A Phase II Study of Accelerated Hypofractionated Radiotherapy (AHF-RT) after Breast Conserving Surgery (BCS) in Medically Underserved Patients.

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Amendment #3:

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ATTACHMENTS:

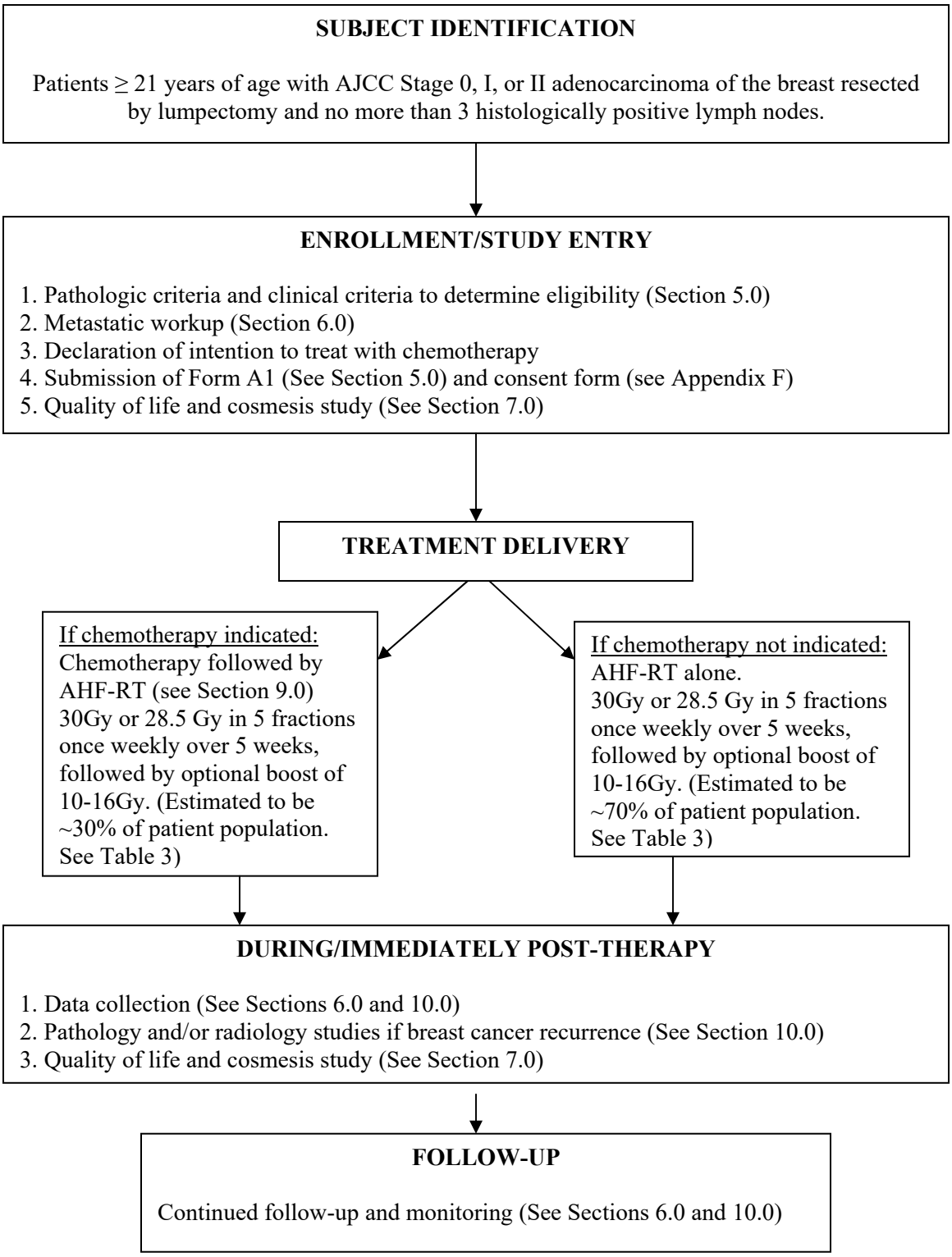
1.0 **STUDY SUMMARY**

This Phase II non-randomized trial will evaluate the effectiveness of whole-breast accelerated hypofractionated radiotherapy (AHF-RT; 28.5 or 30 Gy in 5 fractions delivered once weekly over 5 treatment weeks) following lumpectomy for early stage breast cancer. The study will compare the toxicity, local control, overall survival, recurrence-free survival, and distant disease-free survival to modern studies of standard conventionally fractionated radiotherapy (CF-RT; 50-60 Gy in 25-30 daily fractions delivered over 5-6 weeks) and hypofractionated radiotherapy (HF-RT; 42.5 Gy in 16 daily fractions delivered over 3-4 weeks). It will also look at quality of life (QOL) issues related to cosmesis, fatigue, treatment-related symptoms, and perceived convenience of care. In addition, a cost-effectiveness analysis will be carried out in conjunction with the University of Louisville's School of Public Health for comparative study with other breast radiotherapy regimens.

To qualify for the trial, patients must have stage 0 (DCIS) or stage I or II invasive adenocarcinoma of the breast with no evidence of metastatic disease. Eligibility will be targeted to patients whose home residence is considered rural or Appalachian by Kentucky Cancer Registry criteria, and/or who reside ≥ 10 miles from the nearest radiation oncology center, and/or are uninsured, and/or are members of an underserved minority group, and/or are judged by their treating physicians to suffer significant financial and/or transportation hardship during a typical course of CF-RT or HF-RT. Women must have undergone a lumpectomy with the margins of the resected specimen histologically free of cancer including DCIS. For patients with positive axillary nodes, eligibility is restricted to those with 0 to 3 positive axillary nodes. Patients will be analyzed by subgroups according to disease stage, menopausal status, and intention to receive chemotherapy. Following stratification, patients will be enrolled to receive AHF-RT. Radiotherapy will be given once weekly (ideally on the same day each week) over a period of 5 weeks. Patients scheduled to receive cytotoxic chemotherapy will receive chemotherapy before their radiation therapy.

This trial is designed to accrue approximately 250 patients over a period of 5 years with accrual projected to be approximately 3 patients each month for the first year increasing to 5 patients each month in subsequent years (see Section 2.3). The primary endpoint will be to estimate the cumulative incidence of in-breast tumor recurrence (IBTR), which is anticipated to be no higher than that seen in similar studies of CF-RT and HF-RT (namely, 3-5% at 3-5 years). In addition, detailed data on radiation quality, dose to normal tissues, toxicity and cosmetic outcome (including digital photography) will be collected to facilitate meaningful comparison to recently reported and in-progress studies of varying breast radiotherapy schedules. Finally, cost-effectiveness analysis (CEA) and quality-of-life (QOL) metrics will be incorporated in order to further characterize factors underlying the rural disparity and to track adherence to treatment and follow-up care at multiple longitudinal time points. Please refer to Figure 1 for the study schema and flow diagram.

FIGURE 1: Study Schema/Flow Diagram



2.0 **BACKGROUND**

2.1 **Clinical Background**

Appropriate primary local management of pre-invasive and early stage breast cancers involves the choice of breast conserving surgery (BCS) followed by radiotherapy (RT) verses mastectomy. Long-term data from multiple randomized studies demonstrates equivalence across all major disease-control endpoints for these two approaches, and thus BCS with adjuvant RT is preferred by the overwhelming majority of eligible patients[1-2]. As a result, mastectomy rates across the US have steadily declined over the last few decades[3]. Although recent, less mature studies have suggested that BCS alone may be an appropriate choice for well-selected elderly and ductal carcinoma in situ (DCIS) patients, the addition of RT is recommended for nearly all patients after BCS for superior local control and long-term overall survival[4-6].

As mastectomy rates have decreased over time, the challenge has been to ensure adequate therapy with consistent delivery of RT after BCS, especially among vulnerable populations who may lack access to oncology services[7-8]. In the United States, reports regarding rates of application of RT after BCS contain estimations that vary widely (range: 65%-95%) according to study type and makeup of the analyzed cohort[7-17]. Larger national cross-sectional studies drawn from Surveillance Epidemiology and End Results (SEER) and/or Medicare databases tend to show relatively lower rates of RT (range: 65%-85%)[7-12]. On the other hand, comparatively smaller studies that involve data extracted from prospective trials[17], audits of comprehensive cancer canters[16, 18], and patient self-reports[15] typically show higher RT usage (range: 80-95%). One consistent quality of most of the aforementioned studies is the ability to identify subpopulations of patients underserved with regard to RT access and regular application. These disparities are varied and may be dramatic, and are most often associated with age, race, and geographic region[8-9, 12, 15-20]. In some studies, inadequate treatment has been linked to poorer disease-control endpoints and even overall survival in these patients[14, 21-25].

During the last decade, major cancer centers in large cities have paved the way for significant growth and spread of multidisciplinary breast cancer care with the integration of systemic therapies and access to specialized RT procedures. In the US, approximately 80% of the population lives in or near a major metropolitan center and thus the aforementioned studies are heavily influenced by the inclusion of significant number of urban patients[26]. In fact, subset analyses of nearly all national database studies on this subject indicate that the lowest relative rates of RT use after BCS exist in more sparsely-populated regions, especially the South and/or Southeast[8-10, 12, 17].

The Commonwealth of Kentucky does not encompass a city listed among the top 25 incorporated entities (according to the United States Census Bureau) nor a top 40 metropolitan statistical area (as defined by the United States Office of Management and Budget). Additionally, Kentucky does not contain a National Cancer Institute (NCI) designated cancer center. Recently, a collaborative study between investigators at the University of Louisville's James Graham Brown Cancer Center (Louisville, KY) and the

Kentucky Cancer Registry at the University of Kentucky's Markey Cancer Center (Lexington, KY) was completed with the purpose of identifying factors that influence the receipt of RT after BCS in Kentucky and the resultant impact on outcome. The results of this study will be presented at the 52nd Annual Meeting of the American Society of Radiation Oncology (ASTRO), October 31, 2010.

