant metastases will not be considered a treatment failure unless accompanied by ipsilateral breast recurrence.

8.3 Toxicity Criteria

- Patient will be seen on a daily basis by treating physician while receiving radiation therapy. Toxicities resulting from brachytherapy will be collected and graded according to the Modified RTOG criteria (Appendix IV). **Any toxicities grade 3 or higher will be promptly reported to DSMB and IRB as specified in the appendix.**

8.4 Definitions of Levels of Cosmetic Outcome:

- Patients will be grouped according to chemotherapy or hormonal therapy. Cosmesis will be graded by the patient and the radiation oncologist pre-RT, 6

and 12 months after completion of therapy and at yearly intervals thereafter. Cosmesis will also be evaluated from the photographs submitted to investigators at required intervals. The following established cosmesis scoring system will be used:

- *Excellent* - When compared to the untreated breast, there is minimal or no difference in the size, shape or texture of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.
- *Good* - There is mild asymmetry in the size or shape of the treated breast as compared to the normal breast. The thickening or scar tissue within the breast causes only a mild change in the shape.
- *Fair* - There is obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast.
- *Poor* - There is marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue.

8.5 Photographs

- Routine photographs must be taken of the post-surgical breast prior to catheter placement. At least one photograph of the breast with catheters in place, prior to loading the radioactive sources, is required. Photographs should also be taken at prior to implantation, 4-6 weeks, 6 months, 12 months post-implant, and yearly thereafter. Images will be evaluated for any visible complication, degradation, or improvement of cosmesis or local/regional treatment failure. Digital images will be used. Post surgical *(pre-catheter)* and all follow-up photographs should always follow the guidelines specified in the next section. Photographs will be kept with the patient's medical record.
- The first photograph should be a closeup encompassing only the treated breast at a 45° oblique with arms elevated over the head. The second photograph should 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 and framing or focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry. .

9.0 DATA COLLECTION

9.1 Summary

Prior to brachytherapy

- Eligibility Checklist
- Initial Evaluation Form (Appendix III)
- Patient QOL form (Appendix III)
- Cosmesis Forms (Appendix III)

At completion of brachytherapy

- Patient QOL form (Appendix III)
- Treatment Toxicity Form
- Radiotherapy Treatment/Dosimetry Form (Appendix III)

At 4-6 wks, 6 mo., and 12 months after implant; q 6 months up to 5 years, then annually. Also at progression/relapse and at death

- Follow-up Form (Appendix III) -- Can be done via clinic visit notes from other physicians involved in patient's care or via telephone follow-up

At 6 mo. and 12 months after the completion of therapy, then yearly up to 5 years

- Cosmesis Forms
  - *Patient* (Appendix)

- *Radiation Oncologist* (Appendix III)
- Patient QOL form (Appendix III)

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Ipsilateral breast recurrences

This is a one-arm equivalence trial comparing the local failure rate in 300 patients receiving brachytherapy to the historical mean event rate of 6% (see Table below) among patients given external beam radiation. The null hypothesis thus is that brachytherapy is worse than external beam radiation; the alternative hypothesis is that the two regimens are clinically equivalent, meaning that brachytherapy is not significantly worse than external beam. Symbolically

H_0: Pr(Local Failure, brachy.) > Pr(Local Failure, EB) + Δ

H_A: Pr(Local Failure, brachy.) <= Pr(Local Failure, EB) + Δ,

where "Pr()" denotes the probability of its argument and Δ is the margin of clinical equivalence. That is, we consider two regimens whose event probabilities differ by less than Δ to be equivalent. For this study we take Δ to be 5%.

