

NSABP PROTOCOL B-39 RTOG PROTOCOL 0413

A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

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Version Date: March 7, 2011 (Replaces all other versions)

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National Surgical Adjuvant Breast and Bowel Project (NSABP) Radiation Therapy Oncology Group (RTOG)

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INFORMATION RESOURCES

03/30/06

<p>NSABP Operations Center East Commons Professional Building Four Allegheny Center – 5th Floor Pittsburgh, PA 15212-5234 Phone: (412) 330-4600 Fax: (412) 330-4660</p> <p align="center">http://www.nsabp.pitt.edu</p> <p>RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Phone: (215) 574-3189 Fax: (215) 928-0153</p> <p align="center">http://www.rtog.org</p>	<p>NSABP Biostatistical Center One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 Phone: (412) 624-2666 General office fax: (412) 624-1082</p> <p>RTOG Statistical Center 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Phone: (215) 574-3203 Fax: (215) 928-0153</p>
<p>Questions concerning eligibility</p> <p>NSABP Operations Center Clinical Coordinating Division Phone: 1-800-477-7227 E-mail: ccd@nsabp.org</p>	<p>Questions/problems regarding IRB review & informed consent (see Appendix H)</p> <p>NSABP Operations Center Division of Regulatory Affairs Phone: (412) 330-4600 Fax: (412) 330-4661</p>
<p>Patient entry information (see Section 19.0)</p> <p>NSABP Biostatistical Center Patient Entry Coordinator Phone: (412) 383-4900 Fax: (412) 383-2065</p> <p>Consult the Patient Entry Guidelines section in the Members' Area of the NSABP Web site.</p>	<p>Submission of IRB approval</p> <p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888-823-5923 Fax: (215) 569-0206</p>
<p>Questions regarding radiation therapy treatment (WBI and non-credentialing PBI questions)</p> <p>RTOG RT Quality Assurance Phone: (215) 574-3219</p>	<p>Questions regarding PBI credentialing</p> <p>Radiological Physics Center (RPC) Phone: (713) 745-8989 http://rpc.mdanderson.org/rpc</p>
<p>Questions concerning other clinical issues</p> <p>Clinical Coordinating Division Phone: 1-800-477-7227</p>	<p>Submission of electronic data for credentialing and for PBI case reviews and treatment data</p> <p>Image-guided Therapy QA Center (ITC) http://atc.wustl.edu</p> <p>Submission of CT images for patients randomized to WBI</p> <p>Details found in the Site Tools section of the Radiation Therapy Oncology Group Web site: http://www.rtog.org</p>

<p>Questions regarding QOL/cosmesis study</p> <p>NSABP Biostatistical Center BAHO Compliance Officer Phone: (412) 383-2537</p>	<p>Submission of digital images for cosmesis assessments (see Section 7.2)</p> <p>Details found in the Site Tools section of the Radiation Therapy Oncology Group Web site: http://www.rtog.org</p>
<p>Submission of tumor blocks (see Section 9.1)</p> <p>NSABP Biostatistical Center Address: see page iv. When sending blocks or other materials, please indicate on the package “Pathology Specimens Enclosed.”)</p>	<p>Serum kit requests and submission of blood and serum samples (see Appendix C)</p> <p>Baylor College of Medicine Breast Center NSABP Serum Bank Room N1220 One Baylor Plaza Houston, Texas 77030 Phone: (713) 798-1647 Fax: (713) 798-1642</p>
<p>Arrangements for return of blocks that are not to be stored or to request core biopsy kits</p> <p>NSABP Division of Pathology Phone: (412) 359-3312 Fax: (412) 359-3239 E-mail: pathology.questions@nsabp.org</p>	
<p>Questions concerning data management</p> <p>NSABP Biostatistical Center Phone: (412) 624-2666 Fax: (412) 624-1082</p>	<p>Submission of expedited adverse event reports/questions concerning expedited adverse event reporting (see Section 17.0)</p> <p>NSABP Biostatistical Center Phone: (412) 383-2552 Fax: (412) 622-2113</p>

Cancer Trials Support Unit (CTSU) Information Resources

This study is supported by the NCI CTSU.

Institutions not aligned with the NSABP will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix (Appendix D).

To submit site registration documents:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Phone: 1-888-823-5923
Fax: 1-215-569-0206
E-mail: CTSURegulatory@ctsu.cocccg.org

For patient enrollments:

CTSU Patient Registration
Voice Mail: 1-888-462-3009
Fax: 1-888-691-8039
Hours: 8:00 AM-8:00 PM Eastern
Time, Monday-Friday (excluding
holidays)

[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]

Submit study data directly to the NSABP unless otherwise specified in the protocol:

Preferred method:
Fax: 412-622-2111

NSABP Biostatistical Center

One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

- **For patient eligibility questions, contact the Clinical Coordinating Division at the NSABP Operations Center at 1-800-477-7227.**
- **Contact the RTOG at 215-574-3219 for radiation therapy treatment-related questions.**
- For data submission questions, contact the B-39/0413 Data Manager at the NSABP Biostatistical Center by calling 412-624-2666.

For questions unrelated to patient eligibility, treatment, or data submission, contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at www.ctsu.org

The CTSU Registered Member Web site is located at <https://members.ctsu.org>

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to Appendix D for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to Appendix D for specific instructions and forms to be submitted.
- Data management will be performed by the NSABP. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to the NSABP Biostatistical Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the NSABP Biostatistical Center. Please send query responses and delinquent data to the NSABP Biostatistical Center and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the NSABP Biostatistical Center.

1.0 SUMMARY OF THE STUDY

This Phase III randomized trial will evaluate the effectiveness of partial breast irradiation (PBI) compared to whole breast irradiation (WBI) in providing equivalent local tumor control in the breast following lumpectomy for early stage breast cancer. The study will compare the overall survival, recurrence-free survival, and distant disease-free survival between women receiving PBI and WBI. It will also look at quality of life (QOL) issues related to cosmesis, fatigue, treatment-related symptoms, and perceived convenience of care.

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. If stage II, tumor size must be 3 cm or less. 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 stratified according to disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy. Following stratification, patients will be randomized to receive WBI or PBI.

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WBI for this study will utilize standard techniques delivered over 5 to 7 weeks as outlined in the NSABP B-39/RTOG 0413 protocol. PBI will utilize the technologies of high dose-rate multi-catheter brachytherapy, high dose-rate single-entry intracavitary brachytherapy (MammoSite[®], MammoSite[®] ML, Contura[™] MLB, and SAVI[®]), and three-dimensional conformal external beam radiation therapy. Ideally, PBI therapy will be given twice a day, at least 6 hours apart, on 5 treatment days over a period of 5 to 10 days and the technique selected will depend on technical considerations, radiation oncology facility technique credentialing, as well as patient preference. Patients randomized to WBI will receive chemotherapy, if applicable, before their radiation therapy. Patients randomized to PBI will receive radiation therapy before chemotherapy, if applicable.

For the purpose of this study, consistency between participating facilities is essential for outcome assessment. Therefore, each radiation oncology facility must complete a radiotherapy approval process for quality assurance purposes to assure that appropriate technical and clinical components are available to comply with protocol requirements. It is preferable that at least two methods of PBI be approved at each facility, however, one approved method is sufficient.

Tumor blocks and slides from the initial core biopsy, index tumor, normal breast lobule and positive node (if applicable) as well as serum collection are required for patients who have consented to serum and tissue collection. These materials will be useful for correlative studies.

03/30/06
01/08/07

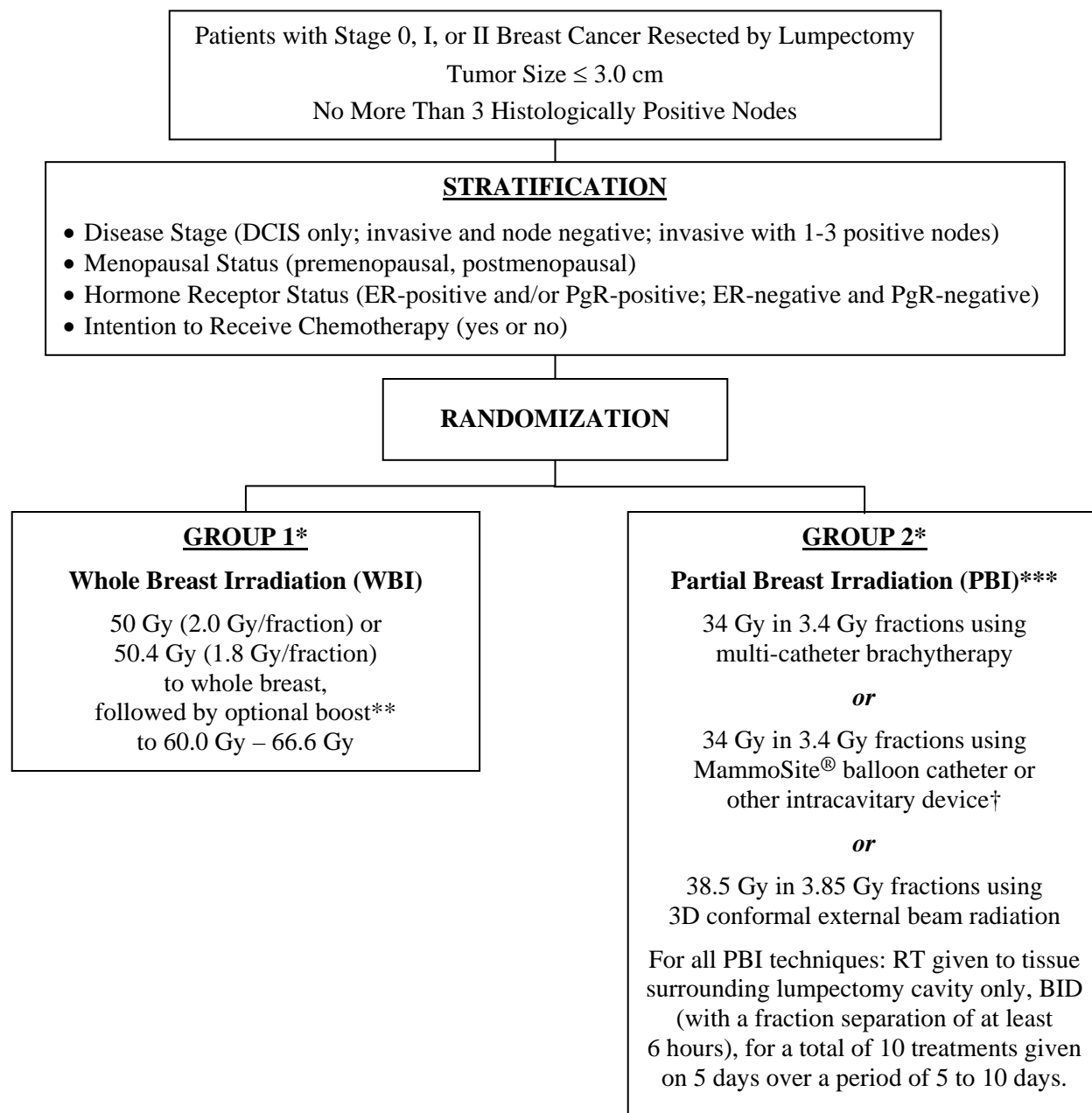
This trial was originally designed to accrue 3000 patients over a period of 2 years and 5 months with accrual projected to be approximately 75 patients each month for the first year increasing to 125 patients each month in subsequent years. A review of the disease stage and tumor characteristics of patients already enrolled on B-39/0413 has shown that there is a disproportionate rate of accrual of low-risk patients. As a result, two actions were taken by the NSABP and the RTOG. First, accrual to specific low-risk patient populations was closed (see Section 19.1). Second, at the time of Amendment #2, the sample size of the trial was increased to 4300 patients to be accrued over 4.6 years, based on the assumption that accrual will continue at the rate that has been observed (see Section 21.5).