We analyzed the rate of adjuvant radiotherapy for 11,914 women who underwent BCS as primary surgical treatment for stage 0, I or II breast cancer between 1998 and 2007 using data from the Kentucky Cancer Registry. We assessed the probability of receiving radiotherapy using multi-variable logistic regression, and impact on outcome using Cox survival analysis. In summary, 66.2% of women received adjuvant radiotherapy for BCS over a 10-year period (annual rate range: 60.9%-70.1%). On multi-variable analysis, the rate of receiving radiotherapy was drastically lower for women older than 70 years (vs. younger, $p<0.0001$) and rural Appalachia (vs. non-Appalachia, $p<0.0001$) populations. The rate was modestly lower for African American (vs. white, $p = 0.0108$) women, and uninsured/government-insured (vs. privately insured, $p = 0.0201$) patients. Lack of radiotherapy was associated with an increased hazard ratio for death of 1.67 (95% CI: 1.508-1.851) on Cox survival analysis factoring age, stage, tumor size, grade, hormone receptors, smoking, and insurance. The ten-year overall survival for patients who received adjuvant radiotherapy vs. BCS alone was 79.7% vs. 67.6% ($p <0.0001$).

As a result, in Kentucky, adjuvant RT after BCS is disproportionately omitted in elderly, rural, racial minority and uninsured populations, and there has been little improvement in this measure over the last decade. This study was the largest of its kind specifically focused on an underserved Southern US population and the largest clinically significant disparity was found among rural patients. This report was one of the largest studies to date to identify an independent association of lack of RT with an increased hazard ratio for death. Lack of application of RT after BCS is a reliable indicator of inadequate access to other adjuvant therapies and poor post-treatment surveillance. Incentive programs focused on multidisciplinary care as a quality endpoint must be targeted to these underserved populations. AHF-RT is a convenient and cost-effective alternative to conventionally-fractionated RT and must be investigated to improve treatment access for rural and other underserved patients.

The provision of breast cancer therapy is a microcosm of the challenges facing the future of healthcare delivery in the United States as a whole. The widening of the so-called "healthcare gap" between the wealthy and poor, urban and rural populations is real, insidious and underway, especially with regard radiation therapy services. The explanation for this trend is simple: the current reimbursement model for radiation therapy services in the US, whether covered by private or governmental payers, depends primarily on the number of treatments delivered over the therapeutic course and/or technical complexity. More pragmatic, cost-effective regimens that are a step toward improvement in access, such as three-week HF-RT, are actually discouraged and underutilized by physicians, even when highly favored by patients.

Public health initiatives, such as AHF-RT, that have the capacity to favorably impact the major factors related to cost and access for a disease as prevalent as breast cancer are few and far-between. As the US population ages and screening tests increase in sensitivity, it is expected that radiotherapy services in the setting of BCS will continue to be in high demand. Thus, a larger annual population of women entering the age of highest risk for breast cancer combined with a projected physician shortage and the questionable long-term solvency of healthcare entitlement programs requires broad-based novel solutions to alter this trend and prevent worsening of current disparities. Safe and effective accelerated radiotherapy regimens that meet the needs of rural populations must be inexpensive, easily implemented and widely applicable. Only then will they result in expansion in access not only to radiotherapy, but other "down-stream" adjuvant chemo/hormonal therapies and follow-up care. The opening of the multidisciplinary breast cancer system to these underserved patients is thereby likely to significantly impact disease-specific endpoints and ultimately mortality.

2.2 **Supporting data for AHF-RT**

Initial studies of BCS combined with RT as an alternative to mastectomy utilized conventionally fractionated radiotherapy (CF-RT), in schedules of daily 1.8-2.0 Gy fractions tp a total dose of 45 to 50 Gy with or without an additional radiation boost to the tumor bed[1-2, 4]. Traditionally, this type of RT schedule, CF-RT has been advocated based upon the theory that small daily fraction sizes lower the risk of late normal tissue toxicity without compromising cancer control[27]. As a result, patterns-of-care studies have indicated that the vast majority of radiation oncologists in the US primarily employ CF-RT schedules in the treatment of breast cancer [28-30]. However, CF-RT has significant limitations, mainly related to the inconvenience to patients associated with undergoing daily treatment for 6 to 7 weeks and the cost of treatment (both direct health care expenditures and opportunity costs to the patient and society due to time away from home and work)[31-32]. In the United Kingdom and Canada, physicians have long used adjuvant hypofractionated radiotherapy (HF-RT), which both the total dose and the number of fractions are decreased compared to CF-WBI schemes. Multiple randomized clinical trials of HF-RT versus CF-RT show equivalent results, with HF-RT enabling shorter total treatment time, enhanced convenience, and lowers cost (Table 1)[27, 32-36 37].

Although 3-weeks of daily HF-RT is a significant improvement over the 6-7 week CF-RT course, the requirement of daily therapy continues to present barriers to underserved populations and regions with scarcity of oncology resources. The favorable results from the randomized clinical trials of HF-RT have yielded sufficient data to enable the investigation of accelerated hypofractionated radiotherapy (AHF-RT). AHF-RT, which delivers approximately 28.5Gy-33Gy to the entire breast in 5-6 Gy per fraction, once or twice weekly, has thus far shown promise in nonrandomized studies throughout France and randomized studies in both the United Kingdom and India (Table 2)[38-41]. Early Phase III data and long-term Phase II results show toxicity, cosmesis, and outcomes that are comparable to other traditional whole breast regimens. These favorable results have led to the current UK FAST trial (n = 900) testing 50 Gy in 25 fractions of whole breast CF-RT against two different regimens of AHF-RT delivered in a five-fraction schedule over

5 weeks (5.7 or 6 Gy per fraction, for a total dose of 28.5 Gy or 30 Gy, respectively)[42]. Our proposed study is the first investigation of AHF-RT in the United States as a public health intervention to increase the provision of adjuvant radiotherapy services to rural women in Kentucky and the wider region. The ultimate goal is increased utilization of RT after BCS among rural and underserved patients.

2.3 **Estimations of Eligible Patients and Enrollment.**

The James Graham Brown Cancer Center (JGBCC) at the University of Louisville School of Medicine (Louisville, KY) houses the only multidisciplinary breast cancer program in Kentucky certified by the National Accreditation Program for Breast Centers (NAPBC). The program is comprehensive in its offering of diagnostic, therapeutic, complementary and supportive resources to an extensive and diverse geographic region in central Kentucky and southern Indiana. Additionally, the program garners substantial clinical trials support, maintains dedicated biostatisticians, and offers a robust nurse navigation network. Table 3 shows the demographics and characteristic of patient seen at JGBCC during the period from 2007-2008. Although eligibility is primarily directed to specific patients who have been identified as belonging to an underserved group, overall accrual and participation is broad-based with ultimate discretion left to the treating physician (see Section 5.1.12). Therefore, a conservative estimate of accrual would be approximately 3 patients per month for the first year, increasing to 5 patients per month in subsequent years at the primary institution.

The University of Louisville Hospital System and School of Medicine maintain dynamic working relationships with the University of Kentucky and University of Indiana as well as with multiple regional community cancer centers. The JGBCC serves as a major entry point for newly diagnosed rural breast cancer patients across the region by way of an active mobile digital mammography program. In terms of radiation oncology resources, there are currently two (and, in the near future, three) rural satellite cancer centers that are staffed with both clinical and physics support from the JGBCC. After IRB approval at the primary site, these affiliated satellite sites and regional partners will be approached for participatory interest so that continuing accrual may be maintained and exceeded.

TABLE 1: Outcomes for selected randomized clinical trials comparing CF-RT to HF-RT.

TRIAL	MEDIAN FOLLOW-UP (YEARS)	*N*	DOSE (Gy)	# FRAC	IBTR* (%)	LRR* (%)	DFS* (%)	OS* (%)	COSMESIS* (% GOOD or EXCELLENT)	ACUTE TOXICITY* (% ≥ GRADE 3)
Canada[35]	10	612	50	25	6.7	--	--	84	71.3	3.0
		622	42.5	16	6.2	--	--	85	69.8	3.0
Royal Marsden[33]	10	470	50	25	12	--	--	--	71	--
		466	42.9	13	9.6	--	--	--	74	--
		474	39	13	15	--	--	--	58†	--
START A[37]	5	749	50	25	3.2	3.6	86	89	--	0.3
		750	41.6	13	3.2	3.5	88	89	--	0.0
		737	39	13	4.6	5.2	85	89	--	0.0
START B[27]	6	1105	50	25	3.3	3.3	86	89	--	1.2
		1110	40	15	2.0	2.2	89	92	--	0.3

Abbreviations: *N* = number of patients; FRAC = fractions; IBTR = in-breast tumor recurrence; LRR = locoregional recurrence; DFS = disease free survival; OS = overall survival.
*All statistical p-values are non-significant in the comparison of CF-RT to HF-RT, unless otherwise specified.
†Measure found to be statistically inferior to CF-RT ($p < 0.05$).

TABLE 2: Outcomes for selected clinical trials of AHF-RT.

TRIAL	DESIGN	MEDIAN FOLLOW-UP (YEARS)	*N*	DOSE (Gy)	# FRAC	IBTR* (%)	LRR* (%)	DFS* (%)	COSMESIS* (% GOOD or EXCELLENT)	ACUTE TOXICITY* (% ≥ GRADE 3)
Ortholan et al.[40]	Prospective, Single Arm	5	150	32.5	5	--	2.3†	80	--	--
Martin, et al.[39]	Prospective, Single Arm	3	59	30	5	0†	0†	--	77	3
Kirova, et al.[38]	Prospective, Non-Randomized	5	317	50	25	--	5‡	96	88	"NS"
			50	32.5	5	--	6‡	95	85	
Saha, et al.[41]	Prospective Randomized	4	62	50	25	--	4.8§	--	87	1.6
			69	30	5	--	5.8§	--	80	0

Abbreviations: *N* = number of patients; FRAC = fractions; IBTR = in-breast tumor recurrence; LRR = locoregional recurrence; DFS = disease free survival.
*All statistical p-values are non-significant in the comparison of CF-RT to HF-RT, unless otherwise specified. †At minimum of 2 year followup. ‡At minimum of 5 years followup. §At minimum of 3 years followup.

TABLE 3: Characteristics of patients who underwent breast conserving surgery at the University of Louisville School of Medicine in 2007-2008 and who would potentially fit eligibility criteria for this protocol (source: JGBCC Tumor Registry).