The analysis will be conducted by calculating an exact 95% confidence interval for the probability of local failure in the brachytherapy group and noting whether it includes 11% (obtained as Pr(Local Failure, EB) + Δ = 6% + 5%). If it does then we will not reject the null hypothesis and equivalence cannot be concluded. If the confidence interval for the probability of local failure given brachytherapy falls entirely below 11% then we conclude that brachytherapy is clinically equivalent (or possibly superior) to external beam radiation as a treatment for these patients. If, among 300 patients, there are 23 local failures (7.7%) then the exact 95% confidence interval for the true failure rate will be (5.2%, 11.2%). If there are 22 failures (7.3%) then the confidence interval will be (5.0%, 10.8%). Therefore we will reject the null hypothesis and conclude equivalence if we observe 22 or fewer local failures.

Power here is the probability that we will reject the null hypothesis and conclude equivalence given that it truly holds. If the two regimens rates are identical, such that Pr(Local Failure, brachy.) = Pr(Local Failure, EB) = 6%, then the power with 300 patients is 86%. If the brachytherapy rate is inferior to external beam by 2%, so that Pr(Local Failure, brachy.) = 8% and Pr(Local Failure, EB) = 6% (which is still within our definition of clinical equivalence) then power drops to 39%. However if the brachytherapy rate is superior to external beam by 2% so that Pr(Local Failure, brachy.) = 4% and Pr(Local Failure, EB) = 6% then the power is 99.8%. Therefore if the local failure is 6% or less in the brachytherapy group then this study is well-powered to conclude equivalence within a margin of 5%.

Study	# Patients	5-year LF Rate (%)	Weighted LF rate
French	88	4.5	396
NSABP B-06	628	5	3140
NCI	121	2	242
Danish	430	5	2150
EORTC	456	11	5016
Milan	352	3	1056
Total/Mean	***2075***	***5.08***	***5.78%***

10.1.2 Toxicity Assessment

Patient will be seen on a daily basis by treating physician while receiving radiation therapy and during each follow-up visit. Toxicities resulting from brachytherapy will be collected and graded according to the Modified RTOG Toxicity Criteria (appendix)**.** Any toxicities grade 3 or higher will be promptly reported to DSMB and IRB.

10.1.3 Cosmesis

Cosmetic results will be assessed by both the physician and the patient pre-brachytherapy, at six and twelve months, then annually. Photographs are to be taken at these time points according to the specifications in Section 8.5.

10.1.4 Quality of Life Assessment

Patient satisfaction with breast brachytherapy will be assessed by a questionnaire at defined intervals: pre-brachytherapy, at completion, 4-6 weeks post-brachytherapy, 6 months post-brachytherapy and annually thereafter. (attached forms)

10.1.5 Dosimetric analysis

Dosimetric analysis will be performed and compared to an external beam plan for each patient. The NTDmeans from dose volume histogram analysis for each individual patient for skin, heart, lung, and contralateral breast will be determined.

10.1.6 Mammography Interpretation

The ability to interpret mammography after interstitial brachytherapy will be prospectively evaluated by the radiologist.

10.1.7 Disease-Free Survival and Mastectomy-Free Survival

All disease recurrences and surgical interventions will be recorded. In disease-free survival (DFS), any tumor recurrence or death will be considered a failure. In mastectomy-free survival (MFS), the failures will be mastectomy and death. Ipsilateral breast recurrence rate (subdivided by in-field, peripheral and extra-field locations) ipsilateral nodal recurrence rate and distant metastasis rate will be calculated.

10.1.9 Overall Survival (OS)

Death from any cause will be considered a failure.

10.2 Study Design

The sample size will be approximately 300 patients. The toxicity rate will be summarized along with exact 95% confidence intervals. DFS, MFS and OS

results will be summarized using Kaplan-Meier curves with the usual Greenwood estimates of standard errors. Summary statistics will be given for cosmesis, quality of life, dosimetric, and mammography interpretation measures. All analyses will be conducted on an intent-to-treat basis; that is, all registered patients will be included in the analyses.