The quality of life and cosmesis population will include 482 enrolled patients who have indicated the intention to receive chemotherapy and 482 patients who have indicated the intention not to receive chemotherapy.

Please refer to Figure 1 for the B-39/0413 study schema. Figure 2 provides a more detailed flow diagram.

Figure 1

NSABP B-39/RTOG 0413 Schema



* See Section 15.0 for instructions regarding chemotherapy and hormonal therapy. Chemotherapy, if given, will be administered before WBI or following PBI.

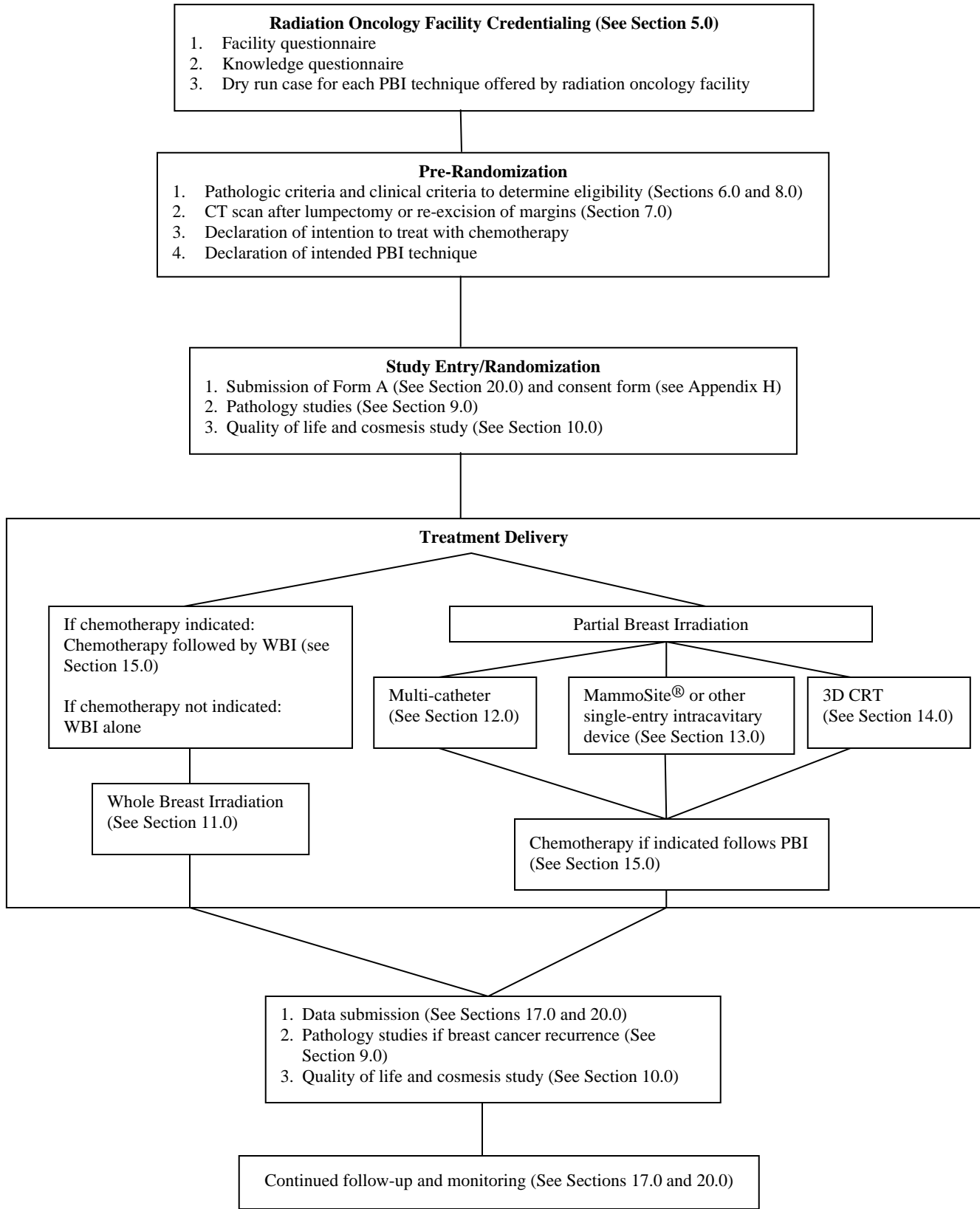
** Brachytherapy boost is not allowed. (See Section 11.1.4.)

*** The PBI technique utilized will be at the physician's discretion and will be based on technical considerations, radiation oncology facility technique credentialing (see Section 5.0), as well as patient preference.

† Options for other single-entry intracavitary devices include these multi-lumen devices: MammoSite® ML, Contura™ MLB, and SAVI® (see Section 13.0).

Figure 2 – NSABP B-39/RTOG 0413 Flow Diagram

03/07/11



2.0 BACKGROUND

01/08/07

2.1 Clinical Background

Breast conserving therapy (BCT) has become an accepted option in the treatment of most patients with stage I and II breast cancer. Multiple retrospective studies as well as six prospective randomized trials have established the long-term equivalence of this treatment approach compared to mastectomy in terms of disease-free and overall survival.^{1,2} The major advantages of BCT are superior cosmetic results and reduced psychological and emotional trauma compared to mastectomy. However, BCT also has relative disadvantages. The technique is a more complex and prolonged treatment regimen requiring approximately 5 to 7 weeks to complete. For patients who are elderly or who live a significant distance from treatment centers, logistical problems can prove to be prohibitive. In addition, with the more frequent use of adjuvant chemotherapy in patients with both node-negative and node-positive breast cancer, substantial delays can occur prior to the initiation of either local breast irradiation (RT) or hormonal therapy. Thus, despite the obvious cosmetic and potential emotional advantages of BCT, only 10%-40% of patients who are candidates for breast conservation actually receive it.³

Most of the logistical problems associated with BCT relate to the protracted course of external beam RT delivered to the whole breast. Standard therapy after tumor excision generally includes 5 (25 fractions) weeks of external beam RT to the whole breast (45-50 Gy) followed by a boost to the tumor bed with either an additional 8 to 10 fractions (1 fraction/day) of external beam RT or a 2 to 3 day interstitial implant. The rationale for this approach is based upon two principles. First, higher doses of RT are given to the "tumor bed" in an attempt to control small foci of cancer which may be left behind after excision alone.⁴ Second, WBI is used to eliminate possible areas of occult multicentric in situ or infiltrating cancer in remote areas of the breast. That such remote, multicentric areas of cancer exist has long been established.⁵ However, the biological significance of these areas of occult cancer is unknown, and the necessity to prophylactically treat the entire breast has recently been questioned. For instance, there are now at least five prospective randomized trials that have been conducted comparing the outcome of patients treated with excisional biopsy alone or followed by WBI. In all of these trials, the majority of recurrences in the breasts of patients who did not receive RT occurred at or in the area of the tumor bed.^{2,6,7,8,9} In addition, the rate of development of new cancers in remote areas of the breast (unrelated to the index lesion) was similar whether or not WBI was administered. Thus, it would appear that RT after tumor excision exerts its maximal effect upon reducing breast cancer recurrence at or near the tumor site.

In a similar pattern to invasive breast cancer, in non-invasive breast cancer (DCIS), 75% of recurrences developed in or adjacent to the original tumor site following breast conservation surgery with or without the use of radiation.¹⁰ Previous work has shown that less than 10% of DCIS cases have satellite lesions more than one centimeter from the original tumor.¹¹ A trial from Ochsner Clinic involving patients with DCIS treated by brachytherapy resulted in a substantially low local recurrence rate.¹² Therefore, patients with DCIS will be candidates for this trial.

Adding additional strength to this argument is the observation that in patients undergoing standard BCT and treated with conventional WBI, the development of new cancers in the ipsilateral breast (remote from the primary lesion) is similar to that observed in the contralateral breast. For example, in the 20 year update of the study by Veronesi et al examining the equivalence of standard BCT to mastectomy, the incidence of new cancers developing in the ipsilateral breast (in a location other than that of the index lesion) was similar to that observed in the contralateral breast (0.42 and 0.66 per 100 women years of observation, respectively).^{1,13} This suggests that elective treatment with RT beyond the quadrantectomy bed provided minimal additional benefit. Similar findings in patients undergoing BCT were recently reported by the Yale group. In a 15-year update on 1152 patients treated with conventional WBI, the actuarial rate of developing new cancers remote from the tumor bed ("elsewhere failures") was 13%.¹⁴ In comparison, the 15-year rate of contralateral breast cancer was only 10%. Collectively, these data question the efficacy of routinely treating the entire breast in all patients.¹⁵

The implications of these observations form the basis of the current study. Can an acceptable outcome be achieved with RT delivered only to the region of the tumor bed? If this were the case, radiation therapy could be delivered in 1 to 2 weeks, thus significantly shortening treatment time and potentially reducing health care costs. A shortened treatment schedule would decrease the burden of care for patients undergoing BCT, thus making available the conservation option for more women. By reducing the length of time required to deliver RT, the logistical problems associated with integrating local and systemic therapies would also be eliminated. Additionally, toxicity to adjacent normal structures (i.e., heart, underlying chest wall, contralateral breast) should be reduced significantly by decreasing the volume of irradiated tissue. Several recent meta-analyses on the use of RT for breast cancer patients clearly document a reduction in cancer-specific mortality during the first 5-10 years after treatment that is partially off-set by late effects of radiation on adjacent tissues.¹⁶ Since it remains uncertain if the additional volume of normal tissue that is irradiated (in order to encompass the entire breast for presumed occult disease) provides any additional benefit in reducing breast cancer recurrence, the potential detrimental effects of this additional RT would be eliminated.

There currently is a large body of mature Phase I and II data (and some preliminary Phase III findings) that have investigated the replacement of WBI after lumpectomy with an accelerated course of radiation therapy delivered in only 4-5 days and restricted to the region of the tumor bed.¹⁷ Five-year results from the majority of these trials have demonstrated local control rates in the breast comparable to those observed after conventional WBI. Most of these data have been generated using interstitial breast brachytherapy. This is an invasive procedure consisting of temporarily placing a series of 10-20 needles or catheters in the breast to encompass the lumpectomy cavity. These catheters are then loaded with a radiation source, which delivers a tumoricidal dose of RT to the lumpectomy cavity region alone in 4-5 consecutive days, generally as an outpatient procedure. With the patient's entire RT course completed, the catheters are then removed.¹⁸ This technique has not yet gained widespread popularity because of the relative complexity associated with performing an interstitial implant and the lack of significant patient interest in an additional invasive procedure. As a consequence, PBI as a potential treatment option has been limited to only a handful of institutions with experience in interstitial breast brachytherapy.

Several recent developments have occurred that are rapidly increasing interest in the use of PBI as a treatment option.

- First, newer “user friendly” interstitial breast brachytherapy techniques have been developed that are more easily taught and performed and that are more comfortable for patients.¹⁸ In addition, two interstitial breast brachytherapy schools (one conducted by the American Brachytherapy Society) have also been developed and are conducted on a regular basis.

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- Second, single-entry, single- and multi-lumen intracavitary FDA approved devices are now available simplifying the brachytherapy technique and providing a more reproducible method to perform breast brachytherapy, allowing many more physicians and institutions the opportunity to deliver high quality PBI. The single-lumen intracavitary balloon was the first available device that was soon followed by three multi-lumen FDA approved intracavitary devices.