CHARACTERISTIC	CATEGORY	#	%
Total Number of Patients		273	100
Stage			
	0	57	20.9
	I	135	49.4
	II	81	29.7
Age			
	<50 years	85	31.1
	51-70years	153	56.0
	>70 years	35	12.9
Geographic Location			
	Urban	177	64.8
	Rural	96	35.2
Race			
	Non-minority	199	72.9
	Minority	74	27.1
Insurance Status			
	Private	132	48.4
	Government/Grant	124	45.4
	Uninsured	17	6.2
Chemotherapy			
	No	186	68.1
	Yes	87	31.9

3.0 **HYPOTHESIS/STUDY AIMS**

3.1 **Hypothesis**

- AHF-RT will be a practical, safe and cost-effective radiotherapy regimen that will offer disease-specific outcomes comparable to those achieved with CF-RT and HF-RT for selected patients with early stage breast cancer. AHF-RT will be widely-applicable for the purpose of correcting disparities in the receipt of radiotherapy observed in medically underserved populations.

3.2 **Primary aims**

- To estimate the in-breast tumor recurrence rate (IBTR) of accelerated hypofractionated radiotherapy (AHF-RT) delivered to the whole breast in five treatments once weekly following breast conserving surgery (BCS) in the local management of early stage breast cancer.

- To monitor for adverse events and futility at a planned interim analysis.

3.3 **Secondary aims**

- To estimate overall survival, recurrence-free survival, and distant disease-free survival among patients receiving AHF-RT and to compare these endpoints and IBTR to historical controls of CF-RT and HF-RT.

- To estimate radiation-induced adverse events (such as radiation dermatitis, radiation-induced pain, lymphedema, and fibrosis) among patients receiving AHF-RT and to compare to historical controls of CF-RT and HF-RT.

- To explore quality-of-life endpoints among patients who undergo AHF-RT (including cosmetic outcome, convenience of care, and treatment-related fatigue) and to compare to historical controls of CF-RT and HF-RT.

- To explore cost-effectiveness endpoints among patients who undergo AHF-RT and to compare to historical controls of CF-RT, APBI and HF-RT.

4.0 **ENDPOINTS**

4.1 **Primary endpoint**

The primary endpoint for analysis is the time from enrollment to the diagnosis of in-breast tumor recurrence (IBTR) as a first event. Ipsilateral chest wall, regional and distant failures, and death prior to IBTR will be treated as competing risks when calculating the frequency, crude hazard and cumulative incidence of IBTR. Contralateral breast and non-breast second primary cancers will not be considered

to be competing risks (i.e., patients will be followed beyond the diagnosis of contralateral breast and non-breast second primary cancers for the subsequent occurrence of IBTRs). Both invasive and non-invasive IBTRs are considered in calculating the primary endpoint.

4.2 **Secondary endpoints**

4.2.1 Distant disease-free interval, defined as the time from enrollment to first diagnosis of distant disease, regardless of the occurrence of any intervening local or regional failure, contralateral breast cancer, or non-breast second primary cancer (see Section 10.0).

4.2.2 Recurrence-free survival defined as the time from enrollment to first diagnosis of a local, regional, or distant recurrence, regardless of any intervening contralateral or other second primary cancer.

4.2.3 Overall survival defined as the time from enrollment to death due to any cause.

4.2.4 Treatment toxicities (acute and late)

4.2.5 Quality of life:

- cosmesis;
- treatment-related symptoms;
- fatigue;
- perceived convenience of care.

4.2.6 Cost effectiveness

5.0 **PATIENT ELIGIBILITY AND INELIGIBILITY**

5.1 **Conditions for patient eligibility**

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

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

5.1.2 Patients must be ≥ 21 years old.

5.1.3 The patient must have stage 0, I, or II breast cancer.

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

5.1.5 Surgical treatment of the breast must have been BCS. The margins of the resected specimen must be histologically free of tumor (including DCIS component). Reexcision of surgical margins is permitted.

5.1.6 Gross disease may be unifocal or multifocal with pathologic (invasive and/or DCIS) tumor size excised with negative margins.

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

5.1.8 The patient must begin adjuvant therapy (chemotherapy or radiotherapy) within 9 weeks following the last surgery for breast cancer (lumpectomy, re-excision of margins, or axillary staging procedure).

5.1.9 Patients must have all usual and customary hormone receptor (ER/PR) and estrogen receptor (ER) analysis performed on the primary tumor prior to enrollment. Patients with invasive disease must have HER2 receptor status determined (positive or negative) with immunohistochemistry (IHC) and/or fluorescent in-situ hybridization (FISH).

5.1.10 At the time of enrollment, patients must have had an H&P within 4 months and a bilateral mammogram within 6 months.

5.1.11 Patients with a history of *non-breast* malignancies are eligible if they have been disease-free for 5 or more years prior to randomization and are deemed by their physician to be at low risk for recurrence. Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.

5.1.12 Patients must live in a county that is designated as Appalachian and/or rural by Kentucky Cancer Registry Criteria (See Figures 2 and 3) and/or must hold their primary residence ≥ 10 miles from the nearest radiation facility. Patients who do not fit these criteria may still be considered eligible if they are determined to suffer significant financial and/or transportation hardship during a typical course of CF-RT or HF-RT (in the judgment of any of their treating physicians). Patients who live outside the Commonwealth of Kentucky are eligible if they fit any of these aforementioned conditions. Form A1 specifying patient's eligibility must be completed prior to enrollment.

5.2 **Conditions for patient ineligibility**

Men are not eligible for this study. Women with one or more of the following conditions also are ineligible for this study.

5.2.1 T3, stage III, or stage IV breast cancer (see Appendix A for TNM nomenclature and staging).

5.2.2 More than 3 histologically positive axillary nodes.

5.2.3 Axillary nodes with definite evidence of microscopic or macroscopic extracapsular extension.

5.2.4 One or more positive *non-axillary* sentinel node(s). (Note that intramammary nodes are staged as axillary nodes.)

5.2.5 Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

5.2.6 *Suspicious* microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign.

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

5.2.8 Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by 4 or more centimeters.

5.2.9 Paget's disease of the nipple.

5.2.10 Synchronous bilateral invasive or non-invasive breast cancer.

5.2.11 History of invasive breast cancer or DCIS. (Patients with a history of LCIS treated by surgery alone are eligible.)

5.2.12 Surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by reexcision, the patient is eligible.)

5.2.13 Treatment plan that includes regional nodal irradiation.

5.2.14 Current therapy with any hormonal agents such as raloxifene (Evista®), tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or breast cancer prevention. (Patients are eligible only if these medications are discontinued prior to enrollment.)

5.2.15 Cosmetic breast implants. (Patients who have had implants removed are eligible.)

5.2.16 Prior breast or thoracic RT for any condition.

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

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

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

FIGURE 2: Kentucky Cancer Registry county designation "Appalachia" (yellow) versus "Non-Appalachia" (red).

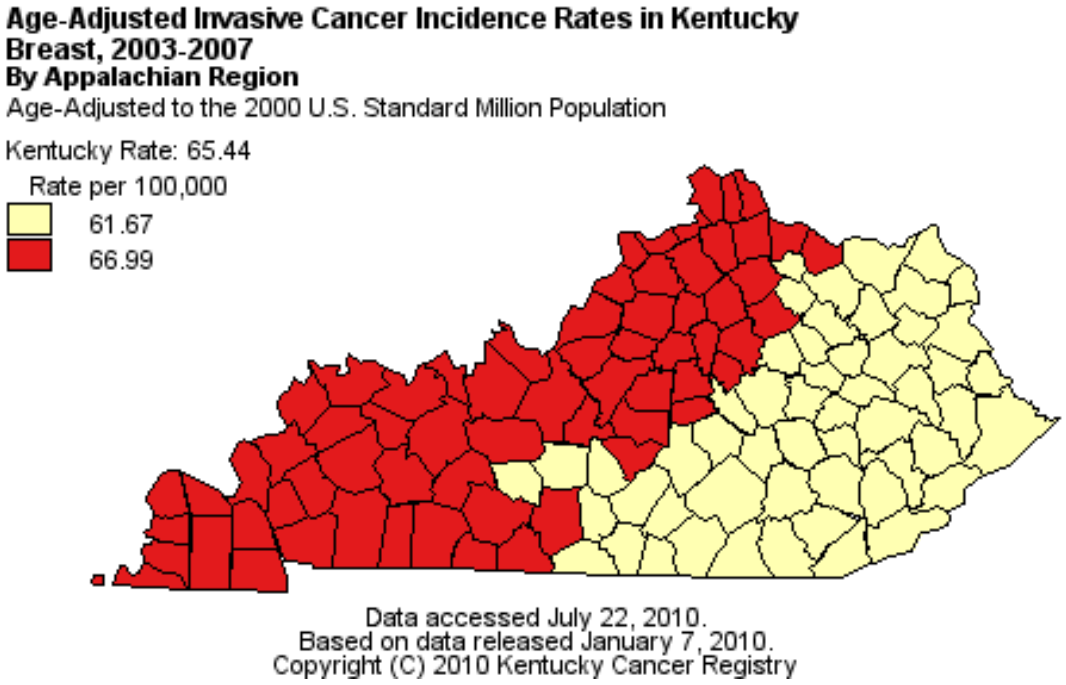


FIGURE 3a: Kentucky Cancer Registry county designation "rural" (yellow) versus "non-rural" (red).

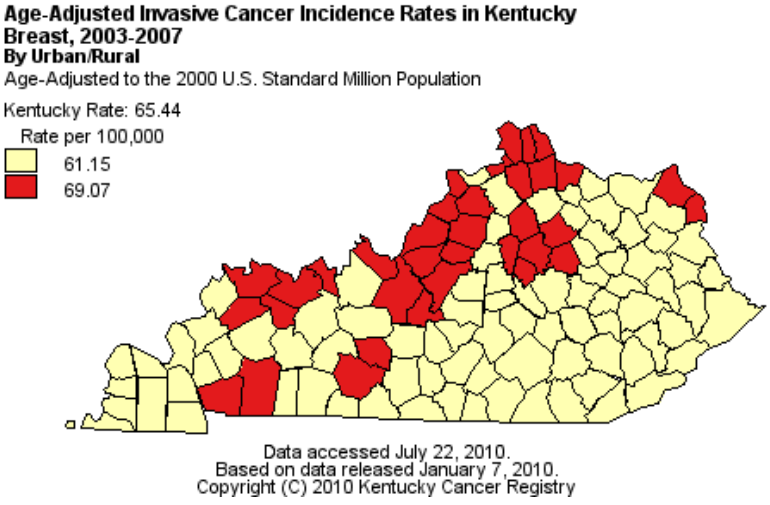


Figure 3b: List of KY "rural" counties.