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Appendix I

Data Safety and Monitoring Plan

Oversight And Monitoring Plan

The UWCCC Clinical Trials Monitoring Committee (CTMC) is responsible for monitoring data quality and patient safety for all UWCCC clinical studies. A summary of CTMC activities follows:

Review of all clinical trials conducted at the UWCCC for progress and safety
Review of all adverse events requiring expedited reporting as defined in the protocol
Review of reports generated by the UWCCC data quality control review process
Submit recommendations for corrective action to the Clinical Affairs Committee (CAC)
Notify the Study Chair of the CTMC recommendation to the CAC
Notify external sites participating in multiple-institutional clinical trials coordinated by the UWCCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.

Monitoring And Reporting Guidelines

Phase I/II and Phase II Trials

Data related to these trials are discussed at regularly scheduled Disease Oriented Working Group meetings where the result of each patient's treatment is discussed and the discussion is documented in the minutes. The discussion will include for each treatment arm/dose level, the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. Twice yearly, summaries will be submitted to the Clinical Trials Monitoring Committee for review.

REVIEW AND OVERSIGHT REQUIREMENTS

Adverse Event – Reported By Phone Within 24 Hours

Adverse events requiring expedited reporting by phone within 24 hours (as described in the protocol) will also be reported by phone to the Clinical Trials Monitoring Committee administrator within one working day. Confirmation that all appropriate parties were notified will be done at this time. Hardcopies or electronic versions of NCI ADEERS form (#3500) and/or any other documentation available at that time will also be reviewed by the Committee Chair who will determine if immediate action is required. Within ten working days all subsequent SAE documentation that is available will be submitted with a completed UWCCC SAE Evaluation Checklist to the Committee Chair who will determine if further action is required. All information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

Adverse Event – Reported within 10 Days

Adverse events requiring expedited AE reports in writing within 10 working days (as described in the protocol) will be sent to the UWCCC Safety Coordinator. Hardcopies or electronic versions of NCI ADEERS form (#3500) or other required forms will be submitted along with a copy of the SAE Evaluation Checklist. The Committee Chair will review these forms and determine if further action is required. This information will be tracked in the UWCCC database.

If the AE occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the event and resulting action within one working day of the determination.

Study Progress – Quarterly Review

Study progress assessment to determine whether accrual projections are being met and to determine if the trial should be continued based upon the likelihood of timely completion are reviewed at quarterly Clinical Trials Monitoring Committee meetings. Cumulative reports of adverse events requiring expedited reporting and any new adverse event requiring expedited reporting are also reviewed at the committee's quarterly meetings.

An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. This information is provided by Disease Group meeting minutes, internal audit and/or response review reports. The committee may request external DSMB reports or further information from the Disease Groups, or Study Chair.

The Clinical Trials Monitoring Committee recommendations for modifications to the trial are forwarded to the Clinical Affairs Committee. The Study Chair is notified of this recommendation in order that he/she may alert all investigators, at the UWCCC and at external sites involved in the trial, about the potential action. At this time the Study Chair may submit to the Clinical Affairs Committee additional information that could affect the Committee's decision. The Clinical Affairs Committee will notify the Study Chair if they concur with the Clinical Trials Monitoring Committee recommendations, including suspension or closure. The Study Chair will notify all investigators involved with the study at UWCCC and external sites, the IRB, the sponsor and the funding agency and provide written documentation of these notifications to the Clinical Affairs Committee.

The UWCCC Clinical Research Committee (CRC), composed of Cancer Center senior leaders oversees these activities.

Review of Adverse Event Rates

Once a month, adverse event rates will be monitored utilizing the UWCCC Clinical Trials database. If any study has had two or more of the same AE reported in a month or more than six of the same AE in six months, the CTMC Chair will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair or the external DSMB if warranted. The Committee Chair will determine if further action is required.

If this occurs on a multiple-institutional clinical trial coordinated by the UWCCC, the Safety Coordinator will insure that all participating sites are notified of the resulting action.

EXPEDITED REPORTING OF ADVERSE EVENTS

Depending on the nature, severity, and attribution of the event an ADR report will be phoned in, submitted in writing, or both according to Tables A-D below. Telephoned Adverse Events must also be reported by phone to the UWCCC Clinical Trials Monitoring Committee within one working day of the event. All adverse events must also be reported to the UW IRB, and any sponsor/funding agency not already included in the list.