Proxima Therapeutics was the first to develop and achieve FDA approval for a new breast brachytherapy catheter (MammoSite®).¹⁹ Since the device consists of only one catheter temporarily positioned in the breast (as opposed to 10-20 needles), patient comfort is potentially improved. From the time of FDA approval in 2002 to 2005, 517 radiation oncologists, 677 surgeons, and 312 physicists in 210 centers had been trained to perform breast brachytherapy using the MammoSite® catheter. During that time, 2761 catheters have been implanted. Five-hundred and eighty patients have been enrolled in a manufacturer-sponsored registry trial designed to determine the technical reproducibility and acute toxicity involved in the large scale use of the device. This registry is now managed by the American Society of Breast Surgeons. The registry contains 81 sites (36 sites are enrolling patients) and 94 surgeons.

Since the initiation of NSABP B-39/RTOG 0413 in 2005, there have been three FDA approved single-entry multi-lumen intracavitary devices that have been introduced to the market: MammoSite® ML (Multi-Lumen), Contura™ MLB (Multi-Lumen Balloon), and SAVI® (Strut-Adjusted Volume Implant). These multi-lumen devices offer a more sophisticated radiation delivery approach as compared to the original single-lumen MammoSite® balloon catheter. All three of these intracavitary devices preserve the single-entry concept while providing the radiation oncologist with the ability to improve dosimetric coverage of the target and reduce dose to nearby rib and skin when needed. Through an increased ability to achieve the dosimetric goals outlined in this protocol, these devices provide the potential to expand the number of patients who can be appropriately treated with an intracavitary brachytherapy approach. These single-entry, multi-lumen intracavitary devices were added as options in Amendment #5 for use in the NSABP B-39/RTOG 0413 study.

- Third, three-dimensional (3D) conformal external beam radiation therapy techniques have also been developed and successfully used to treat patients with PBI using a similar, shortened treatment schedule. This 3D technology is readily available in the majority of radiation facilities allowing many more radiation oncologist groups that do not perform brachytherapy to deliver PBI.²⁰ Perhaps the greatest advantage of this method of PBI is the fact no additional invasive procedure is required.

Collectively, these three developments have generated tremendous interest in PBI since there are now several comparable and reproducible techniques available along with 5-year interstitial breast brachytherapy data demonstrating efficacy. Despite these

findings, mature Phase III data documenting the long-term efficacy of this treatment approach and the group of patients most suitable for its application are not yet available. Since the majority of patients treated in the Phase I/II PBI studies discussed above were highly selected and treated at only a handful of institutions, it remains to be determined if the excellent results observed to date are a reflection of the true efficacy of PBI or to other confounding factors. The only scientifically valid approach to resolve this concern is in the completion of a well-designed, sufficiently powered Phase III study comparing outcome in similarly staged and selected patients randomized between standard WBI versus accelerated PBI.

Therefore, NSABP B-39/RTOG 0413 proposes that selected patients undergoing BCT for stages 0, I, and II breast cancer be randomly assigned after lumpectomy to either standard WBI or PBI. Patients randomized to the PBI arm will be treated with one of three different types of PBI depending upon the experience and credentialing of the participating institution, technical considerations, and patient preference. This study will be designed to (1) establish the equivalency in local control and overall survival of PBI to WBI, (2) establish the equivalency in cosmetic outcome between the two treatment approaches, and (3) analyze potential differences in fatigue, treatment-related symptoms, and convenience of care among patients undergoing PBI versus WBI.

2.2 **Supporting data for PBI**

Numerous groups have studied the efficacy of PBI in the management of early stage breast cancer patients treated with BCT. Both interstitial brachytherapy techniques as well as external beam irradiation protocols have been implemented (see Table 1). Results from these trials have been very encouraging and the techniques have been shown to be safe, tolerable, and highly reproducible. Studies with the largest number of patients and the longest follow-up are reviewed in Table 1.

TABLE 1. Partial breast irradiation studies

Institution	# Cases	Median F/U (mo)	Scheme (cGy)	Total Dose (cGy)	% Local Recurrence	% Good/Excellent Cosmetic Results
<i>HDR Brachytherapy Series</i>						
Ochsner Clinic ¹² New Orleans, Louisiana	26	75	400 x 8	3200	2 ^a	75 ^a
Royal Devon/Exeter Hospital, Exeter, England ²¹	45	18	1000 x 2 700 x 4 600 x 6	2000 2800 3600	8.8	95
National Institute of Oncology, Budapest, Hungary Phase I/II Trial	45	60	520 x 7 433 x 7	3640 3030	4.4	97
National Institute of Oncology, Budapest, Hungary Phase III Trial ²²	221	30	520 x 7 (HDR) 200 x 25 ^b (EBRT)	3640 5000	0 < 1	not stated Not stated
London Regional Cancer Center London, Ontario ^{23,24}	39	20	372 x 10	3720	2.6 ^a	Not stated
William Beaumont Hospital ^{25,26}	79	52	400 x 8	3200	1	100
Radiation Therapy Oncology Group ²⁷	66	32	340 x 10	3400	---	---
MammoSite® (Proxima Therapeutics) ^c	43	8	340 x 10	3400	0	97
Tufts-New England Medical Center ²⁸	32	33	340 x 10	3400	3	88
<i>LDR Brachytherapy Series</i>						
Ochsner Clinic ¹²	26	75	> 40 cGy/hr	4500	2 ^a	75 ^a
Guy's Hospital ^{29,30}	27	72	40 cGy/hr	5500	37	83
Florence, Italy ³¹	90	27	Not stated	5000-6000	4.4	Not stated
University of Kansas ³²	25	47	---	2000-2500	0	100
William Beaumont Hospital ²⁵	120	82	52 cGy/hr	4992	1	91
Radiation Therapy Oncology Group ²⁷	33	36	---	4500	---	---
Massachusetts General Hospital ^c	48	23	50	5000-6000	0	92
<i>External Beam Radiotherapy Series</i>						
Christie Hospital, Manchester, England ^{33,34}	353	65	500-531 x 8	4000-4200	25 ^d	---
William Beaumont Hospital ^c	22	20	340-385 x 10	3400-3850	0	100
Keck School Medicine/New York University ³⁵	9	36	500-600 x 5	2500-3000	0	100
<i>Intra-Operative Radiotherapy Series</i>						
European Institute of Oncology ³⁶	84	8	1700-2100 x 1	1700-2100	---	---
University College of London ³⁷	3	24	500-750 x 1	500-750	0	---
a = LDR/HDR patients combined b = Whole breast irradiation c = Personal communication d = Eight year rate HDR = High dose rate brachytherapy LDR = Low dose rate brachytherapy EBRT = External beam radiation therapy						

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Interstitial breast brachytherapy, MammoSite[®] or other single-entry intracavitary device, and 3D conformal external beam radiotherapy (EBRT) are the PBI techniques proposed in the NSABP B-39/RTOG 0413 study. Interstitial brachytherapy has been the most commonly used PBI technique with the longest clinical follow-up. Published techniques are available outlining its clinical use either at the time of lumpectomy or shortly after surgery with closed cavity techniques.^{18,38} Its safety, reproducibility and acute toxicity as a PBI technique have been studied in a Phase II trial by the Radiation Therapy Oncology Group. In addition, the American Brachytherapy Society (ABS) provides annual training for optimal use of interstitial brachytherapy in the PBI setting.

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The U.S. Food and Drug Administration approved the single-entry, single-lumen MammoSite[®] as a breast brachytherapy catheter in May 2002. Published data from the initial clinical use of the device revealed that the applicator performed well clinically with all eligible patients completing treatment.¹⁹ Side effects were mild to moderate and self-limiting in the trial. Skin-balloon surface distance and balloon-cavity conformance were the main factors limiting the initial use of the device. It has now become the most frequently used PBI technique due to its ease of use, reproducibility, and to dosimetric data demonstrating its comparability to traditional interstitial breast brachytherapy techniques.³⁹ In addition, formal training is provided by the manufacturer and is a prerequisite for its clinical use. The optimal application of the device in the PBI setting is also formally taught by the ABS.

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Since the FDA approval and clinical introduction of the three single-entry, multi-lumen devices (MammoSite[®] ML, Contura[™] MLB, and SAVI[®]), publications have reported their ability to meet dosimetric guidelines as applied in the NSABP B-39/RTOG 0413 study. The dosimetric performance of the multi-lumen balloon is described by an experience reported by Brown et al.⁴⁰ In this experience, 33 patients treated with a multi-lumen balloon were compared to 33 patients treated with a single-lumen balloon. The percentage of the prescribed dose covering the planning target volume, the maximum skin and rib dose as a percentage of the prescribed dose and the volume to normal tissue receiving 150% and 200% of the prescribed dose, were used as dosimetric measurements of device capabilities. Results confirmed that the multi-lumen balloon devices have the ability to not only perform as well as a single-lumen balloon, important for justifying inclusion as a device option within this study, but also produced clinically significant improvements in dosimetric endpoints (e.g., reduced skin and rib doses and improved PTV coverage) in most clinical scenarios. Yashar et al reported on the first 102 patients treated with the SAVI[®] multi-lumen device.⁴¹ The dosimetric performance was similarly evaluated looking specifically at the dose coverage of the target, the maximum skin and rib dose and the volume to normal tissue receiving 150% and 200% of the prescribed dose, which were used as dosimetric measurements of device capabilities. This device also was able to deliver dose distributions that were equivalent and exceeded that required of the single-lumen balloon.

Finally, 3D conformal EBRT has also been investigated as a PBI technique. Recent Phase I/II data by Vicini et al demonstrated a high degree of conformality (comparable to interstitial brachytherapy PBI techniques) achievable in all 16 patients examined in their dosimetric study.²⁰ In addition, acute radiation effects in the first 9 patients treated on the study were minimal. Similar results were observed by Formenti et al suggesting that 3D conformal external beam RT as a PBI technique can be applied safely and with a high degree of reproducibility at multiple centers. A Phase I/II trial by the RTOG (RTOG 0319) evaluating 3D conformal EBRT closed after completing accrual in April 2004.

2.2.1 *Interstitial brachytherapy*

Interstitial breast brachytherapy has been used successfully as a technique to deliver PBI for over a decade. In 1993, Vicini et al initiated a pilot trial of low dose rate (LDR) brachytherapy as the sole radiation modality with BCT.^{25,42,43} Flexible afterloading brachytherapy catheters were placed around the lumpectomy bed either during or after surgery to deliver 50 Gy to the tumor site as an inpatient procedure over 96 hours. As of February 2001, 120 patients have been treated on this study. With a median follow-up of 82 months, only 4 patients have developed a local recurrence (0.9% 5-year actuarial rate of recurrence), and cosmetic results were judged as good to excellent in 91% of patients.⁴⁴ In addition, no adverse sequelae were noted in the study. More recently, a second study employing high dose rate (HDR) brachytherapy (in the same subset of patients) was also initiated at the same institution.²⁶ Afterloading HDR brachytherapy needles were placed around the lumpectomy bed either at the time of surgery or shortly thereafter. A total of 34-38 Gy were delivered in 10 fractions (two fractions per day) as an outpatient procedure to the tumor bed region. Vicini et al recently updated the results of their combined patient population (120 LDR and 79 HDR patients). With a median follow-up of 65 months, the 5-year actuarial rate of local recurrence was 1.2 % and cosmetic results were judged to be good/excellent in 98% of patients.⁴⁴

The next largest published experience of interstitial brachytherapy with the longest follow-up was reported by King et al in a series of 51 patients treated at the Ochsner Clinic in New Orleans, Louisiana. Both LDR and HDR interstitial brachytherapy techniques were employed. With a median follow-up of 74 months, RT limited to the tumor bed after breast conserving surgery produced a 5-year actuarial rate of local recurrence of only 1.4%.¹² Again, cosmetic results were judged as good/excellent in the vast majority of patients, and late sequelae were minimal.