Adair	Hart	Morgan
Bath	Jackson	Nicholas
Bell	Johnson	Owsley
Boyd	Knott	Perry
Breathitt	Knox	Pike
Carter	Laurel	Powell
Casey	Lawrence	Pulaski
Clark	Lee	Robertson
Clay	Leslie	Rockcastle
Clinton	Letcher	Rowan
Cumberland	Lewis	Russell
Edmonson	Lincoln	Wayne
Elliott	Madison	Whitley
Estill	Magoffin	Wolfe
Fleming	Martin	
Floyd	McCreary	
Garrard	Menifee	
Green	Metcalfe	
Greenup	Monroe	
Harlan	Montgomery	

6.0 **REQUIRED ENTRY AND FOLLOW-UP STUDIES**

TABLE 3: All studies required for study entry; studies required during study therapy; studies required as part of long-term follow-up.

		Acute Toxicity		Late Toxicity/Disease Outcome	
Required studies[1]	Prior to enrollment	At end of RT	At 4 weeks following therapy[2]	At 6 months and 12 months following therapy[2]	Years 2-5
History & physical exam, including Breast exam	X[3]	X[4]	X[4]	X[4]	X[4,5]
Adverse event assessment[7]		X	X	X	X[6]
Menopausal status[8]	X				
Routine serologic studies[9]	X				
Pregnancy test (serum beta HCG) [9]	X				
Routine radiologic imaging (perioperative) [9]	X				
Routine radiologic imaging (staging) [9]	X				
Bilateral mammogram	X[10]			X[11]	X[6]

[1]H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently according to physician preference and when symptoms suggest metastatic disease.
[2]From end of RT (if no chemotherapy) or from end of both RT and chemotherapy (if chemotherapy is given).
[3]Complete H&P within 4 months prior to enrollment.
[4]Updated H&P including disease status.
[5]Every 6 months.
[6]Every 12 months.
[7]RT-related assessment; refer to Section 11.0 for timing of Form AE submissions.
[8]See Appendix B.
[9]At the discretion of treating physicians (radiology, surgery, medical oncology and/or radiation oncology)
[10]Within 6 months prior to enrollment.
[11]A mammogram of the ipsilateral breast is required at 6 months following study therapy. The next bilateral mammogram should be timed to be no more than 12 months from the most recent
bilateral mammogram.

TABLE 4. Required studies for QOL and cosmesis patient population (see Section 7.0)

Required Studies	Prior to enrollment	Peri-treatment period			Follow-up[1]		
		Last Day of AHF-RT	4 weeks after AHF-RT	6 months after AHF-RT	Year 1	Year 2	Year 3
QOL Questionnaire(s)	X	X	X	X	X	X	X
BCTOS	X			X	X		X
MD-Reported Cosmesis	X[2]			X[2]	X[2]		X
Digital Images (Breast Photos)	X			X	X		X

[1]From end of AHF-RT.
[2]A radiation oncologist should complete these reports. If this is not possible, the patient's surgeon may complete the reports.
Every effort should be made to have these assessments performed by the same physician at all 3 time points.

7.0 **QUALITY OF LIFE, COSMESIS AND COST-EFFECTIVENESS ANALYSIS**

Primary hypothesis:

- Cosmetic results after AHF-RT following lumpectomy will be comparable to that historically reported in modern clinical trials of CF-RT vs. HF-RT (Table 1).

Secondary hypotheses:

- Among patients not receiving chemotherapy, treatment-related symptoms at the end of radiotherapy for patients undergoing AHF-RT will be comparable to that historically reported in modern clinical trials of CF-RT vs. HF-RT (Table 1).
- The perceived convenience of care and treatment compliance will be greater for patients undergoing AHF-RT than for patients historically reported in modern clinical trials of CF-RT vs. HF-RT (Table 1).
- The cost effectiveness of delivery of adjuvant radiotherapy will be superior for AHF-RT than comparable studies of CF-RT, HF-RT and accelerated partial breast irradiation.

7.1 **Cosmesis**

The quality of life component contains provisions to evaluate cosmetic results.
In terms of cosmesis, we expect that AHF-RT will yield equivalent results to published studies of HF-RT. Because cosmetic outcome stabilizes several years post-treatment, the primary cosmetic endpointwill be taken 3 years post-treatment, however intervening data will be collected for the purpose of early result reporting as well as for tracking how cosmetic outcome resolves over time.

Cosmetic results will be evaluated in several ways. First, the Breast Cancer Treatment

Outcome Scale (BCTOS, Form BE)[43] will be used to assess cosmetic results using patient self reports. 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 randomization. The BCTOS will be used to assess cosmesis, pain and functionality at baseline, 6 months, 1 year and at the final 3-year endpoint. (see Table 4). Second, after consent but prior to randomization, a cosmetic evaluation will be made by the radiation oncologist (or surgeon), using the physician-assessed Harvard Scale (Form CE). Ratings of cosmetic outcome will then be made by the radiation oncologist (or surgeon) at baseline, 6 months, 1 year and at the final 3-year endpoint. (see Table 4). This will facilitate comparison of physician-generated versus patient-generated ratings, and to characterize the evolution of cosmetic outcome from multiple perspectives.

Finally, digital images (photographs) will be taken of the treated and untreated breasts at baseline, 6 months, 1 year and at the final 3-year endpoint. (see Table 4). 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. 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 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 evaluated for cosmetic results by a panel of physicians using diagnostic criteria (e.g., degree of scarring, extent of pock marks and/or dimpling, degree of symmetry between the breasts, extent of changes to the skin). In total, these multiple measures of cosmetic outcome will be used to assess the degree of correspondence between physician-generated and patient-generated outcomes.

7.2 **Quality of life**

Studies of women receiving breast-conserving surgery followed by WBI generally report adequate quality of life[43-45]. The current trial presents an excellent opportunity tostudy the treatment-relevant components of quality of life of women undergoing AHF-RT and to compare their experiences to historical controls of women undergoing various breast radiotherapy regimens. Patients undergoing AHF-RT will receive a higher dose-per-fraction of radiation than patients who undergo CF-RT or HF-RT. However, due to the fewer overall treatments and fewer weekly trips to the radiation facility, we believe the ratings of fatigue and treatment-related symptoms at the end of radiotherapy will be lower than those historically reported. We also believe that women undergoing AHF-RT will perceive their convenience of care to be greater than that historically reported with CF-RT or HF-RT. Although ratings of fatigue, treatment-related symptoms, and perceived convenience of care among women receiving AHF-RT will be clearest among women who receive radiation therapy alone, not in combination with chemotherapy. To examine this possibility, we plan to measure fatigue, treatment-related symptoms, and convenience of care among women who receive both treatment modalities at the point at which their combined treatment ends.

7.2.1 **QOL Metrics:** The following validated QOL metrics will be employed in-whole or in-part to assess QOL at baseline and regular intervals during and after AHF-RT:

- The EORTC QLQ-BR23 (Form QOL02), a validated breast-cancer specific QOL instrument.

All appropriate and required permissions for use will be obtained for the aforementioned instrument prior to its use in this study.

7.3 **QOL and cosmesis instructions**

The patient-completed quality of life questionnaire will be administered at baseline, after informed consent has been obtained and after enrollment. It will also be completed by patients in both arms at the close of adjuvant (non-hormonal) therapy (i.e., at the end of radiotherapy for the RT only group and at the end of both chemotherapy and RT for the combined therapy group). Other patient-administered follow-ups will occur approximately 4 weeks after the completion of adjuvant (non-hormonal) therapy (i.e., at the end of radiotherapy for the RT only group and at the end of both chemotherapy and RT for the combined therapy group), and at 6 months, 1 year, 2 years, and 3 years following completion of adjuvant(non-hormonal) therapy. The timing of assessments will coincide with other protocol requirements wherever possible in order to reduce patient burden and enhance compliance. The QOL questionnaires should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. When absolutely necessary, it may also be administered by mail or phone. A planned interim QOL analysis will be conducted and reported according to section 13.10.

7.4 **Cost Effectiveness Analysis**

The provision of breast cancer therapy is a microcosm of the challenges facing the future of healthcare delivery in the United States as a whole. The widening of the so-called "healthcare gap" between the wealthy and poor, urban and rural populations is real, insidious and underway, especially with regard radiation therapy services. Well-funded, highly specialized facilities in large urban centers continue to compete with one another. Investments are made in novel, expensive and largely unproven modalities such as robotic radiosurgery, intraoperative radiotherapy, and proton/particle therapy. Often, the solvency of these major capital investments depends on the treatment of a high volume of privately-insured patients from a large referral base with the financial means to provide their own transportation and housing during a course of therapy.

The explanation for this trend is simple: the current reimbursement model for radiation therapy services in the US, whether covered by private or governmental payers, depends primarily on the number of treatments delivered over the therapeutic course and/or technical complexity. More pragmatic, cost-effective regimens that are a step toward improvement in access, such as three-week HF-RT, are actually discouraged and underutilized by physicians, even when highly favored by patients. Most accelerated radiotherapy courses currently under investigation in the treatment of breast cancer

involve the more expensive treatment-delivery techniques of accelerated partial breast irradiation (APBI). Given that APBI requires specialized training on the part of physicians and significant capital equipment investment by hospitals, they are likely to be accessible mainly to urban and suburban populations. Thus far, the popular accelerated regimens of APBI have significantly broadened the menu of choices for women already in the system, but have had little impact on healthcare disparity. As a result, they not only put undesirable upward pressure on healthcare costs, but also further widen the access gap currently experienced by rural breast cancer populations.

In terms of broader public-health impact, AHF-RT has a significant potential for the generation of cost-effectiveness data that will be vital to the debate over allocation of limited healthcare resources. Provision of oncology resources is problematic for many patients in the more sparsely populated states of the Southeast, Southwest and Midwest/Mountain regions of the US. The availability of multidisciplinary care centers is insufficient. Financial assistance for or coordination of transportation services for lower-income rural patients varies widely from community to community. Even when free transportation is provided, rural patients disproportionately shoulder the burden of loss of time and productivity due to daily round-trip travel and treatment times, which may total several hours per day.

Detailed cost-effectiveness analysis (CEA) will be performed during this study in order to quantify these factors and make valuable comparisons with other forms of breast radiotherapy: CF-RT, HF-RT and APBI. Similar models have been employed to model cost-effectiveness and quality-adjusted life years to compare CF-RT to HF-RT and APBI (breast brachytherapy and 3-dimensional conformal radiotherapy)[31, 46]. Similar standard analysis techniques (will be developed to make meaningful comparisons of AHF-RT with these previously published studies. A planned interim CEA will be conducted and reported according to section 13.10.