Telephone reports to: *Rakesh Patel, M.D.* *(608)263-8500 Phone* *(608)263-3526 fax* UWCCC Clinical Trials Monitoring Committee Administrator 608-263-0169 within one working day of the event
Written reports to: *Rakesh Patel, M.D.* *(608)263-8500 Phone* *(608)263-3526 fax* UWCCC Clinical Trials Monitoring Committee Administrator – FAX 608-263-8613 or deliver to K4/642 UW IRB – Copy of final written report to Sponsor.

Summary of Reporting Requirements for Adverse Events on Trials Involving Commercial Agents with No IND Is Voluntary (Med Watch Form)			
EXPEDITED REPORTING FOR PHASE 2 AND PHASE 3 STUDIES			
Unexpected Event		**Expected Event**	
GRADES 2 - 3 Attribution of Possible, Probable, or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5, Regardless of Attribution**
Expedited report within 15 working days to FDA. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days.	Adverse Event Expedited Reporting NOT required.	Report by phone to FDA within 24 hrs. Expedited report to follow within 15 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 15 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

Note: Use Med Watch Form

For Hospitalization Only – Any medical event equivalent to the CTC Grade 3,4,5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.

Expedited reporting may not be appropriate for specific expected adverse events for certain later phase 2 and phase 3 protocols. In those situations the adverse events that will not have expedited reporting must be specified in the text of the approved protocol. An expected Grade 3 event that is using the generic reporting criteria, for instance. In a trial of

investigational agents where grade 3 diarrhea requiring hospitalization is expected, only diarrhea requiring ICU care (Grade 4) might be designated for expedited reporting.

Appendix III: Initial Evaluation Form (Page 1)

Patient's Initials | **Study ID #**

If this is a revised or corrected form, indicate by checking box. ☐

INSTRUCTIONS: Submit this form at time of patient's entry on study. Use -1 for unknown or not applicable unless otherwise specified in the code table. Record dates as mm/dd/yyyy.

☐☐ **AGE AT REGISTRATION**

MAMMOGRAPHIC FINDINGS
a. PRE-BIOPSY MAMMOGRAPHIC FINDINGS

1 No
2 Yes
9 Unknown

☐ Microcalcifications associated with malignancy
☐ Microcalcifications not associated with malignancy
☐ Mass
☐ Parenchymal distortion
☐ Multicentric lesion

b. ☐ **PRESENCE OF MICROCALCIFICATIONS ON POST-EXCISION / TYLECTOMY MAMMOGRAM?**

1 No
2 Yes, associated with site of malignancy
3 Yes, not associated with malignancy
9 Unknown

☐ **IF MULTIPLE LESIONS IN ONE QUADRANT, ARE LESIONS < 4CM APART?**

1 No
2 Yes

TUMOR MEASUREMENTS (CLINICAL)
Maximum Diameter

☐.☐ **cm** (On pre-biopsy mammogram)
☐.☐ **cm** (On palpation, if not palpable enter '0')

a. ☐ **AFFECTED BREAST**

1 Left
2 Right
3 Bilateral
9 Unknown

b. ☐☐ **LOCATION OF LESION**

01 Upper outer quadrant
02 Upper inner quadrant
03 Lower outer quadrant
04 Lower inner quadrant
05 Central

Mark Incision site and lesion location on diagrams above

☐ **CHEMOTHERAPY**

1 No
2 Yes, prior to XRT, end date_____-____-____
3 Yes, after XRT
9 Unknown

☐ **HORMONAL THERAPY**

1 No
2 Yes, specify agent:_____

☐ **PRIOR RADIATION THERAPY TO EITHER BREAST?**

1 No
2 Yes

☐ **FAMILY HISTORY OF CANCER?** *(Mark relationship below)*

*If yes, breast CA?*_____
*other CA?*_____

GYNECOLOGIC HISTORY:
G__P__
Menopausal status:_____**Age at Menopause**_____
Age at Menarche:_____
Age at 1st pregnancy_____
Exogenous Hormonal Exposure_____
Previous Breast Biopsies_____