The Radiation Therapy Oncology Group (RTOG) completed accrual in 2000 to a prospective Phase I/II cooperative group study of brachytherapy used as the sole radiation modality after lumpectomy.²⁷ The trial was designed to test the feasibility, reproducibility, toxicity, cosmesis, local control, and disease-free survival of brachytherapy alone for select patients treated with lumpectomy and axillary dissection. From August 1997 to March 2000, 100 patients were accrued of which 99 met all eligibility criteria. Thirty-one patients were treated with LDR brachytherapy (45 Gy in 4.5 days) and 68 with HDR brachytherapy (34 Gy in 10 fractions over 5 days). On quality assurance review, 95 patients were treated per protocol with only 4 minor protocol deviations and no major deviations. Adequate coverage of the target volume was achieved in 97% of patients with acceptable dose homogeneity in 99%. With a median follow-up of 2.7 years, the acute toxicity during treatment and at the most recent follow-up has been reported.⁴⁵ During PBI, 73% of patients had mild (grade 1-2) toxicity, with radiation-related reddening of the skin being the most frequently seen. Grade 3 and 4 toxicities were noted in 4% and 1%, respectively, during PBI. At the latest follow-up, 29%, 12%, and 4% grade 1, 2, and 3 toxicities, respectively, were reported. Breast thickening and tenderness were the most frequently noted toxicities at this point. There was no grade 4 toxicity noted following PBI. No published data on tumor control are available yet.

Data on local control in the RTOG 95-17 brachytherapy-alone trial were recently reported. With a median follow-up of 3.7 years (range 0.6 to 5.7), 3 patients failed in the ipsilateral breast for a 4-year actuarial rate of local recurrence of 3%. In addition, 2 nodal recurrences were observed (3% 4-year actuarial rate).⁴⁶

One of the most recently published experiences with PBI comes from the National Institute of Oncology, Budapest, Hungary.²² In a Phase I/II study of 45 patients treated with HDR brachytherapy (see Table 1), 2 (4.4%) local recurrences were noted with a median follow-up of 60 months. The authors recently updated their experience with PBI in these 45 patients. With a median follow-up of 81 months, the crude rate of total ipsilateral breast failure was 6.7% (3 of 45 patients) for (5- and 7-year actuarial rates of 4.4% and 9%, respectively).⁴⁷ In a Phase III trial at the same institution comparing PBI (90 patients treated with 7 x 5.2 Gy of HDR brachytherapy and 21 with 50 Gy of wide-field electron irradiation) versus WBI (110 treated with 50 Gy to the whole breast in 2 Gy fractions), two local recurrences were observed in each arm with a median follow-up of 30 months.⁴⁸

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2.2.2 *Intracavitary catheter*

Proxima Therapeutics received FDA approval of the MammoSite® balloon catheter in 2002 for use with intracavitary HDR breast brachytherapy. In their preliminary study, 70 patients were enrolled in a multi-center prospective trial testing the applicator for safety and performance. Fifty-four patients were implanted and 43 patients were ultimately eligible for and received brachytherapy as the sole radiation modality after lumpectomy. Patients were staged T₁N₀M₀ with negative pathologic margins and age ≥ 45 years. A dose of 34 Gy was delivered in 10 fractions over 5 days prescribed to 1 cm from the applicator surface using iridium-192 high dose rate brachytherapy. A minimum skin-to-balloon surface distance of 7 mm was required for treatment. Device performance, complications, and cosmesis were assessed. The balloon breast brachytherapy applicator performed well clinically. All eligible patients completed treatment.¹⁹ Side effects were mild to moderate and self-limiting. Skin-balloon surface distance and balloon-cavity conformance were the main factors limiting the initial use of the device. In the 2-year update of this experience in these 43 patients, Keisch et al. reported good-to-excellent cosmetic results in 88% of patients with no patient developing adverse sequelae requiring surgical correction or chronic analgesics.⁴⁹ A previously published dosimetric study on the clinical use of the catheter revealed a high degree of reproducibility from physician to physician with comparable tumor bed coverage to traditional interstitial breast brachytherapy.³⁹

In response to the enthusiasm generated by the introduction of the MammoSite® coupled with the recognition of this device's limitations, three FDA approved single-entry multi-lumen devices have been developed and increasingly incorporated into practice. These include the MammoSite® ML, Contura™ MLB, and SAVI®. Each of these devices address the identified limitations of a single-lumen balloon and increase the frequency at which dosimetric goals can be achieved and treatment successfully delivered. Each of these devices are now approved for use in the NSABP B-39/RTOG 0413 study when enrolled patients are randomized to PBI (Group 2).

2.2.3 *Intraoperative radiation therapy*

Intra-operative external beam irradiation has also recently been explored as an additional method of delivering post-lumpectomy PBI in an accelerated fashion. Veronesi et al from the European Institute of Oncology in Milan, Italy recently published their preliminary results from a Phase I/II dose escalation study of single-fraction irradiation given immediately after quadrantectomy.³⁶ With minimal toxicity in the first 86 patients treated with dose levels of 17, 19, and 21 Gy per fraction using 3 - 9 MeV electrons, the authors have now proceeded with a Phase III trial comparing standard WBI (50 Gy plus a 10 Gy boost) to a 21 Gy intra-operative single fraction. As of February 2002, more than 250 patients have been enrolled in this equivalency trial with an accrual goal of over 800 patients.⁵⁰

Vaidya et al recently published their experience with intra-operative partial breast radiation therapy as boost treatment.³⁷ As of December 2002, 31 patients have been treated in a pilot study of 35 patients. In this study, the tissue surrounding the operative bed is treated with a single intraoperative 5 Gy fraction utilizing the Photon Radiosurgery System. A ball-shaped applicator is inserted intraoperatively into the lumpectomy cavity, and the applicator emits soft x-rays into the adjacent tissue. With a median follow-up of 24 months, there have been no major complications. The authors have now initiated a randomized study for patients to receive either standard WBI after surgery or the same surgery followed by a single, intraoperative dose of RT (5 Gy). No preliminary results are yet available. The NSABP B-39/RTOG 0413 treatment regimen will not include intraoperative methods.

2.2.4 *3D conformal external beam irradiation*

Three-dimensional conformal external beam radiotherapy techniques for delivering PBI have also been tested in two other Phase I/II trials. Formenti et al recently published their experience treating nine patients with early stage breast cancer after lumpectomy with 3D conformal radiation therapy using various fraction sizes and total doses. Patients received 5 fractions over 10 days (total dose range, 25-30 Gy); three received 5.0 Gy per fraction; four received 5.5 Gy; and two received 6.0 Gy. At a minimum follow-up of 36 months (range of 36-53 months), all patients were alive and disease free with good-to-excellent cosmesis.³⁵

In addition, Vicini et al also initiated a pilot study in 1999 of 3D conformal external beam RT using similar selection criteria as RTOG 95-17. As of December 2002, 28 patients have been treated with 10 fractions of radiation (3.4 Gy or 3.85 Gy per fraction bid separated by 6 hours) to total doses of 34 Gy or 38.5 Gy. Patients were treated in the supine position and the clinical target volume (CTV) was specified as the lumpectomy cavity (as outlined by surgical clips) plus a 1.5 cm margin.²⁰ The planning target volume (PTV) consisted of the CTV plus 1.0 cm. This PTV margin was added for breathing motion and treatment set-up uncertainties that were analyzed prospectively. No adverse sequelae were noted.⁴⁴

Although little additional external beam PBI data exist, radiobiological models suggest that this fractionation schedule of 38.5 Gy in 10 fractions should produce an acceptable control rate in the breast and comparable late effects as brachytherapy. These models estimate that the proposed radiation scheme (3.85 Gy x 10) should provide a biologically equivalent dose (BED) of 45 Gy in 1.8 Gy fractions assuming an α/β ratio of 10. It should be noted that this dosing schedule is considerably more conservative than that used in a similar protocol of partial breast irradiation employed in a Phase III trial performed at the Christie Hospital and Holt Radium Institute. This trial randomized 708 patients with lesions 4 cm or less in diameter and without axillary dissection to receive either: (1) tumor bed (quadrant) irradiation alone, typically 10 MeV electron beam to an average field size of 6 x 8 cm, 42.50 Gy in fractions (531 cGy per fraction), or (2) tangential WBI (standard therapy). Results between the two treatment arms were similar with respect to local recurrence in patients with infiltrating ductal carcinoma. More importantly, complication rates were also similar between the two groups (< 3%) at 7 years.^{33,34} RTOG successfully concluded accrual to a Phase I/II study (RTOG 0319) evaluating PBI using 3D conformal external beam irradiation with 58 patients. This will add to the expanding knowledge base and experience in 3D conformal external beam irradiation. The 3D conformal external beam irradiation technique will be allowed in this trial.

2.3 Considerations regarding axillary staging

The usefulness of complete axillary lymph node dissection (ALND) for patients with breast cancer has been questioned, since it now has a less important role in selecting subsequent therapy and is associated with significant morbidity. Sentinel node biopsy may be an alternative to axillary node dissection, both in patients with negative and positive sentinel nodes. However, long term outcome data await the completion of ongoing clinical trials. The value of sentinel axillary lymph node biopsy is presently being ascertained in NSABP Protocol B-32, which uses a standard method with isotope and blue dye. However, there are now several successful methods of identifying the sentinel node. Therefore, the technique selected by each surgeon will be acceptable in the NSABP B-39/RTOG 0413 study. Sentinel lymph nodes should be analyzed by processing each node as outlined by the College of American Pathologists. A minimum of 6 axillary nodes must be evaluated; no more than 3 nodes may be positive.

2.4 Considerations regarding accelerated WBI schedule

Recently, Whelan reported on the use of accelerated WBI delivered in 3 weeks versus 5 weeks.⁵¹ During development of the NSABP Partial Breast Irradiation Concept, careful consideration was given as to whether or not the use of the Canadian accelerated breast irradiation schedule should be permitted in patients randomly assigned to the control arm in addition to the 5-week schedule that is the currently accepted standard in the United States. While we desire to be as inclusive as possible, it was concluded that permitting use of the accelerated schedule on this protocol would present a logical contradiction in the study design that could complicate interpretation of data. Specifically, currently published evidence in support of the accelerated schedule is not yet sufficient to rule out differences which, under our proposed analysis plan, would be defined to be inferior. The proposed analysis plan defines PBI to be inferior to WBI if it permits as much as a 50% increase in hazard rate of IBTR; therefore, in order to declare equivalence we will need to rule out the possibility at the .05 level of significance (see

Section 21.0). In order to maintain internal consistency of our study, if we were to include the accelerated regimen, we should require evidence of its non-inferiority using criteria which are at least as stringent as these, and preferably, considerably more stringent.

Unfortunately, if our test for non-inferiority were applied to the currently published data comparing the accelerated schedule with the longer schedule, the hypothesis of inferiority would not be rejected. This is not to say that the currently available data demonstrate inferiority (they do not), but rather they are not sufficiently extensive to rule it out using the criteria we have prospectively chosen for our study. If additional follow-up of the accelerated schedule trial does eventually demonstrate equivalence under the criteria proposed for use in our study, then this issue will be re-evaluated.

3.0 **STUDY AIMS**

3.1 **Primary aim**

To determine whether partial breast irradiation (PBI) limited to the region of the tumor bed following lumpectomy provides equivalent local tumor control in the breast compared to conventional whole breast irradiation (WBI) in the local management of early stage breast cancer.

3.2 **Secondary aims**

- To compare overall survival, recurrence-free survival, and distant disease-free survival between women receiving PBI and women receiving WBI.
- To determine whether PBI delivered on 5 treatment days over a period of 5 to 10 days can provide a comparable cosmetic result to WBI.
- To determine if PBI produces less fatigue and treatment-related symptoms compared to WBI.
- To determine if perceived convenience of care is greater for women receiving PBI compared to women receiving WBI.
- To compare acute and late toxicities between the radiation therapy regimens.