8.0 **ACCELERATED HYPOFRACTIONATED RADIOTHERAPY (AHF-RT)**

The intent of AHF-RT is to treat the entire breast through tangential fields and ensure that the lumpectomy cavity is dosimetrically covered within the irradiated volume.

8.1 **Treatment overview**

8.1.1 ***Treatment planning***

- CT-based treatment planning is required. Any CT-based treatment approach can be used, including forward-planned, segment-weighted approaches. Acceptable coverage of the lumpectomy cavity within the whole breast dose must be documented. (See Section 8.2.)

- Regional nodal irradiation is NOT allowed.

- Fluoroscopic 2-D treatment planning is NOT allowed.

8.1.2 ***Timing***

- If the patient is not receiving chemotherapy, AHF-RT is to be initiated within 9 weeks following lumpectomy or re-excision of margins and within 3 weeks following study entry.

- For patients receiving chemotherapy, AHF-RT is to begin no fewer than 2 weeks and no more than 8 weeks after the last cycle of chemotherapy.

8.1.3 ***AHF-RT Whole breast dose***

- Acceptable dose for the AHF-RT prescription point/volume is 30Gy in 6Gy per fraction, or 28.5Gy in 5.7Gy per fraction, delivered once weekly over 5 treatment weeks. Total dose prescribed is left to the discretion of the treating physician.

8.1.4 ***Boosts***

- Boost therapy by either photons or electrons to the lumpectomy cavity plus margin is permitted but not required. Brachytherapy or intraoperative boosts are allowed. The boost technique and dose is left to the discretion of the treating radiation oncologist, but CT-based targeting/planning is encouraged.

- Total boost dose to the prescription point/volume is to be between 10-16Gy in a fractionation schedule to be determined by the treating radiation oncologist, based on the technique used.

8.1.5 ***Patient positioning/immobilization***

- Patient positioning and immobilization should be performed according to usual and customary facility standards with regard to CT-based planning. The patient's position must be reproducible through the entire course of treatment. Typically, patients are treated in the supine position with the arms extended overhead using immobilization techniques, such as a tilt board, to ensure reproducibility. Prone positioning is permitted.

8.1.6 ***Equipment***

- Linear accelerator (LinAc) with minimal photon energies of 4MV.

8.2 **CT-based WBI treatment plan**

8.2.1 ***CT planning***

- Must include dose distribution evaluated on multiple CT levels after the target breast volume is defined on CT and tangents. Dose distribution based on dose-volume specification to breast tissue and constraints for critical non-target structures must also be specified.

8.2.2 ***Target breast volumes***

- At the time of the simulation/CT, the clinical breast volume to be targeted in the tangent fields, with appropriate margin, is determined by the radiation oncologist. 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. This is meant to be only an approximation of the actual breast tissue volume, and it is recognized that the chest wall and 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

8.2.3 ***Tangential fields***

- The borders for the tangent fields are set so that they include the targeted clinical breast volume determined above plus a 1–2 cm margin. Examples of typical clinical boundaries for tangent fields are:
    - Medial: usually midsternum
    - Lateral: usually midaxillary line
    - Caudad: 1-2 cm below the inframammary line
    - Cephalad: commonly at the base of the clavicle heads or the sternal-manubrial joint

- For CT-based planning, radiopaque markers are placed on these borders. These boundaries may need to be modified depending on the location of the lumpectomy cavity when it is visualized on CT. It is recommended that techniques be applied that assure posterior or deep borders are co-planar in order to minimize exit into the lungs.

8.2.4 ***Constraints for critical non-target organs***

- Contouring of critical structures:
    - **Ipsilateral Lung:** The lung tissue is easily visible on "mediastinal window preset" of a non-contrast CT due to the differential Houndsfield units from surrounding tissue. All ipsilateral lung tissue should be contoured. The "autocontour" feature available on some treatment planning CT scans may be used.
    - **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 inferiormost extent near the diaphragm. If one can identify the esophagus, this structure should be excluded. One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

- The perpendicular distance from the chest wall to the posterior field edge can include **at maximum** 3 cm of lung tissue at any point along the length of the digitally reconstructed radiograph (DRR) of the tangentialfield. For left-sided cancers, field arrangements that minimize inclusion of the heart in the field should be used.

8.2.5 ***Dose prescription and evaluation of isodose distribution***

- The dose will be prescribed to the 100% isodose line encompassing at least 90% of the breast tissue as specified on the CT contours OR to a point located at two thirds the perpendicular distance from the skin overlying the breast to the posterior border of the tangent field at mid-separation on the central axis slice (also specified on CT plan). Wedges, compensators, etc. are to be used to keep the maximum dose less than 115% of the prescription, and, ideally less than 110% of the prescription dose. Dose calculations are to be done WITH heterogeneity corrections.

8.2.6 ***Verification of lumpectomy cavity coverage within the prescription isodose for the whole breast***

- **Verification process for the lumpectomy cavity:** Review of the dose distribution on CT slices that include the lumpectomy cavity is requested to verify that the cavity (identified on CT by either the post-operative seroma, postoperative scar, surgical clips or a combination thereof) is covered by the 100% isodose line. Acceptable AHF-RT must demonstrate that the entire cavity is included in ≥ 90% isodose line. If not, changes in the field width, gantry, collimator, or selection of wedges or other adjustment must be done to achieve this.

8.2.7 ***Boost***

- Refer to Section 8.1.4.

9.0 **SYSTEMIC THERAPY**

9.1 **Chemotherapy**

Chemotherapy may be given at the discretion of the patient's medical oncologist. The use of concurrent chemotherapeutic agents during radiation therapy is not allowed. For patients undergoing chemotherapy, the adjuvant chemotherapy will be given prior to AHF-RT, as prescribed by the treating physician. Initiation of AHF-RT should be at least 2 weeks after the last cycle of chemotherapy.

9.2 **Hormonal therapy**

Patients with ER-positive and/or PR-positive tumors should be treated with hormonal therapy for a minimum of 5 years. The dose and schedule of the drug(s) used for hormonal therapy should be consistent with the instructions in the drug package insert(s).

9.2.1 ***Patients receiving chemotherapy***

Hormonal therapy should begin no sooner than 3 weeks and no later than 12 weeks after the last dose of chemotherapy.

9.2.2 ***Patients not receiving chemotherapy***

Hormonal therapy may be initiated before, during, or after completion of AHF-RT at the discretion of the investigator.

9.3 **Trastuzumab**

Trastuzumab is permitted at the investigator's discretion for patients whose tumors are HER2-positive. The timing and other treatment logistics are also at the investigator's discretion. Concurrent use with AHF-RT is permitted.

10.0 DIAGNOSIS OF BREAST CANCER EVENTS

The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when both the clinical and laboratory findings meet "acceptable" criteria as defined below. All documentation will be performed using Form F. Suspicious findings do not constitute criteria for breast cancer recurrence, nor are they an indication to alter protocol therapy. The listing below is offered as a guide.

Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

Patients will be followed beyond the diagnosis of contralateral breast and non-breast second primary cancers for the subsequent occurrence of IBTRs.

10.1 **Ipsilateral in-breast recurrence**

Defined as evidence of invasive or in situ breast cancer (except LCIS) in the ipsilateral breast. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast must have a biopsy of the suspicious lesion to confirm the diagnosis with documentation of the location.

Acceptable: positive histologic biopsy (positive cytology is not acceptable)

10.2 **Local chest wall recurrence**

Defined as evidence of invasive or in situ breast cancer (except LCIS) in the ipsilateral chest wall. Patients who develop clinical evidence of tumor recurrence in the ipsilateral chest wall must have a biopsy of the suspicious lesion to confirm the diagnosis.

Acceptable: positive histologic biopsy (positive cytology is not acceptable)

10.3 **Regional recurrence**

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after operation.

Acceptable: positive cytology or histologic biopsy

10.4 **Distant recurrence**

Defined as evidence of tumor in any area of the body, with the exception of those described in Sections 10.1 and 10.2.

Acceptable: positive cytology, histologic biopsy, or clear and convincing radiologic evidence of metastatic disease.

10.5 **Second primary breast cancer**
Defined as evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary cancer must be confirmed histologically.
Acceptable: positive histologic biopsy

10.6 **Second primary cancer (non-breast)**

Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the cervix will be reported on Form F. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

10.7 **Documentation requested following death**

Autopsy reports should be secured whenever possible and should be submitted into the medical record. A copy of the death certificate should be submitted into the medical record if it is readily available or if it contains important cause-of-death information not documented elsewhere. A physician's note summarizing the death will suffice if the aforementioned are not obtainable.

11.0 **ADVERSE EVENT REPORTING REQUIREMENTS**

Please refer to Appendix C "Information Basics for Adverse Event Reporting" for general information required for adverse event reporting.

11.1 **Definitions for adverse event reporting**

Study therapy: In this study, therapy is AHF-RT.

11.2 **Adverse event assessment**

The NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 must be used to identify the type and to grade the severity of the adverse events in this study.

11.2.1 ***Pregnancy occurring while patient is on study therapy***

If a patient becomes pregnant while receiving study therapy, notify the PI or any Co-Investigators immediately.

11.2.2 ***Other recipients of adverse event reports***

Adverse events determined to be reportable must also be reported by the investigator to the Institutional Review Board responsible for oversight of the patient according to the local policy and procedures.

11.3 **Routine reporting of adverse events**
Routine reporting includes adverse events for which expedited reporting was required, as well as those events that do not require expedited reporting. All adverse events must be reported on Form

AE (Adverse Event Form) as described below and according to instructions on the Form AE.

11.3.1 ***Reporting on Form AE***

Report all grade 1, 2, 3, 4, and 5 adverse events resulting from AHF-RT.