PAST MEDICAL HISTORY:
Conditions/ Surgeries:_____

Medications:_____

Allergies: _____

☐ **HISTORY OF COLLAGEN VASCULAR DISEASE?**
(Systemic Lupus Erythematosis, scleroderma, dermatomyositis with elevated CPK level)

SMOKING HISTORY: ____YRS _____packs/day

Appendix III: Initial Evaluation Form (Page 2)

PATHOLOGY DETAILS

SURGICAL PROCEDURES — **Date**

- ☐ FINE NEEDLE ASPIRATION ___-___-____
- ☐ CORE NEEDLE BIOPSY ___-___-____
- ☐ EXCISIONAL BIOPSY ___-___-____
- ☐ TYLECTOMY ___-___-____
- ☐ RE-EXCISION ___-___-____

PATH MEASUREMENT OF PRIMARY LESION

☐☐.☐ cm X ☐☐.☐ cm X ☐☐.☐ cm
Maximum diameter — Cross diameter — Cross diameter

☐ **HISTOLOGIC CONFIRMATION**
1 Invasive ductal
2 Medullary
3 Papillary
4 Colloid (mucinous)
5 Tubular

☐ **TUMOR GRADE**

PATHOLOGIC CHARACTERSITICS
1 NOT PRESENT
2 PRESENT
3 UNKNOWN

- ☐ EXTENSIVE INTRADUCTAL COMPONENT
- ☐ SKIN INVOLVEMENT
- ☐ LYMPHATIC VESSEL INVASION
- ☐ OTHER, SPECIFY _____

☐ **FINAL SURGICAL MARGINS**

1 Negative inked margin (Circle: <2mm, 2-10mm, >10 mm)
2 Positive margin initially with negative re-excision

☐ **EXCISION CAVITY DEFINED WITH SURGICAL CLIPS**
1 No
2 Yes

☐ **AXILLARY NODE DISSECTION**
0 None (skip to Q#10)
1 Sampling / Level I nodes
2 Sampling / Level I, II nodes
3 Sampling / Level I, II, III nodes
4 Complete resection / Level I, II
5 Complete resection / Level I, II, III
6 Other, specify_____

☐ **SENTINEL NODE SAMPLING**
1 No
2 Yes*

☐ *If yes, was Immunohistochemical (IHC) method used?

☐☐ **NUMBER OF NODES EXAMINED**

☐☐ **NUMBER OF NODES POSITIVE**

☐ **EXTRACAPSULAR EXTENSION**

AJCC STAGE

T ☐ N ☐ M ☐

☐ **WAS A PRE-TREATMENT PHOTOGRAPH TAKEN**

1 No
2 Yes

_____ Signature of person completing this form:

___-___-____ Date form completed

Appendix III: Follow-up Form

If this is a revised or corrected form, indicate by checking box. ☐

INSTRUCTIONS: Submit this form at the appropriate follow-up interval and whenever there is a change in the patient's status. Use - 1 for unknown or not applicable unless otherwise specified in code table. Enter dates in mm-dd-yyyy.

PATIENT INITIALS: _____

STUDY ID#: _____

DATE OF EVALUATION ____-____-____

☐ # MONTHS SINCE BRACHYTHERAPY PROCEDURE

☐ PATIENT QUALITY OF LIFE FORMED COMPLETED?

☐ PATIENT COSMESIS FORM COMPLETED?