4.0 ENDPOINTS

4.1 Primary endpoint

The primary endpoint for analysis is the time from randomization 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 randomization 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 16.0).
- 4.2.2 Recurrence-free survival defined as the time from randomization 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 randomization to death due to any cause.
- 4.2.4 Quality of life:
 - cosmesis;
 - treatment-related symptoms;
 - fatigue; and
 - perceived convenience of care.
- 4.2.5 Treatment toxicities (acute and late)

RADIATION ONCOLOGY FACILITY CREDENTIALING AND QUALITY ASSURANCE

Several treatment techniques and dosimetric guidelines have been developed for PBI. Although there is a degree of variability, each technique has merit. For the purpose of this study, consistency between participating radiation oncology facilities is necessary for outcome assessment. To achieve this, guidelines have been established that will help standardize the infrastructure of the radiation oncology facility as well as the techniques for treatment delivery. The quality assurance (QA) program will cover the delivery of both WBI and PBI. However, it is assumed, since WBI is widely practiced, that the majority of the approval process will focus on PBI, and that guidelines set for the WBI arm will be easily adopted and monitored.

5.1 Radiation oncology facility credentialing

Prior to enrolling any patients, regardless of previous approval for other protocols, each radiation oncology facility will need to complete a radiotherapy approval process to assure that appropriate technical and clinical components are available to comply with protocol requirements. This will assure that each radiation oncology facility has the following: access to the necessary equipment; staff who have reviewed and understand the protocol and have a basic understanding of treatment planning and delivery techniques so that WBI and PBI will be delivered with reproducible quality; and functional digital submission capability. The Radiological Physics Center (RPC) will oversee the credentialing process in coordination with the Image-guided Therapy Center (ITC). Two questionnaires, (facility and knowledge assessment), coupled with a **CT-based dry run case for each of the following PBI techniques** (MammoSite[®], multi-catheter brachytherapy, 3D conformal external beam) that the radiation oncology facility will offer, will be used in the process. It is preferable that at least two methods of PBI are available at each facility; however, credentialing in only one technique is acceptable for participation.

Note: Institutions planning to utilize any of the intracavitary devices added as options at the time of Amendment #5 (MammoSite[®] ML, Contura[™] MLB, and SAVI[®]) must first have documented that the CT-based dry run case for the MammoSite[®] has been completed. Additionally, the first five submitted cases will be routed through the rapid review and timely review process as outlined in Section 5.2.

In summary, the facility must complete a Facility Questionnaire and dry-run case for each PBI method in order to be credentialed. However, every radiation oncologist who is planning to enroll patients on this trial at the credentialed facility must complete a Knowledge Assessment Questionnaire and Sections I and II of the PBI Facility Questionnaire for each PBI method they will be using.

The instructions and forms for radiation oncology facility credentialing may be found on the Radiological Physics Center Web site at <http://rpc.mdanderson.org/rpc> or on the Advanced Technology Consortium (ATC) Web site at <http://atc.wustl.edu> by clicking on "Credentialing". **It is required that the questionnaires be completed online to facilitate the processing of submitted data. Questionnaires and cases submitted on a Friday will not be reviewed until the following Monday.**

5.2 PBI quality assurance program

The quality assurance program, with close monitoring and institutional feedback, is an essential component in assuring radiation oncology facility competency in PBI treatment delivery and the overall success of this study. Submission of all requested components with complete and appropriate contouring is necessary for continued protocol participation. Each PBI case will be submitted digitally to the ITC where it will be processed and made available for review by study chairs or designees, the RPC, and the RTOG Headquarters Dosimetry Group.

03/07/11

5.2.1 *Rapid review of PBI cases*

The first case for each PBI technique (single-entry intracavitary devices including MammoSite[®], MammoSite[®] ML, Contura[™] MLB, and SAVI[®]; multicatheter brachytherapy; and 3D conformal external beam) from each radiation oncology facility will undergo rapid review. For radiation oncology facilities using both the MammoSite[®] ML and the Contura[™] MLB, a rapid review case is required for only one of these two, multi-lumen, balloon devices because of the similarities in contouring requirements. **In this process, the case will be planned, electronically submitted, reviewed, and approved prior to the start of treatment. Additional patients may not be enrolled for the specific PBI technique that is undergoing the rapid review process until approval for the rapid review case is received.**

Allow 3 business days for the results of the rapid review process. Cases that are submitted on a Friday will not be processed until the following Monday. The rapid review process will not start until all required data is received by the ITC. Cases that do not meet contouring and quality assurance criteria will not be approved and corrections will need to be made to obtain approval for accrual and treatment. If corrections or additional documentation is requested, the subsequent submission of the case will be not given priority review.

03/07/11

5.2.2 *Timely review of PBI cases*

Following rapid review, there will be a timely review of the subsequent 4 cases for each PBI technique (single-entry intracavitary devices including MammoSite[®], MammoSite[®] ML, Contura[™] MLB, and SAVI[®]; multicatheter brachytherapy; and 3D conformal external beam). For radiation oncology facilities using both the MammoSite[®] ML and Contura[™] MLB, the 4 timely review cases may be any combination of these two, multi-lumen, balloon devices. Each of these cases may proceed to treatment following planning without waiting for review and approval. It is requested that the treatment plan be submitted within one week. These cases will be reviewed in a timely manner with feedback given to the submitting radiation oncology facility. Corrections and resubmission of data will be requested for cases that do not meet contouring and quality assurance criteria.

Once the rapid review case and 4 timely review cases have been submitted, all 5 cases will be re-evaluated together. This process will occur for each PBI technique to be offered at a radiation oncology facility. Feedback regarding treatment guideline compliance will be forwarded to the radiation oncology

facility. *During the period of **timely review**, the radiation oncology facility will be permitted to continue accrual.*

If the review of cases 4 and 5 demonstrates a treatment plan that is unacceptable, the radiation oncology facility will be required to repeat the rapid review and timely review process. Additional patients may not be enrolled for the specific PBI technique that is undergoing the rapid review process until approval for the rapid review case is received.

5.2.3 ***Random case monitoring for PBI cases***

Additional PBI case review will be done in a random fashion. Corrections and resubmission of data will be requested for cases that do not meet contouring and quality assurance criteria. If protocol non-compliance is documented, the radiation oncology facility will be required to repeat the timely review process (4 cases) if the facility is to continue participating in the B-39/0413 trial. *The radiation oncology facility will be permitted to continue accrual.*

5.3 **WBI quality assurance program**

Requested material documenting adequate coverage of the lumpectomy cavity with whole breast irradiation plans will be submitted to RTOG for review ***within one week of the start of treatment.***

5.3.1 ***Timely review of WBI cases***

The first 5 WBI cases from each radiation oncology facility will be reviewed for adequate documentation in a timely manner with feedback given to the submitting radiation oncology facility. If unacceptable, timely reviews will be required for the next 4 cases. *Treatment will continue during this process. The radiation oncology facility will be able to continue accrual.*

5.3.2 ***Random case monitoring for WBI cases***

Additional case review will be done in a random fashion after the first five cases of WBI have been reviewed. Feedback will be given to the submitting radiation oncology facility as necessary. If protocol non-compliance is documented, the radiation oncology facility may be required to repeat the timely review process.

6.0 PATIENT ELIGIBILITY AND INELIGIBILITY

6.1 Conditions for patient eligibility

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

- 6.1.1 The patient must consent to be in the study and must have signed an approved consent form conforming with federal and institutional guidelines.
- 6.1.2 Patients must be ≥ 18 years old.
- 6.1.3 The patient should have a life expectancy of at least ten years, excluding her diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)
- 01/08/07 6.1.4 The patient must have stage 0, I, or II breast cancer. If stage II, the tumor size must be 3 cm or less. (*See Section 19.1 for information regarding accrual closure to low-risk patient populations.*)
- 6.1.5 On histological examination, the tumor must be DCIS or invasive adenocarcinoma of the breast.
- 6.1.6 Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (DCIS and invasive). Re-excision of surgical margins is permitted.
- 6.1.7 Gross disease must be unifocal with pathologic (invasive and/or DCIS) tumor size 3 cm or less. (Patients with microscopic multifocality are eligible as long as total pathologic tumor size is 3 cm or less.)
- 6.1.8 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.)
- 6.1.9 The patient must be randomized within 42 days following the last surgery for breast cancer (lumpectomy, re-excision of margins, or axillary staging procedure).
- 01/08/07 6.1.10 Patients must have an estrogen receptor (ER) analysis performed on the primary tumor prior to randomization. If ER analysis is negative, then progesterone receptor (PgR) analysis must be performed. If ER analysis is positive, PgR analysis is desired but not mandatory. ("Marginal" or "borderline" results [i.e., those not definitively negative] will be considered positive regardless of the methodology used.) (*See Section 19.1 for information regarding accrual closure to low-risk patient populations.*)

- 6.1.11 The target lumpectomy cavity must be clearly delineated and the target lumpectomy cavity/whole breast reference volume must be $\leq 30\%$ based on the postoperative/pre-randomization CT scan.
- 6.1.12 Patients are eligible if, based on the postoperative/pre-randomization CT scan, PBI is judged to be technically deliverable by a technique for which the radiation oncology facility has been credentialed.
- 6.1.13 At the time of randomization, patients must have had an H&P within 4 months and a bilateral mammogram within 6 months.
- 6.1.14 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.

6.2 **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.

- 6.2.1 T₂ (> 3.0 cm), T₃, stage III, or stage IV breast cancer (see Appendix A for TNM nomenclature and staging).
- 6.2.2 More than 3 histologically positive axillary nodes.
- 6.2.3 Axillary nodes with definite evidence of microscopic or macroscopic extracapsular extension.
- 6.2.4 One or more positive *non-axillary* sentinel node(s). (Note that intramammary nodes are staged as axillary nodes.)
- 6.2.5 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.
- 6.2.6 *Suspicious* microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign.
- 6.2.7 Non-epithelial breast malignancies such as sarcoma or lymphoma.
- 6.2.8 Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by 4 or more centimeters.
- 6.2.9 Paget's disease of the nipple.
- 6.2.10 Synchronous bilateral invasive or non-invasive breast cancer.
- 6.2.11 History of invasive breast cancer or DCIS. (Patients with a history of LCIS treated by surgery alone are eligible.)

- 6.2.12 Surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by re-excision, the patient is eligible.)
- 6.2.13 Clear delineation of the extent of the target lumpectomy cavity not possible.
- 6.2.14 Treatment plan that includes regional nodal irradiation.
- 6.2.15 Any treatment with radiation therapy, chemotherapy, biotherapy, and/or hormonal therapy administered for the currently diagnosed breast cancer prior to randomization. The only exception is hormonal therapy, which may have been given for no more than a total of 28 days anytime after diagnosis and before randomization. For patients who will be receiving chemotherapy, hormonal therapy must stop at or before randomization and resume following completion of chemotherapy. For patients who will not be receiving chemotherapy, hormonal therapy may continue. (Refer to Section 15.2 for information on hormonal therapy.)
- 6.2.16 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 randomization.)
- 6.2.17 Breast implants. (Patients who have had implants removed are eligible.)
- 6.2.18 Prior breast or thoracic RT for any condition.
- 6.2.19 Collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosus, or scleroderma.
- 6.2.20 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.
- 6.2.21 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

7.0 PRE-RANDOMIZATION ASSESSMENTS

7.1 Pre-randomization breast CT for treatment planning

03/30/06

- 7.1.1 CT-imaging of the ipsilateral breast is required prior to study entry. It is recommended that the pre-randomization CT be performed within 14 days following surgery; however, it will be acceptable as long as it is performed within 42 days following surgery.
- 7.1.2 Technical feasibility for PBI techniques will be determined by size, shape and location of the lumpectomy cavity and the lumpectomy cavity/whole breast volume ratio which is required to be $\leq 30\%$.
- 7.1.3 If the initial CT documents a lumpectomy cavity that exceeds criteria ($> 30\%$), it is acceptable to proceed with study entry if a repeat CT scan documents that the cavity has changed such that eligibility requirements are met (as long as this is determined within the required 42-day time constraint). This CT scan will be performed in the external beam treatment position so that assessment of the lumpectomy cavity volume in relationship to the ipsilateral whole breast reference volume can be determined.
- 7.1.4 Proper positioning for this CT scan will also allow this data set to be used for future treatment planning if appropriate. See Appendix F for contouring instructions. Field borders that could be used for whole breast treatment should be identified and marked but not tattooed. This CT data set will then be evaluated on a 3D planning system. Using a virtual whole breast treatment field as a guide, the whole breast reference volume and lumpectomy cavity will be delineated. The ratio between the lumpectomy cavity and whole breast reference volumes will be generated and this ratio is required to be $\leq 30\%$.