The following adverse events do not require routine reporting on Form AE: adverse events resulting from chemotherapy, hormonal therapy, or any other systemic cancer therapy, adverse events which occur after breast cancer recurrence or development of a second primary cancer

11.3.2 ***Submission of Form AE***

For patients who receive radiotherapy (RT) without chemotherapy, submit Form AE according to the following schedule or until the time of breast cancer recurrence or second primary cancer:

- At the end of RT
- 4 weeks from end of RT
- 6 months from end of RT
- 12 months from end of RT and every 12 months thereafter

For patients who receive radiotherapy and chemotherapy, submit Form AE according to the following schedule or until the time of breast cancer recurrence or second primary cancer:

- At the end of RT
- 4 weeks from end of RT and chemotherapy
- 6 months from end of RT and chemotherapy
- 12 months from end of RT and chemotherapy and every 12 months thereafter

11.4 **Reporting on follow-up Form F**

Report breast cancer recurrence and all second primary malignancies on followup form (Form F). Submit supporting documentation that confirms the breast cancer recurrence or second primary cancer diagnosis.

12.0 **PATIENT ENTRY AND WITHDRAWAL PROCEDURES**

12.1 **Patient entry and consent form**
Patents considered for this trial must conform to all eligibility and ineligibility criteria outlined in Section 5.0. Before the patient is entered, the consent form (see Appendix F), including any

addenda, must be signed and dated by the patient and the person who explains the study to that patient.

12.1.1 **Patient study number**

After all of the faxed eligibility criteria have been completed, the institution will assign the patient an individual, coded study number.

12.2 **Patient-initiated discontinuation of study therapy**

Even after a patient agrees to take part in this study, she may stop study therapy or withdraw from the study at any time. If she stops study therapy but still allows the study doctor to follow her care, she should continue to be followed according to the study schedule and should be encouraged to continue the QOL/cosmesis assessments on schedule. Alternatively, she may choose to have no further interaction regarding the study. In this case, the investigator must provide the clinical trials office writtendocumentation of the patient's decision to fully withdraw from the study.

12.3 **Investigator-initiated discontinuation of study therapy**

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- The patient develops a serious side effect that she cannot tolerate or that cannot be controlled with medications,
- The patient's health gets worse,
- The patient is unable to meet the study requirements, or
- New information about other treatments for breast cancer becomes available.

If study therapy is stopped but she still allows the study doctor to follow her care, she should continue to be followed according to the study schedule. Patients should be encouraged to complete the QOL/cosmesis assessments on schedule unless they have a second primary cancer or a breast cancer recurrence.

13.0 **STATISTICAL CONSIDERATIONS**

13.1 **End-Point Definitions**

- **Primary endpoint:** The primary endpoint for analysis is diagnosis of in-breast tumor recurrence (IBTR) as a first event. Regional and distant failures and death prior to IBTR will be treated as competing risks when calculating the frequency, crude hazard and cumulative incidence of IBTR. Contralateral breast and non-breast second primary cancers will not be considered to be competing risks, i.e. patients will be followed beyond the diagnosis of contralateral breast and non-breast second primary cancers for the subsequent occurrence of IBTRs. Both invasive and non-invasive IBTRs are considered in calculating the primary endpoint.

- **Secondary endpoints:** Secondary endpoints include distant disease-free interval, recurrence-free survival, and overall survival (S). Distant disease-free interval is

defined to be the time of enrollment to first diagnosis of distant disease, regardless of the occurrence of any intervening local or regional failure, contralateral breast cancer, or non-breast second primaries. Recurrence-free survival is defined as the time from enrollment to first diagnosis of a local, regional, or distant recurrence, regardless of any intervening contralateral or other second primary cancer. Overall survival is based on deaths due to all causes. Quality of life endpoints include cosmesis, breast-related symptoms, fatigue, and perceived convenience of care.

13.2 **Sample Size**

There is no concrete data from this center to support the sample size justification based on efficacy of this treatment combination and low dose involved field RT. Table 2, lists some similar studies. When combined IBTR and LRR, the recurrence rate is around 6% with an approximate 95% confidence interval of (0-0.12), which is very wide due to small sample size. We justify the sample size using the precision analysis approach (Chow et al., 2008, chapter 1.3). Due to limited resources we plan to enroll about 250 subjects, with n=250 and at alpha=5%, we will have a precision of about 12%.

13.3 **Accrual**

We estimate that accrual rate will be 60 patients annually. Given the current accrual rate, the study will need approximately 4-year accrual with 1-year follow-up. All patients will be followed after the closure of the study to accrual.

13.4 **Statistical Analysis**

Descriptive statistics related to patient characteristics, treatment, and prognostic factors will be produced. The Kaplan-Meier method will be used to estimate the overall survival (OS), disease-free survival (DFS), and cumulative incidence (CI) in the absence of competing risk for the entire cohort and for subgroups of patients. Survival differences will be compared using the un-weighted log-rank test. The OS time will be determined as the time from enrollment on protocol until death or last follow-up evaluation. DFS will be defined as the time from enrollment on protocol until the first adverse event (i.e., disease progression, relapse, second malignancy, or death due to any cause). The time to local failure will be defined as the time from enrollment on protocol until local recurrence, either with or without simultaneous distant recurrence and with other events (only distant failure, death, second malignancy), classified as competing risks. To investigate the independent prognostic significance of pretreatment factors, we will conduct a multivariable analysis using the Cox regression method.

The CI of local failure will be estimated and effects of prognostic factors will be estimated. Effect of competing risk (distant failure, second malignancy and death) will be taken into account.

Descriptive statistics will be provided regarding incidence rates of toxicity. Presence of grade 3 or 4 toxicity will be modeled using logistic regression to identify key risk factors.

We will explore relationship between quality of life measures and demographic and treatment related covariates using regression (linear or logistic) models for repeated data[47]. Multiple correlation structures will be explored for modeling the correlation among repeated measurements on the same subject. The most common structure is a first-order autoregressive correlation structure, which specifies decreased correlation for observations taken further apart in time, with a random subject effect. Since the QOL measures are based on questionnaire data (summing the countable numbers), the normality assumptions may not be valid for some measures. In such cases, we will perform analyses on the logit transformed data, provided normality assumption is accepted[48]. If normality is rejected after logit transformation as well, we will use non-parametric regression which is based on ranks.

All calculations will be performed with SAS statistical software (SAS Institute Inc., Cary, NC). Analyses for specific aims are outlined below.

13.5 **Data Safety Monitoring Board**

The protocol progress will be reviewed and monitored by the BCC Data Safety Monitoring Board (DSMB). Data summaries will be provided by the Biostatistics Office after review by the Principal Investigator (PI). The data will include patient accrual, demographic summaries, grade 3/4 toxicities, major adverse events (i.e., deaths, relapses, second malignancies), and results of interim and final analyses of various endpoints as specified in the protocol. The PI, in conjunction with the CRAs, will inform the biostatistician when the appropriate number of patients has been evaluated; this event will thereby trigger interim or final analysis. The first report will be provided to the DSMB after all the patients enrolled during the first 6 months of the trial have completed chemotherapy. At the DSMB meeting to review the protocol data, the PI and appropriate co-Investigators will meet with the DSMB to discuss any relevant issues with the DSMB. The DSMB's report summarizing their evaluation of the data will be simultaneously forwarded to the PI, the IRB, and the chief medical officer (CMO). If the investigators disagree with the evaluation, a rebuttal will be made within 10 days to the DSMB, and a copy of the rebuttal will be sent to the IRB and the CMO. The PI will inform the chair of the IRB and the CMO if a rebuttal will be made so that the IRB can decide whether to postpone review of the protocol until the rebuttal has been received. If no excessive, unexpected events are observed during the first 6 months of the trial, subsequent reports to the DSMB will be made every 6 months or annually (as deemed appropriate by the DSMB) according to the schedule of the DSMB. The reports to the DSMB may not necessarily coincide with the continuing review reports submitted to the IRB.

13.6 **Monitoring Rule**

Safety monitoring of outcome is intended to identify significant deviations from expected results sufficiently early in the clinical trial to reduce the number of patients exposed to ineffective therapy. If the observed 3-year cumulative IBTR for falls above 12 % margin, we will consider early closure of enrollment. This monitoring rule will serve as a guideline for decisions regarding early stopping of the protocol.

13.7 **Missing Observations**

Most of the missing data will be related to QOL measures. In the following, we consider some special cases of missing observations. There are two primary mechanisms through which missing data may arise in the present study: 1) patients and their parents were unavailable due to various reasons and therefore did not complete assessments, or 2) patient deaths. In the event that data on some subjects are missing at some time points, the entire subject history is not excluded from the analysis; the following steps will be taken:

- If independent variables are missing, but the corresponding dependent variable is present, we will do multiple imputations for the missing values in order to simplify the analysis.

- If the dependent variable is partially missing (i.e., follow-up data are available at some time points) and the missing mechanism is random, the entire subject history is not excluded from the analysis (using the Mixed Procedure in SAS), just the missing observations.

- If the dependent variable is partially missing and the missing mechanism is nonrandom (those experienced event with compromised QOL), but depends on a covariate, we will include that covariate always in the model. Violations of the missing at random assumption may be investigated[49].

- If the dependent variable is completely missing (i.e., no follow-up data available at all the time points), then that subject's data will be deleted.

When computing a total score for a scale or subscale, items missing will be handled by assigning the average score from that subject's nonmissing items to the missing item(s) if the subject's item missing rate is no more than 30%. When the missing rate is greater than 30%, the scale (or subscale) total will not be computed and will be treated as missing.

13.8 **Monitoring of adverse events**

The occurrence of adverse events, including toxicities, second primary cancers, and deaths (on therapy or prior to evidence of disease progression), will be monitored continuously. Requirements for reporting adverse events to all appropriate parties are detailed in Section 11.0. In addition, summaries of adverse events and toxicities will be prepared quarterly and reviewed by the PI, clinical trials office, and statisticians.

Throughout the accrual and active treatment periods of the trial, progress reports will be prepared and presented to the institutional review board (IRB) at 12-month intervals. These reports will include an assessment of toxicities, second primary cancers and on-therapy deaths, a comparison of actual and projected accrual, and an assessment of data quality, including data delinquency and rates of eligibility. After accrual is closed, adverse events and other information will be presented to the IRB, together with interim analysis results.

13.9 **Analysis schedule**

13.9.1 **Primary endpoint of ipsilateral breast tumor recurrence (IBTR)**

The first interim analysis of the primary endpoint will take place after 3 years or 150 patients have been accrued, whichever timepoint is reached first. Subsequent definitive analyses, which include estimates of overall survival, recurrence-free survival, and distant disease-free survival, toxicity and cosmesiswill take place approximately 5- and 10-years following the initiation of the trial.