1 EXCELLENT
2 GOOD
3 FAIR
4 POOR

☐ PHYSICIAN COSMESIS FORM COMPLETED? (Initials:_____)

1 EXCELLENT
2 GOOD
3 FAIR
4 POOR

☐ RTOG TOXICITY SCORE: SKIN

GRADE 0 None
GRADE 1 Slight atrophy; Pigmentation change; Some hair loss
GRADE 2 Patch atrophy; Moderate telangiectasia; Total hair loss
GRADE 3 Marked atrophy; Gross telangiectasia
GRADE 4 Ulceration

☐ RTOG TOXICITY SCORE: SUBCUTANEOUS TISSUE

GRADE 0 None
GRADE 1 Slight induration (fibrosis) and loss of subcutaneous fat
GRADE 2 Moderate fibrosis but asymptomatic;
<10% linear reduction;Slight field contracture
GRADE 3 Severe induration and loss of subcutaneous tissue;
>10% linear measurement;Field contracture
GRADE 4 Necrosis

CURRENT TUMOR STATUS

☐ NO EVIDENCE OF DISEASE

☐ IPSILATERAL BREAST TUMOR RECURRENCE

☐ LOCAL (infield) - within the prescription isodose volume

☐ PERIPHERAL - between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume.

☐ NON-CONTIGUOUS/EXTRA-FIELD - beyond the peripheral volume described above.

☐ OTHER SITES OF CANCER RECURRENCE

☐ NODAL (Specify location)_____

☐ CONTRALATERAL BREAST_____

☐ DISTANT METS (Specifiy location)_____

☐ NEW PRIMARY LESION (Specify location)_____

☐ MAMMOGRAM SINCE LAST VISIT

1 No
2 Yes *
*If yes, date of study ____-____-____

☐ SUSPICIOUS FINDINGS ON MAMMOGRAM

0 Not applicable/no mammogram
1 Negative mammogram
2 Microcalcifications only
3 Mass density only
4 Both, mass and microcalcifications
5 Other, Specify _____

☐ WERE PHOTOGRAPHS TAKEN DURING THIS VISIT?

Appendix III: Patient Cosmesis Form

INSTRUCTIONS: The first page of this form is completed by the clinical staff. You have been treated with breast conserving therapy for breast cancer. As you know, a reason for choosing this treatment is to keep a breast that looks and feels as close to normal as possible. Your opinion concerning the appearance of your breast is valuable to us. This form will be confidential. Circle the number next to the word that best describes how your breast looks now. Circle only one answer per question. Use -1 for N/A or unknown unless otherwise specified in codetable. Dates are recorded mm/dd/yyyy unless otherwise specified.

☐ DE

1 ___-___-____ **DATE QUESTIONNAIRE COMPLETED**

2

1 EXCELLENT: when compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.

2 GOOD: there is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.

3 FAIR: obvious differences in the size and shape of the treated breast. This change involves a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.

4 POOR: marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

3 **MY SATISFACTION ABOUT THE TREATMENT AND RESULTS IS:(CIRCLE THE NUMBER NEXT TO THE ITEM THAT BEST DESCRIBES YOUR SATISFACTION.)**

1 I am totally satisfied with the treatment and results
2 I am not totally satisfied, but would choose brachytherapy (radioactive implants) again
3 I am not totally satisfied and would choose the standard 5 or 6 weeks of external beam therapy if I had it to do over again
4 I am dissatisfied with the brachytherapy (radioactive implants)

4 **BEFORE ANY TREATMENT TO YOUR BREAST, THE SIZE OF YOUR BREASTS WAS (CIRCLE THE NUMBER THAT BEST DESCRIBES YOUR BREAST SIZE PRIOR TO TREATMENT)**

1 The same on both sides
2 Larger on right
3 Larger on left

5 **THE SIZE OF YOUR BREASTS NOW IS (CIRCLE THE NUMBER THAT BEST DESCRIBES YOUR BREAST SIZE NOW)**

1 The same on both sides
2 Larger on right
3 Larger on left

Initials_____

Appendix III: Physician Cosmesis Form

The physician should not share his evaluation with the patient, as it may influence subsequent patient evaluations. Do not compare to previous evaluations. It is the evolution of cosmetic changes we are studying. Attach cover sheet before submission. Dates are recorded mm/dd/yyyy unless otherwise specified.