To determine if a patient would be an appropriate candidate for 3D-CRT, the planning target volume (PTV) to reference breast volume should be calculated and not exceed 20%-25%. If the percentage is higher, it is likely that it will not be possible to meet the Dose-Volume Histogram (DVH) constraints.

7.2 Pre-treatment digital images for patients in the QOL and cosmesis population

03/30/06

- 7.2.1 Digital images of the patient's breasts taken prior to initiation of therapy (chemotherapy and radiation therapy) are required for the patients in the QOL and cosmesis patient population (see Section 10.4). The first digital image should be a close-up encompassing only the ipsilateral breast to be treated at a 45° oblique with arms elevated over the patient's head. The second digital image should be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands on her hips, taking care to exclude her face. (See Section 10.1 for more information regarding plans for the cosmesis study.)

03/30/06

- 7.2.2 RTOG will provide a Web-based Image Management System, which will allow the participating sites to securely log on to the RTOG Web site and upload digital images that have been submitted as JPEG files. Users will be required to enter contact information for the person submitting the photos, the NSABP Patient ID

number, patient's initials, NCI site ID, image type, view type, time point, and the date photographs were taken. These parameters will be associated with each image set and are vital for archiving and identifying the digital images for retrieval purposes. As soon as the digital image files are uploaded to the server, they will be transferred to an alternate site location on the server. A history log of each image will be maintained in the NSABP/RTOG database. Access to this secure Web site will be provided to NSABP reviewers. In order to access the digital images, the NSABP reviewers will log on to a secure Web site and enter required variables to retrieve relevant digital image sets.

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

Table 2 lists: 1) all studies required for study entry; 2) all studies required during study therapy; and 3) all studies required as part of long-term follow-up. *See Table 3 for QOL and cosmesis requirements.*

TABLE 2. Studies required

03/30/06, 01/08/07, 03/13/07, 11/02/09

Required studies ^a	Prior to randomization	At end of RT	At 4 weeks following therapy ^b	At 6 months and 12 months following therapy ^b	Years 2 through 5		Year 6+
					Every 6 months ^b	Every 12 months ^b	Every 12 months ^b
History & physical exam	X ^c	X ^d	X ^d	X ^d	X ^d		X ^d
Breast assessment/exam	X (postop)	X	X	X	X		X
Adverse event assessment ^f		X	X	X		X	X
Weight	X (postop)			X			
Menopausal status ^g	X						
CBC	X ^e						
Platelet count	X ^e						
Alkaline phosphatase	X ^e						
AST <i>or</i> ALT	X ^e						
Pregnancy test (serum beta HCG)	X ^h						
Chest imaging ⁱ	X						
Abdominal CT	X ^j						
Ipsilateral breast CT	X ^k						
Bone scan	X ^l						
Bilateral mammogram	X ^m			X ⁿ		X	X
QOL and cosmesis (See Table 3)							
Serum collection ^o							
Tissue blocks/slides ^p							

- a** H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently according to physician preference and when symptoms suggest metastatic disease.
- b** From end of RT (if no chemotherapy) or from end of both RT and chemotherapy (if chemotherapy is given).
- c** Complete H&P within 4 months prior to randomization.
- d** Updated H&P including disease status.
- e** May be preoperative or postoperative assessment.
- f** **RT-related** assessment; refer to Section 17.4.2 for timing of Form AE submissions.
- g** See Appendix B.
- h** Within 2 weeks prior to randomization for women of childbearing potential.
- i** Chest CT or chest x-ray.
- j** In the presence of hepatomegaly or alkaline phosphatase, AST/ALT, or bilirubin > ULN for the lab.
- k** CT should be performed within 14 days following surgery; however, any time following surgery and before entry is acceptable. (See Section 7.0 for pre-randomization requirements.)
- l** If alkaline phosphatase is elevated and/or the patient c/o pain or other symptoms suggestive of skeletal metastasis.
- m** Within 6 months prior to randomization.
- n** 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. Subsequent mammograms must be performed at least every 12 months.
- o** For patients who have agreed to serum banking, *after randomization but before therapy begins*; and at time of first breast cancer recurrence. (See Section 9.2)
- p** For patients who have agreed to tissue submission, blocks and slides are required; submit within 3 months following randomization. (See Section 9.1.3)

TABLE 3. Required studies for QOL and cosmesis patient population (see Section 10.4)

Note: Accrual to the BAHO substudy was closed on May 27, 2009. All BAHO substudy related requirements listed in Table 3 (the QOL questionnaires, MD-reported cosmesis assessments, and digital images) continue to be required for women who are currently participating in the BAHO substudy.

03/30/06, 11/02/09

Required Studies	Prior to randomization	Treatment with chemotherapy?						Follow-up ^a		
		No			Yes			Year 1	Year 2	Year 3
		Last day of RT	4 weeks after RT	6 months after RT	Last day of last therapy ^b	4 weeks after RT and chemotherapy	6 months after RT and chemotherapy			
QOL Questionnaire	X	X	X	X	X	X	X	X	X	
MD-Reported Cosmesis	X ^c						X ^c		X ^c	
Digital Images (Breast Photos)	X ^d						X		X	

a From end of RT (if no chemotherapy) or from end of both RT and chemotherapy (if chemotherapy is given).
b If Group 1 (WBI), last therapy will be RT. If Group 2 (PBI), last therapy will be chemotherapy.
c 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.
d Photographs may also be taken after randomization but before any adjuvant treatment begins.

9.0 REQUIRED PATHOLOGY STUDIES

This study requires the collection and submission of tumor and serum samples by all institutions. However, an individual patient may refuse the collection, storage, and use of her tissue and serum by answering "No" to the appropriate questions in the B-39/0413 consent form. These patients may still participate in the trial; however, tumor samples should **not** be submitted for patients who have answered "No" to the first two of the three questions (Questions #1 and #2 as presented in the NSABP Sample Consent Form [Appendix H]). If the patient answered "Yes" to either question (Question #1 or #2), a sample should be submitted. Non-submission of index tumor or serum samples will be a protocol violation unless a patient has not consented to the collection, use, and storage of her tumor and serum.

NOTE: The tissue and serum samples that will be collected in this study will be used for future studies as described in Section 9.1, as well as for other unspecified future research. *The specimens procured will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used.* Analysis of a patient's tumor pathology will not be reported to the patient or her physician, and will not have any bearing on how she is treated and followed on the study.

Submitted slides and blocks are initially logged into the database at the NSABP Biostatistical Center. These samples are then stripped of patient identifiers except NSABP study numbers and forwarded to the NSABP Division of Pathology (refer to Information Resources, page v) where they are assigned a code number for further processing and study. Three replica tissue microarrays of 0.6 mm cores will be constructed from collected blocks. Serum samples are submitted to the NSABP Serum Bank at Baylor where they are logged into the database and assigned a serum bank number. Serum samples are stripped of patient identifiers except NSABP study numbers, processed, and stored.

01/08/07

9.1 Summary of pathology and correlative science studies

9.1.1 Overview

The following is an outline of the future studies that are being considered. When concepts are fully developed in the future, these studies will be submitted as separate correlative science protocols.

The aim of the pathology and correlative science for this trial is to identify potential predictors of selective advantage for WBI versus PBI. There will be two important aspects for correlative science studies: 1) predictors of multicentricity and local recurrence after lumpectomy without radiotherapy will have significant bearing on outcome of patients in the PBI arm, and 2) markers of radiosensitivity/resistance should be examined since, if the tumor cells are resistant to radiotherapy, the local recurrence rate will not be influenced by the field of radiation.

We will procure hematoxylin eosin (H&E) stained slides to centrally examine the histopathological features that may be associated with IBTR, especially those interacting with method of treatment. We will also procure paraffin blocks from the initial diagnostic core biopsy for the purpose of extracting DNA and RNA for comprehensive analysis of genome and transcriptome. Tissue microarrays will

be created from paraffin blocks from index tumors and used to screen conventional markers such as p53, HER, ER, PR, EGFR, HIF-1alpha, VEGF, etc. by immunohistochemical methods. We will also make tissue arrays available to the general scientific community. Representative blocks from histologically normal lobules at the margin of lumpectomy specimens will be obtained for the purpose of examining the LOHs in normal cells implicated in IBTR.

Predictors of multicentricity and local recurrence have been examined in the NSABP Protocol B-06 by Dr. Edwin Fisher. A recent 15-year update has shown that young age, poor nuclear grade, presence of an intraductal carcinoma component, and lymphocytic infiltrates were associated with increased risk of IBTR. However, molecular markers have not been examined in B-06. We will design a comprehensive pathology reporting form to collect relevant histopathological features. The H&E stained slides will be collected and centrally reviewed. The slides also will be scanned with Aperio ScanScope® for web-based publication to the scientific community. Studies by UCSF investigators have suggested that presence of loss of heterozygosity of certain genomic loci in histologically normal lobules is implicated in IBTR.⁵² We will procure paraffin blocks from both index tumor and surrounding normal tissue to examine those loci by polymerase chain reaction.

There are many proposed molecular predictors of radiosensitivity or radioresistance. These include molecules involved in DNA excision repair, cell cycle arrest, apoptosis, and hypoxia. The role of hypoxia in radiation resistance is a well-known phenomenon. There is a fairly detailed description of the molecular pathway for hypoxic response governed by Hypoxia inducible factor 1 alpha (HIF-1alpha), which is a transcriptional factor that induces many genes including vascular endothelial growth factor. Many signal transduction pathways, including those of EGFR and HER2, induce HIF-1alpha, also. By the time the accrual of this trial is over, there will be a much more clear elucidation of the hypoxic pathway and many more markers of radiotherapy response. Therefore, we will have to have ways to examine the genome and transcriptome on a global scale. We will procure paraffin blocks of pre-lumpectomy diagnostic core biopsy specimens for the purpose of gene expression and copy number profiling using microarray. We are currently evaluating various whole genome amplification methods that will allow examination of many genomic markers such as CGH, SNPs and LOHs using small amounts of DNA extracted from microdissected tumor cells. We also have developed collaborations with companies that have developed gene expression profiling of RNA extracted from paraffin blocks using real time RT-PCR or microarrays.

9.1.2 *Specific hypotheses*

- The rate of IBTR in the PBI arm may be higher for those subsets of patients at high risk of IBTR.
- Molecular profiling may identify risk factors for higher risk IBTR in PBI patients compared to WBI patients.

9.1.3 *Tissue submission requirements*

- *Tissue requirements*

- Paraffin block of the initial diagnostic core biopsy, if available.
- Representative H&E slides from the index tumor.
- Representative paraffin block from index tumor.
- Representative paraffin block containing normal lobule at lumpectomy margin.
- Representative paraffin block from positive lymph node, if applicable.