13.9.2 **Interim analysis of adverse events**
Interim analysis of adverse events is planned after 1.5 year or accrual of 75 patients, whichever timepoint is reached first. Rates of radiation dermatitis or radiation-induced pain ≥ to grade 3 (CTCE v.3.0) occurring in ≥ 5% of the study population will be considered grounds for trial suspension and review.

13.9.3 **Interim analysis of quality of life (QOL)**
Interim analysis of QOL and cosmesis is planned after 2 years or accrual of 100 patients, whichever timepoint is reached first.

13.9.4 **Interim analysis of cost effectiveness**
Interim analysis of QOL and cosmesis is planned after 1 year or accrual of 35 patients, whichever timepoint is reached first.

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Amendment 1:

The first analysis of the UK FAST Trial, referred to in section 2.2, above has been published[50], and the early results show equivalent disease control among all three arms of the study. The only difference in toxicity was with regard to cosmetic appearance of the breast whish was slightly, but statistically improved among patients who received 28.5 Gy vs. those who received 30 Gy in 5 weekly fractions. These results were updated and presented at the 2012 San Antonio Breast Cancer Symposium, December 4-8, 2012. As a result, this amendment is being made to allow the PI to use 28.5Gy in 5 fractions as an acceptable choice for radiation total dose on this trial. Appropriate changes were made where applicable in the body of the protocol.

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APPENDIX A

TNM NOMENCLATURE AND STAGING FOR BREAST CANCER (Based on AJCC Staging Manual, 7th ed. 2010)

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
    - Tis (DCIS) Ductal carcinoma in situ
    - Tis (LCIS) Lobular carcinoma in situ
    - Tis (Paget's) Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
- T1 Tumor ≤ 20 mm in greatest dimension
    - T1mi Tumor ≤ 1 mm in greatest dimension
    - T1a Tumor >1 mm but ≤ 5 mm in greatest dimension
    - T1b Tumor >5 mm but ≤ 10 mm in greatest dimension
    - T1c Tumor >10 mm but ≤ 20 mm in greatest dimension
- T2 Tumor >20 mm but ≤ 50 mm in greatest dimension
- T3 Tumor >50 mm in greatest dimension
- T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules). *Note*: Invasion of the dermis alone does not qualify as T4
    - T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion
    - T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
    - T4c Both T4a and T4b
    - T4d Inflammatory carcinoma. *Note:* Inflammatory carinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass. These clinical findings should involve the majority of the skin of the breast. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinicalfindings. In addition to the clinical picture, however, a biopsy is still necessary to demonstrate cancer either within the dermal lymphatics or in breast parenchyma itself.

Regional Lymph Nodes (N) *Clinical*

- NX Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0 No regional lymph node metastases

- N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or inclinically detected * ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
    - N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
    - N2b Metastases only in clinically detected * ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
- N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected *ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
    - N3a Metastases in ipsilateral infraclavicular lymph node(s)
    - N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
    - N3c Metastases in ipsilateral supraclavicular lymph node(s)

* *Note* : *Clinically detected* is defi ned as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fi ne needle aspiration biopsy with cytologic examination.

Regional Lymph Nodes (N) *Pathologic (pN)**

- pNX Regional lymph nodes cannot be assessed (e.g., 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 fi ndings (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 ten 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 ten 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

Notes: * Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for"sentinel node," for example, pN0(sn). ** RT-PCR: reverse transcriptase/polymerase chain reaction. *** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination. **** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

ANATOMIC STAGE/PROGNOSTIC GROUPS

• 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	M0
	T4	N1	M0
	T4	N2	M0
• Stage IIIC	Any T	N3	M0
• Stage IV	Any T	Any N	M1

Notes: * T1 includes T1mi. ** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

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APPENDIX B

DETERMINATION OF MENOPAUSAL STATUS

Menopausal Status Determination

The following criteria will be used to define ***postmenopausal***:

- A prior documented bilateral oophorectomy, **or**
- A history of at least 12 months without spontaneous menstrual bleeding, **or**
- Age 55 or older with a prior hysterectomy, **or**
- Age 54 or younger with a prior hysterectomy without oophorectomy (or in whom the status of the ovaries is unknown), with a documented FSH level demonstrating confirmatory elevation in the lab's postmenopausal range.

Women failing to meet one of these criteria will be classified as pre-menopausal.

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APPENDIX C

INFORMATION BASICS FOR ADVERSE EVENT REPORTING

1.0 **PURPOSE**
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in the future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial.

2.0 **DEFINITIONS FOR ADVERSE EVENT REPORTING**

2.1 **Study therapy**
Study therapy is the required treatment or procedure(s) as defined by the protocol.

2.2 **Non-protocol therapy**
For the purpose of adverse event reporting, non-protocol therapy is defined as any treatment or procedure which is described in the protocol as either optional or prohibited.

2.3 **Adverse event assessment**
Reporting requirements are determined by the assessment of the following adverse event characteristics: the *type* or nature of the event; the *grade* (severity); the *relationship to the study therapy* (attribution); *prior experience* (expectedness) of the adverse event; and whether the patient has received an *investigational or commercial agent or both*. The recommended assessment steps include:

- *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0*. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov).
- *Grade* the severity of the adverse event using the NCI CTCAE Version 3.0.
- *Determine whether the adverse event is related to the study therapy.* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.
- *Determine the prior experience of the adverse event*. Expected events are those that have been previously identified as resulting from either whole breast radiation therapy or partial breast irradiation. For expedited reporting purposes, an adverse event is considered unexpected when either the type of event or the severity of the event is not listed in the protocol consent.

3.0 **PROTECTING PATIENT CONFIDENTIALITY**
Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation. All telephone calls and written reports must reference the protocol number, and the patient's study number.

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Form A1

CHECKLIST FOR PATIENT ELIGIBILITY AND INELIGIBILITY

Conditions for patient eligibility (must satisfy all of the following conditions):

_____**(Y)** The patient must consent to be in the study and must have signed an approved consent form conforming with federal and institutional guidelines.

_____**(Y)** Patients must be **>** 18 years old.

_____**(Y)** The patient must have stage 0, I, or II breast cancer.

_____**(Y)** On histological examination, the tumor must be DCIS or invasive adenocarcinoma of the breast.

_____**(Y)** Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor.

_____**(Y)** Gross disease may be unifocal or multifocal with pathologic (invasive and/or DCIS) tumor size excised with negative margins.

_____**(Y/N)** Patients with *invasive* breast cancer are required to have axillary staging Axillary staging is not required for patients with DCIS.

_____**(Y)** The patient must begin adjuvant therapy (chemotherapy or radiotherapy) within 42 days following the last surgery for breast cancer (lumpectomy, re-excision of margins, or axillary staging procedure).

_____**(Y)** Patients must have all usual and customary hormone receptor (ER/PR) an estrogen receptor (ER) analysis performed on the primary tumor prior to enrollment

_____**(Y)** At the time of enrollment, patients must have had an H&P within 4 months and a bilateral mammogram within 6 months.

_____**(Y/N)** Patients must live in a county that is designated as Appalachian and/or rural by Kentucky Cancer Registry Criteria **and/or** _____**(Y/N)** must hold their primary residence **≥ 10** miles from the nearest radiation facility **(distance:_____).**

_____**(Y/N)** Patients who do not fit these criteria may still be considered eligible if they are determined to suffer significant financial and/or transportation hardship during a typical course of CF-RT or HF-RT, in the judgment of any of their treating physicians (**Reason Specification Required**: _____ _____).

CHECKLIST FOR PATIENT ELIGIBILITY AND INELIGIBILITY (FORM A1)
(CONTINUED)

Conditions for patient ineligibility (men are not eligible/ women with one or more of the following conditions also are ineligible).

_____**(N)** T3, stage III, or stage IV breast cancer.

_____**(N)** More than 3 histologically positive axillary nodes.

_____**(N)** Axillary nodes with definite evidence of microscopic or macroscopic extracapsular extension.

_____**(N)** One or more positive *non-axillary* sentinel node(s). (Note that intramammary nodes are staged as axillary nodes.)

_____**(N)** Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

_____**(N)** *Suspicious* microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign.

_____**(N)** Non-epithelial breast malignancies such as sarcoma or lymphoma.

_____**(N)** Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by 4 or more centimeters.

_____**(N)** Paget's disease of the nipple.

_____**(N)** Synchronous bilateral invasive or non-invasive breast cancer.

_____**(N)** History of invasive breast cancer or DCIS. (Patients with a history of LCIS treated by surgery alone are eligible.)

_____**(N)** Surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by reexcision, the patient is eligible.)

_____**(N)** Treatment plan that includes regional nodal irradiation.

_____**(N)** Current therapy with any hormonal agents such as raloxifene (Evista®), tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or breast cancer prevention. (Patients are eligible only if these medications are discontinued prior to enrollment.)

CHECKLIST FOR PATIENT ELIGIBILITY AND INELIGIBILITY (FORM A1)
(CONTINUED)

_____**(N)** Cosmetic breast implants. (Patients who have had implants removed are eligible.)

_____**(N)** Prior breast or thoracic RT for any condition.

_____**(N)** Collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.

_____**(N)** Pregnancy or lactation at the time of proposed randomization. Women of reproductive potential must agree to use an effective non-hormonal method of contraception during therapy.

_____**(N)** Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

_____
Signature of Individual Completing this Form

_____
Signature of PI

_____
Date

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FORM AE

ADVERSE EVENT FORM FOR RADIATION THERAPY

*If patient started radiation therapy (RT), use Form AE to report adverse events that are **possibly, probably, or definitely related to RT.** If patient did not start RT, do not submit Form AE.*

Instructions for completing this form:

- Form AE collects only adverse events that are possibly, probably, or definitely related to **Accelerated Hypofractionated Radiation Therapy (AHF-RT))**, regardless of whether these adverse events are expected or unexpected. Do not report adverse events resulting from chemotherapy, hormonal therapy or any other systemic cancer therapy.
- Complete Form AE at the end of each **Reporting Period**, as defined on page 1 of form. The **Reporting Period Start Date** should not lapse or overlap with the **Reporting Period End Date** of the prior Form AE. If the patient has a **breast cancer recurrence** or **second primary cancer**, please use the ***date of the cancer event*** as the ***reporting period end date*** and submit the form. ***No additional AE forms will be required for this patient.***
- Use **NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0** to report all ***grade 1,2, 3, 4 and 5*** adverse events. Access the CTCAE v3.0 by going to the NCI/CTEP web site at http://ctep.cancer.gov.
- When the adverse event is listed on page 2 of the form, circle the highest grade that occurred during this reporting period.
- When the adverse event is not listed on page 2, write the specified information in the table provided at the bottom of page 2. It is very important that the ***exact wording*** of each **CTCAE v3.0 Short Name** and each **CTACE v3.0 "Select Term"** (when applicable) be used when reporting adverse events. Please do not omit words or abbreviate terms that are spelled out in the CTCAE, Version 3.0.
- Submit pages 1 and 2 of Form AE at the end of each reporting period, as defined on page 1 of form. Please do not submit this instruction page.