☐ DE

1 ____-____-_____DATE EVALUATION DONE

2 **PLEASE ASSESS THE COSMETIC RESULTS OF BREAST CONSERVATION THERAPY AT THIS TIME. (Circle the number next to the word that** best describes the cosmetic results.)

1 EXCELLENT: when compared to the untreated breast or the original appearance of the treated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue, or seroma within the breast but not enough to change the appearance.

2 GOOD: there is mild asymmetry between the breasts, which means that there is some acceptable difference in the size or shape of the treated breast as compared to the opposite breast or the appearance of the breast before treatment. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes a mild change in its shape or size.

3 FAIR: moderate deformity of the breast, with an obvious difference in the shape and size of the treated breast. This change involves 1/4 or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast and there may be obvious color changes.

4 POOR: marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue. The skin change may be obvious and detract from the appearance. Severe scarring and thickening of the breast which clearly alters its appearance may be present. In retrospect, the breast may have been better treated by a mastectomy.

3 **CODE A RESPONSE FOR EACH OF THE FOLLOWING ITEMS**

1 None
2 Yes, seen on close observation
3 Yes, obvious on casual observation

☐ **SKIN TELANGIECTASIA**

☐ **SKIN ATROPHY**

☐ **POCK MARKS**

☐ **HYPERPIGMENTATION**

☐ **ERYTHEMA**

☐ **FIBROSIS**

☐ **SKIN DIMPLING OR INDENTATION**

☐ **OTHER SIGNIFICANT TREATMENT EFFECTS**

SPECIFY_____

COMMENTS_____

_____ ____-____-_____

Signature **Date**

Appendix III: Spitzer Quality of Life Index (SQLI)

Instructions: Score each item **A** through **E,** either 2, 1, or 0 which describes how you felt **during the last week.** Circle only one answer for each item.

A	**ACTIVITY**	**DURING THE LAST WEEK I HAVE:**
	2	been carrying out my normal activities, working or studying full-time, or nearly so, in usual occupation; or managing own household, or participating in unpaid voluntary activities, whether retired or not.
	1	been working or studying, in usual occupation or managing own household or participating in unpaid volunteer activities but requiring major assistance or a significant reduction in hours worked or a sheltered situation or was on sick leave.
	0	not been working or studying in any capacity and not managing own household.
B	**DAILY LIVING**	**DURING THE LAST WEEK I HAVE:**
	2	been self-reliant in eating, washing, toileting and dressing; using public transportation or driving
	1	been requiring assistance (another person or special equipment) for daily acitivities and transportation but performing light tasks.
	0	not been managing personal care or light tasks and/or did not leave own home or institution at all.
C	**HEALTH**	**DURING THE LAST WEEK I HAVE:**
	2	been appearing to feel well or reporting feeling "great" most of the time.
	1	been lacking energy or not feeling entirely "up to par" more than just occasionally.
	0	been feeling very ill or "lousy", seeming weak and washed out most of the time.

Appendix III: Spitzer Quality of Life Index (SQLI)

D	**SUPPORT**	**DURING THE LAST WEEK I HAVE:**
	2	been having good relationships with others and receiving strong support from at least one family member and/or friend.
	1	received or perceived the support from my family and friends as being limited which may be related to my condition.
	0	received support infrequently or only when absolutely necessary.
E	**OUTLOOK**	**DURING THE LAST WEEK I HAVE:**
	2	usually been appearing calm and positive in outlook, accepting and in control of personal circumstances, including surroundings.
	1	sometimes been troubled because not fully in control of personal circumstances or have been having periods of obvious anxiety or depression.
	0	been seriously confused or very frightened or consistently anxious and depressed.

IF YOU HAVE COMMENTS, PLEASE WRITE THEM HERE:_____

_____

_____

Patient's Initials _____ Date_____

Appendix IV: Toxicity Scale

RTOG Acute Toxicity Scoring

TISSUE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 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 desquamatiom other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

RTOG Late Toxicity Scoring

ORGAN TISSUE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) 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

Appendix III: Radiotherapy Treatment/Dosimetry Form