- *Timing*

Tissue submission, as described above, within 3 months after randomization is mandated in this protocol (for patients who have consented to tissue submission).

- *Alternate submission*

While it is desirable that paraffin blocks are submitted, for institutions that do not allow submission of the paraffin blocks, we recommend submitting the following two items as a substitute for each type of block:

- 20 to 30 unstained sections of four or five micron thickness
- a 2 mm core sampling of the existing tumor block from an area rich in tumor cells or a similar size fragment cut from the original block (Biopsy kits can be obtained from the NSABP Division of Pathology. [See Information Resources on page v.]

9.1.4 *Submission instructions*

Submit all NSABP pathology material to the NSABP Biostatistical Center at the address listed under "Information Resources" (see page iv).

01/08/07
03/30/06

9.2 **Serum collection**

9.2.1 *Timing of serum collections*

Serum will be collected at the following timepoints:

- baseline (*after randomization but before therapy begins*); and
- at the time of first locoregional or distant recurrence.

Please note: The baseline specimen will be collected before therapy begins. Subsequent specimens should be collected as soon as possible following diagnosis of a breast cancer event regardless of whether or not new therapy has started.

01/08/07

9.2.2 ***Instructions for serum collection***

Investigators must follow the procedures outlined in Appendix C, *Procedure for Collecting, Processing, and Shipping Serum Specimens*.

9.2.3 ***Use of serum specimens***

Decisions about tests to be performed on these specimens will be made by the members of the NSABP Breast Committee and consulting researchers with expertise in this area.

Collected sera at baseline will be used for proteomics studies in order to examine protein markers (or entire serum proteins) that may be prognostic and/or predictive of response to regimens used in the study. Sera collected at subsequent timepoints will be used for proteomics studies in order to examine protein markers that may be predictive of relapse or new primary breast cancers. Since the field of proteomics is rapidly evolving, we are not yet committed to any one methodology. At the end of the trial, the best methodologies will be identified and employed.

11/02/09 10.0 **BEHAVIORAL AND HEALTH OUTCOMES (BAHO) ASSESSMENTS**

Note: Accrual to the BAHO substudy was closed on May 27, 2009. All BAHO substudy related requirements listed in Table 3 (the QOL questionnaires, MD-reported cosmesis assessments, and digital images) continue to be required for women who are currently participating in the BAHO substudy.

Primary hypotheses:

- Cosmetic results 3 years after PBI using any of the 3 treatment approaches following lumpectomy will be comparable to that obtained 3 years after external beam WBI.
- Among patients not receiving chemotherapy, fatigue at the end of radiotherapy will be less for patients undergoing PBI using any of the 3 treatment approaches than for patients undergoing WBI. Among patients receiving combined RT and chemotherapy, fatigue at the end of combined treatment will be less for patients undergoing PBI using any of the 3 treatment approaches than for patients undergoing WBI.

Secondary hypotheses:

- Among patients not receiving chemotherapy, treatment-related symptoms at the end of radiotherapy will be less for patients undergoing PBI using any of the 3 treatment approaches than patients undergoing WBI. Among patients receiving combined RT and chemotherapy, treatment-related symptoms at the end of combined treatment will be less for patients undergoing PBI using any of the 3 treatment approaches than for patients undergoing WBI.
- Among patients not receiving chemotherapy, the perceived convenience of care will be greater for patients undergoing PBI using any of the 3 treatment approaches than for patients undergoing WBI. Among patients receiving combined RT and chemotherapy, convenience of care at the end of combined treatment will be greater for patients undergoing PBI using any of the 3 treatment approaches than for patients undergoing WBI.

03/30/06 10.1 **Cosmesis**

The quality of life component contains provisions to evaluate cosmetic results. As noted earlier in the proposal, BCT has become an accepted option in the treatment of most patients with stage I and II breast cancer. One of the major advantages of BCT is the superior cosmetic results that are produced relative to mastectomy. Since there is a paucity of data evaluating cosmetic results following breast-conserving surgery and PBI, cosmetic endpoints are important to study empirically. In terms of cosmesis, we expect the PBI and WBI will have equivalent outcomes. Because cosmetic outcome improves over time and only stabilizes several years post-treatment, our primary cosmetic endpoint will be taken 3 years post-treatment. We also plan to collect intervening data, however, in order to be able to characterize the manner in which cosmetic outcome resolves over time.

Cosmetic results will be evaluated in several ways. First, the Breast Cancer Treatment Outcome Scale (BCTOS)⁵³ 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 both at our final 3-year endpoint and at intervening assessment points along the way including 1-year follow-up (see Table 5B).

Second, after consent but prior to randomization, a cosmetic evaluation will be made by the radiation oncologist (or surgeon), using criteria established in previous RTOG trials. Ratings of cosmetic outcome will then be made by the radiation oncologist (or surgeon) at 1-year and 3-year follow-up (see Table 5B), in order to be able to compare 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, again using RTOG established protocol. For practical reasons, these digital images will only be taken at three points in time, at baseline (prior to beginning any treatment) and at the 1-year and 3-year (final) assessment points. Two digital images will be taken at each of these assessment points. One will be a close up of the treated breast alone, in order to provide detailed information regarding the treatment effects. 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 (see also Section 7.2). These digital images will then be evaluated for cosmetic results by a panel of physicians using diagnostic criteria established in previous RTOG trials (e.g., degree of scarring, extent of pock marks and/or dimpling, degree of symmetry between the breasts, extent of changes to the skin).

We think it is of interest and important to obtain multiple measures of cosmetic outcome, in order to assess the degree of correspondence between physician-generated and patient-generated outcomes. Prior research, taken together with data generated from previous NSABP trials, suggests that physician-generated ratings often underestimate the degree of dissatisfaction experienced and problems perceived by the patient. Our plan is to use the patient's self-report as our primary cosmetic endpoint.

10.2 **Quality of life**

Studies of women receiving breast-conserving surgery followed by WBI generally report adequate quality of life.^{53,54} However, little is known about quality of life following breast-conserving surgery and PBI. The current trial presents an excellent opportunity to study the treatment-relevant components of quality of life of women undergoing PBI, and to compare their experiences to those of women undergoing WBI. Patients in the PBI arm will receive 5 days of intensive radiation treatment, while those assigned to the WBI arm will receive 5 to 7 weeks of standard fractionated radiotherapy. Given the nature of this trial, there is no reason to believe that the two arms will differ in terms of global quality of life, and no such measures are contained in the protocol. Differences between the two arms are expected to be limited to sequelae of treatment-related side-effects (as reflected in ratings of fatigue and treatment-relevant symptoms, including pain) and to perceived convenience of care.

Patients in the PBI arm will receive higher intensity and more dose-dense radiation than patients in the WBI arm. However, due to the shorter duration of their treatment, we believe the ratings of fatigue and treatment-related symptoms at the end of radiotherapy will be lower among women in the PBI arm than among women in the WBI arm. We also believe that women in the PBI arm will perceive their convenience of care to be greater than women in the WBI arm. We note that prediction concerning differences in fatigue, treatment-related symptoms, and perceived convenience of care among women receiving PBI versus WBI is clearest among women who receive radiation therapy alone,

not in combination with chemotherapy. This is the case because the differences in the sequencing of radiotherapy and chemotherapy across the two arms may cause the benefits of PBI to be obscured and overridden by the effects of the accompanying chemotherapy treatment by the time the combined treatment ends. However, it is also possible that PBI will produce superior overall results compared to WBI even when radiotherapy is given in sequence 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.

The BCTOS also will be used as a primary measure to assess breast-related symptoms and treatment effects. For this trial, the BCTOS will be augmented with a brief set of additional items that focus specifically on radiotherapy-relevant symptoms (e.g., reports of skin problems, tenderness in the breast, hardness in the breast due to enhanced fibrosis, and pain). The Convenience of Care scale includes several items designed to assess how disruptive the treatment is on the patients' daily activities and life styles, as well as how satisfied the patients are with the duration of their treatment. The MOS SF-36 Vitality Scale, a widely used measure with high reliability and validity, will assess fatigue.^{55,56}

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10.3 QOL and cosmesis instructions

The patient-completed quality of life questionnaire will be administered at baseline, after informed consent has been obtained and prior to randomization (see Figure 3). 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). Because the end of treatment will occur at different times in the two arms (e.g., at approximately 5 to 7 weeks for the WBI arm versus 5 to 10 days for the PBI arm, among patients not receiving chemotherapy), we think it is important to equate the two arms in terms of what point they are at in their treatment regimens, rather than the amount of time elapsed from baseline. 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. There are four versions of the quality of life questionnaire: QLB (baseline), QLT (end of treatment), QLP (post-treatment), and QLF (follow-up).

The radiation oncologist (or surgeon)-completed cosmesis questionnaire (Form COS) will be completed by the radiation oncologist at baseline and at 1 and 3 years after the completion of adjuvant (non-hormonal) therapy. If the radiation oncologist will not be available to make these assessments, they may be made by the surgeon. We strongly urge that all three assessments be performed by the same individual.

The photographs will be taken at the same time points as Form COS: baseline, 1 year and 3 years after therapy. However, the baseline photographs may be taken after randomization (but prior to the start of chemotherapy and radiation therapy), whereas Forms QLB and COS must be completed prior to randomization.

Patients who never initiate study treatment should complete QOL and cosmesis assessments as scheduled through year 3. When a patient's follow-up office visit is

delayed, the assessment may also be delayed (see the NSABP Web site for QOL/cosmesis guidelines). Patients who experience a breast cancer recurrence or second primary cancer will not be expected to continue the quality of life or cosmesis assessments. Patients who discontinue protocol therapy for other reasons will be expected to continue the assessments on schedule. If a patient declines to complete a scheduled quality of life assessment or if the questionnaire is not completed for any other reason (and if the questionnaire cannot be completed by phone or mail), a Quality of Life Missing Data (QMD) Form should be submitted by the institution instead. If the physician is unable to complete a scheduled cosmesis assessment, or if the photographs are not taken for a given assessment time point, a Cosmesis Missing Data (CMD) Form should be submitted by the institution instead. All questionnaires and missing data forms should be submitted to the NSABP Biostatistical Center.