Supporting Documentation for Form AE

- Include supporting documentation for all grade 3, 4 and 5 adverse events (AEs) If the patient was hospitalized for 24 hours or more, include supporting documentation (e.g., H&P, hospital discharge summary, pertinent laboratory and radiology reports, consults, physician progress notes).
- Remove patient names and identifiers such as social security number, address, telephone number, etc. from supporting documentation. Each page of supporting documentation and all written reports must reference the patient's protocol study number.

A Phase II Study of Accelerated Hypofractionated Radiotherapy (AHF-RT) after Breast Conserving Surgery (BCS) in Medically Underserved Patients.

ADVERSE EVENT FORM FOR RADIATION THERAPY (FORM AE)

*If patient started radiation therapy (RT), use Form AE to report adverse events that are **possibly, probably, or definitely related to RT.** If patient did not start RT, do not submit Form AE.*

Patient Initials:_____ Protocol ID #:_____

Instructions for Determining Start Date and End Date for each Reporting Period			
Reporting Period	Reporting Period Start Date	Reporting Period End Date *	
		Chemotherapy Not Received	Chemotherapy Received
1	Day 1 of RT	End of RT	End of RT
2	First day after end of RT	4 weeks from end of RT	4 weeks from end of RT and chemotherapy
3	One day after end date of previous reporting period	6 months from end of RT	6 months from end of RT and chemotherapy
4	One day after end date of previous reporting period	12 months from end of RT	12 months from end of RT and chemotherapy
All Subsequent Reports (at 12-month intervals) 5	One day after end date of previous reporting period	12 months after start date for this reporting period	12 months after start date for this reporting period

* *If the patient has a local, regional, or distant cancer recurrence or a second primary cancer after the START DATE of the reporting period, use the date of the cancer event as the END DATE of the reporting period. No later AE forms should be submitted.*

Reporting Period START DATE (*as defined in above table*) Month ☐☐ Day ☐☐ Year ☐☐☐☐

Reporting Period END DATE (*as defined in above table*) Month ☐☐ Day ☐☐ Year ☐☐☐☐

Was patient hospitalized for 24 hours or more? ○ Yes ○ No (*if yes, provide supporting documentation*)

Please mark Reporting Period on page 2 also.

Reporting Period

1	2	3	4	5
○	○	○	○	○

Mark Circles Like This: → ●

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ADVERSE EVENT FORM FOR RADIATION THERAPY (FORM AE)

(CONTINUED)

Patient Initials:_____ Protocol ID #:_____

CTCAE (v3.0) SHORT NAME - CTCAE (v3.0) "SELECT" TERM	CTCAE (v3.0) GRADE				
Constitutional Symptoms					
Fatigue	1	2	3	4	--
Dermatology/Skin					
Hyperpigmentation	1	2	--	--	--
Induration	1	2	3	--	--
Dermatitis - Select - Chemoradiation	1	2	3	4	5
- Radiation	1	2	3	4	5
Telangiectasia	1	2	3	--	--
Ulceration	--	2	3	4	5
Wound complication, non-infectious	1	2	3	4	5
Infection					
Infection with normal ANC - Select - Skin	--	2	3	4	5
- Wound	--	2	3	4	5
Lymphatics					
Edema: limb	1	2	3	4	5
Edema: trunk/genital (breast only)	1	2	3	4	5

CTCAE (v3.0) SHORT NAME - CTCAE (v3.0) "SELECT" TERM	CTCAE (v3.0) GRADE				
Musculoskeletal/Soft Tissue					
Fibrosis-cosmesis	1	2	3	--	--
Fibrosis-deep connective tissue	1	2	3	4	5
Seroma	1	2	3	--	--
Soft tissue necrosis - Select - Thorax	--	2	3	4	5
Pain					
Pain - Select - Breast	1	2	3	4	--
- Other	1	2	3	4	--
Pulmonary					
Cough	1	2	3	--	--
Dyspnea	1	2	3	4	5
Pneumonitis	1	2	3	4	5
Sexual/Reproductive Function					
Nipple/areolar	1	2	3	--	--
Breast (hypoplasia)	1	2	3	--	--

*OTHER : Use this section to report adverse events not listed above that were **possibly, probably, or definitely related to radiation therapy.***

CTCAE v3.0 Short Name	CTCAE v3.0 "Select" Term (if applicable)	CTCAE v3.0 Grade
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		

Please mark Reporting Period on page 2 also.

Reporting Period

1 ○ 2 ○ 3 ○ 4 ○ 5 ○

Mark Circles Like This: → ●

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FORM BE

BCTOS PATIENT BREAST EVALUATION FORM

Patient Initials:_____ Protocol ID #:_____ Date:_____

Assessment Point: □ Baseline □ 6 Months □ 1 year □ 3 years

This form is being filled out: (*Mark one.*)

O By participant in doctor's office O By clinical staff, on phone with participant

O By participant not in doctor's office O Other

Thank you for completing this questionnaire.
We are interested in your evaluation of your physical appearance and functioning since you have been treated for breast cancer. Please rate the following items on this four-point scale, according to your evaluation at this point in time.

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

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FORM CE

COSMESIS PHYSICIAN EVALUATION FORM

Patient Initials:_____ Protocol ID #:_____

Person Completing Form:_____ Date:_____

Assessment Point: ☐ Baseline ☐ 6 Months ☐ 1 year ☐ 3 years

PLEASE ASSESS BREAST COSMESIS 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 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 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.

Please circle one (1) number for each of the following treatment effects.

	None	Yes, present but does not affect cosmesis	Yes, present and affects cosmesis
Skin telangiectasia	0	1	2
Skin atrophy	0	1	2
Scarring	0	1	2
Pigment change	0	1	2
Erythema	0	1	2
Fat necrosis	0	1	2
Fibrosis	0	1	2
Retraction or contour defect	0	1	2
Volume loss	0	1	2
Other significant treatment effects Specify:	0	1	2

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FORM F

FOLLOW UP EVALUATION FORM

Patient Initials:_____ Protocol ID #:_____ Date:_____

Interval since completion of XRT: _____

Vital Status

Patient's Vital Status
- O Alive
- O Dead

Date of Last Contact or Death
Month Day Year

Source of Survival Information (if alive)
- O Documentation of hospital or clinic visit
- O Phone contact to patient
- O Other.....

(if dead)
Primary Cause of Death
- O Due to this disease (breast cancer)
- O Due to protocol treatment
- O Due to other cause
- O Unknown

Describe Cause of Death: (*provide documentation*)
.....
.....
.....

Was there evidence of recurrence at the time of death?
- O Yes
- O No
- O Unknown

if yes, **Type of Evidence**
- O Clinical
- O Autopsy

Cancer Follow-up Status

Has the patient had a documented clinical assessment for this cancer (since submission of the last follow-up form)?
- O Yes
- O No

Date of Last Clinical Assessment (*if applicable*)
Month Day Year

First Local-Regional Recurrence

Has the patient been diagnosed with <u>first</u> local-regional recurrence (since submission of the last follow-up form)?
- O Yes (*provide documentation*)
- O No

Date of First Local-Regional Recurrence (if applicable)
Month Day Year

Site(s) of First Local-Regional Recurrence
(*mark all <u>ipsilateral</u> sites that apply*)
- O **Ipsilateral breast**
- O Chest wall
- O Axilla
- O Axillary nodes
- O Internal mammary nodes
- O Infraclavicular nodes
- O Supraclavicular nodes

First Distant Recurrence

Has the patient been diagnosed with <u>first</u> distant recurrence/progression (since submission of the last follow-up form)?
- O Yes (*provide documentation*)
- O No

Date of First Distant Recurrence (*if applicable*)
Month Day Year

Site(s) of First Distant Recurrence.....
.....
.....

New Primary Cancer or MDS

Has a new primary cancer or MDS been diagnosed that has not been previously reported?
- O Yes (*provide documentation*)
- O No

Date of Diagnosis (*if applicable*)
month *day* *year*

Site(s) of New Primary.....

A Phase II Study of Accelerated Hypofractionated Radiotherapy (AHF-RT) after Breast Conserving Surgery (BCS) in Medically Underserved Patients.

FOLLOW UP EVALUATION FORM (FORM F)
(CONTINUED)

Since the last follow-up, has the patient received any adjuvant hormonal therapy?
(*prior to cancer recurrence or second primary cancer*)

O Yes O No (*if yes, mark all that apply*)

O **SERM**
(e.g., tamoxifen, raloxifene)

O **Aromatase inhibitor**
(e.g., letrozole, exemestane, anastrozole)

O **Other**

Has the patient undergone total mastectomy of the ipsilateral breast that was not previously reported on Form F?

O Yes O No

If yes, record date and provide documentation.

Total Mastectomy Date (ipsilateral breast only)

☐☐ ☐☐ ☐☐☐☐
Month Day Year

IN-BREAST TUMOR RECURRENCE (IBTR)

This section relates only to patients who had IBTR prior to regional or distant recurrence. Omit this section if the information was provided on an earlier follow-up form.

To determine the location of the primary tumor and the IBTR, review the following types of reports: diagnostic tests (e.g. mammogram, ultrasound, and MRI); operative and pathology reports; office notes from the patient's radiation oncologist or surgeon. If these records are not sufficient to allow a comparison of the site of primary tumor and the IBTR, contact the patient's radiation oncologist or surgeon for assistance.

DATE OF IBTR

☐☐ ☐☐ ☐☐☐☐
Month Day Year

LOCATION OF IBTR

O At the site of the primary tumor

O Elsewhere in the breast

Submit any documentation needed to answer this question, excluding documents previously submitted with Form ON.

TREATMENT OF IBTR

O Lumpectomy without RT

O Lumpectomy followed (or to be followed) by RT

O Mastectomy without RT

O Mastectomy followed (or to be followed) by RT

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you have a dry mouth?	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4

During the past <u>four</u> weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4