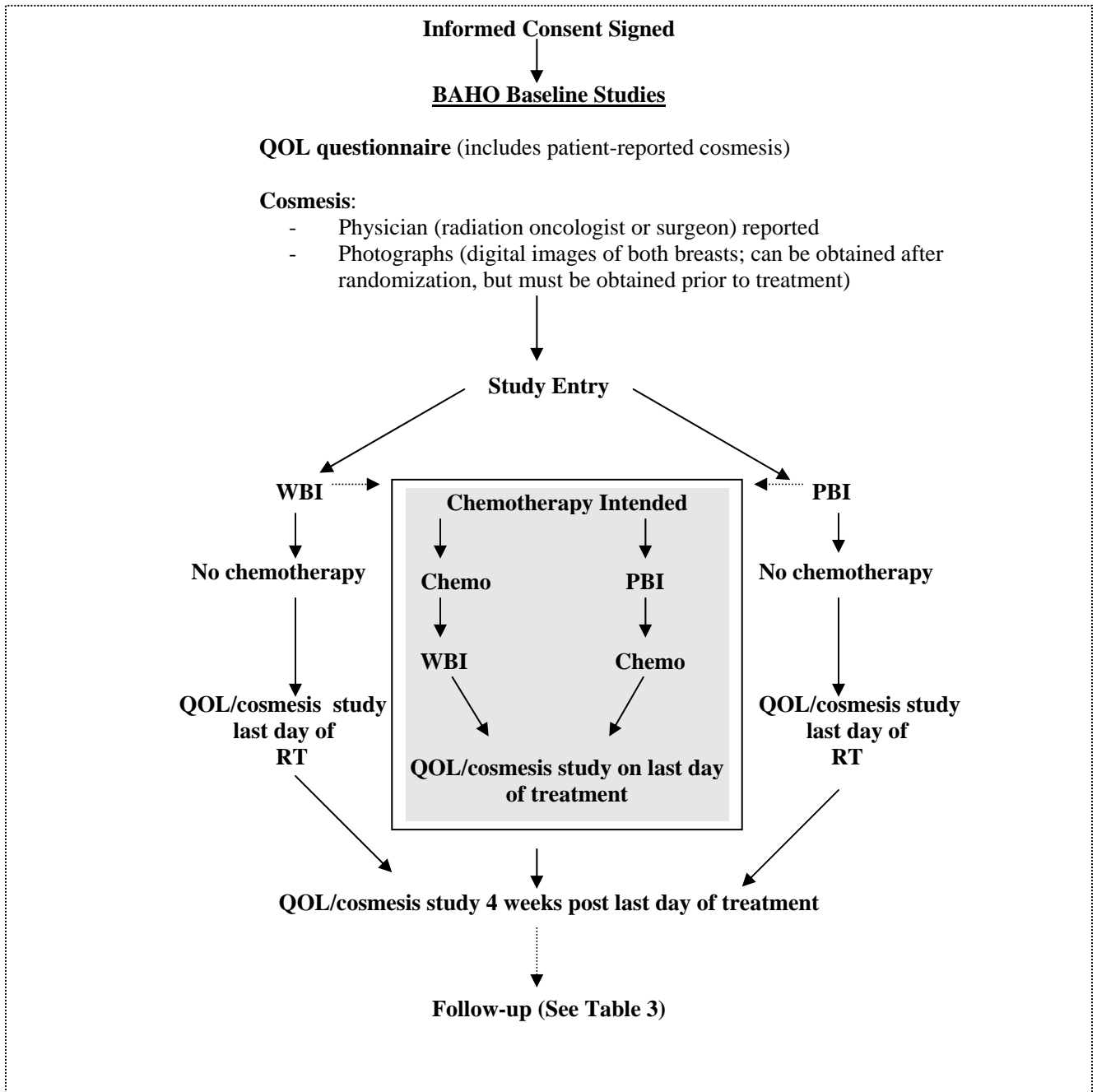
The QOL questionnaire should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaire is completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. Instructions for administering the QOL questionnaire, including details such as how to administer it over the phone, can be found in the Members' Area of the NSABP Web site.

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10.4 **Quality of life and cosmesis patient population**

B-39/0413 patients who are in the QOL and cosmesis patient population should be discouraged from participating in other QOL or symptom management studies.

The quality of life and cosmesis population will include 482 patients who have indicated the intention to receive chemotherapy, and 482 patients who have indicated the intention not to receive chemotherapy. Patients must also read English, French, or Spanish. ***For a patient to be included in the QOL and cosmesis population, the baseline QOL and COS questionnaires must be completed before randomization*** and submitted to the NSABP Biostatistical Center, and the cosmesis digital photographs must be submitted to the designated RTOG Web site in a timely manner.



11.0 WHOLE BREAST IRRADIATION – GROUP 1

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

11.1 Treatment overview

Note the following:

- Regional nodal irradiation is NOT allowed.
- Intensity modulated radiotherapy (IMRT) is not allowed (see Section 18.1.1).

11.1.1 Treatment planning

- CT-based treatment planning is preferred and strongly encouraged. Any CT-based treatment approach can be used except those employing dynamic multi-leaf delivery. Acceptable coverage of the lumpectomy cavity within the whole breast dose must be documented. (See Section 11.2.)
- Fluoroscopic 2-D treatment planning is acceptable **if** there are clips documenting the presence of the lumpectomy cavity within the tangent fields with a 2 cm margin. (See Section 11.3.)

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11.1.2 Timing

If the patient is not receiving chemotherapy, WBI 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, WBI is to begin no fewer than 2 weeks and no more than 8 weeks after the last cycle of chemotherapy.

11.1.3 Whole breast dose

Acceptable dose to the WBI prescription point/volume is either 50 Gy in 2 Gy per day fractionation or 50.4 Gy in 1.8 Gy per day fractionation, 5 days per week.

11.1.4 Boosts

- Boost therapy by either photons or electrons to the lumpectomy cavity plus margin is permitted but not required. **Brachytherapy boosts are NOT allowed.** The boost technique is left to the discretion of the radiation oncologist, but accurate targeting/planning is encouraged.
- Boost dose to the prescription point/volume is to be between 10-16.2 Gy at 1.8-2.0 Gy/fraction. Maximal permitted cumulative prescription dose to the lumpectomy cavity plus margin is 66.6 Gy.

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11.1.5 Patient positioning/immobilization

Patient positioning and immobilization should be performed according to each radiation oncology facility's standard operating procedures. Patient position and immobilization should be amenable to "fitting" through the bore of the CT

scanner so that the patient's CT position accurately reflects the treatment position. 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 alpha cradle, vac-fixx, or commercial breast boards to ensure reproducibility. Prone position for WBI is permitted.

11.1.6 *Equipment*

Linear accelerator with minimal photon energies of 4MV.

11.2 **CT-based WBI treatment plan**

11.2.1 *CT planning*

This includes dose distribution evaluated on a single central axis CT slice or multiple CT levels after tangents are established clinically (by fluoroscopy or CT) **or** target breast volume defined on CT and tangents and dose distribution based on dose-volume specification to breast and constraints for critical non-target organs.

11.2.2 *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.

11.2.3 *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 manubrium joint

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

11.2.4 *Constraints for critical non-target organs*

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 tangent on a film, or a digitally reconstructed radiograph (DRR) of the field. For left-sided cancers, field arrangements that minimize inclusion of the heart in the field should be used.

11.2.5 *Dose prescription and evaluation of isodose distribution*

The dose will be prescribed 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. Wedges, compensators, etc. are to be used to keep the maximum dose within 15% of the prescription. The use of bolus is strongly discouraged. Dose calculations are to be done without heterogeneity corrections.

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

- **Verification process when the lumpectomy cavity can be identified on CT:** Review of the dose distribution on CT slices that include the lumpectomy cavity is requested to verify that the cavity is being covered by the prescription isodose. Acceptable WBI for the NSABP B-39/RTOG 0413 protocol must demonstrate that the cavity is included in $\geq 90\%$ isodose line. If not, changes in the field width, gantry, collimator, or selection of wedges or other adjustment must be done to achieve this. The radiation oncology facility is to submit one axial CT slice demonstrating that the identified lumpectomy cavity is covered by $> 90\%$ isodose line and a DRR of the tangent field. (See Appendix E.)
- **Verification process when the lumpectomy cavity cannot be identified on CT:** For some patients receiving WBI after chemotherapy, the lumpectomy cavity may have resolved and is no longer visible on the CT for radiation planning. In these instances, the postoperative CT submitted for registration to this study (see Section 7.0) can be used. The radiation oncologist can identify on the postoperative registration CT a representative axial slice with the lumpectomy cavity present. A comparable anatomic axial slice from the radiation planning CT with the isodoses present should be found and verify that the $\geq 90\%$ isodose line is covering the region where the lumpectomy cavity was previously visible. Both the CT slice from the registration scan demonstrating the cavity location and the radiation planning scan documenting the isodose coverage are to be submitted. A DRR of the WBI tangent fields should also be submitted.

11.2.7 *Boost*

Refer to Section 11.1.4.

11.3 **Fluoroscopy-based WBI treatment plan**

11.3.1 *Fluoroscopy-based plan*

Dose distribution is evaluated on an external patient contour at central axis after tangents are established clinically with fluoroscopy. **The lumpectomy cavity must have been marked with surgical clips. Ideally, surgical clips should mark the cephalad, caudad, medial, lateral, anterior and posterior extent of the lumpectomy cavity.**

11.3.2 *Target breast volume*

At the time of simulation the clinical breast volume to be targeted in the tangent fields with appropriate margin is determined by the radiation oncologist.

11.3.3 *Tangent fields*

The borders for the tangent fields are set so that it includes the targeted clinical breast volume determined above plus a 1–2 cm margin. Examples of typical clinical boundaries for tangent fields are listed in Section 11.2.3.

It is recommended that techniques be applied that assure posterior or deep borders are co-planar in order to minimize exit into the lungs.

11.3.4 *Constraints for critical non-target organs*

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 tangent on a film. For left-sided cancers, field arrangements should be used that minimize inclusion of the heart-shadow seen on fluoro/film within the field.

11.3.5 *External contour dose prescription and evaluation of isodose distribution*

An external patient contour through the central axis is used for dose prescription. The whole breast dose will be prescribed to two thirds the perpendicular distance from the anterior/apical contour surface to the posterior border of the tangent field at mid-separation. Wedges, compensators, etc. are to be used to keep the maximum dose within 15% of the prescription.

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

The tangent fields must include the clips that demarcate the lumpectomy cavity with a 2 cm margin. The radiation oncology facility must submit a scanned copy or digital picture of one of the tangent films demonstrating the coverage of the clips around the lumpectomy cavity. (See Appendix E.)

11.3.7 *Boosts*

Refer to Section 11.1.4.

12.0 **PARTIAL BREAST IRRADIATION (PBI) BY MULTI-CATHETER BRACHYTHERAPY –GROUP 2**

It is not within the purview of this study to provide instruction on catheter placement techniques. Image guided techniques are recommended, however, the methodology of catheter placement will be up to the radiation oncology facility. It is the responsibility of each participating radiation oncology facility to assure that the radiation oncology staff have a thorough understanding of the proper placement and management of the multi-catheter technique to be used. Competency will be determined and monitored as per the Quality Assurance program as outlined in Section 5.0 and will be based on the radiation oncology facility's ability to adhere to contouring requirements and to achieve dosimetric target coverage as outlined.

12.1 **PBI by multi-catheter brachytherapy**

Administer the PBI technique that was indicated at the time of patient registration. If a PBI technique is attempted but aborted prior to initiation of therapy because treatment cannot be delivered according to guidelines, then an alternative PBI technique may be attempted if the radiation oncology facility is credentialed for an alternative technique and if the substitute PBI treatment can be completed within time constraints. In the rare circumstance that treatment has been initiated but cannot be completed, further management of the patient is at the physician's discretion.

Please note that boosts are not permitted with any of the PBI techniques.

03/30/06

12.1.1 ***Interstitial catheter placement and treatment planning***

Interstitial catheters will be placed with closed cavity placement technique, as soon *after randomization* as possible to increase cavity visibility and allow treatment to begin within the time requirements. Method of catheter placement, catheter number, and configuration are at the discretion of the physician. The radioactive source location, number of positions and dwell times are also at the discretion of the physician and will be determined by High Dose Rate (HDR) CT-based 3D treatment planning to produce the optimal conformal plan in accordance with volume definition and dose requirements. The treatment plan used for each patient will be based on analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the planning target volume for evaluation (PTV_EVAL) and critical normal tissues. If initial evaluation determines the catheter configuration to be unacceptable, adding catheters or moving their position to achieve an acceptable configuration is appropriate as long as treatment can be started within 3 weeks of study entry.

12.1.2 ***Imaging***

A treatment planning CT scan with the patient in a supine position will be required. The CT should start at or above the mandible and extend several cm below the inframammary fold (including the entire lung). A CT scan thickness of ≤ 0.5 cm should be employed. The following structures will be contoured: the

excision cavity, the clinical target volume (CTV), the planning target volume (PTV) and the PTV_EVAL (see Section 12.1.3), and ipsilateral breast. The chin, shoulders and entire ipsilateral breast should be included in the scan. The target and normal tissue structures must be outlined on all CT slices.

12.1.3 *Target volumes*

The excision cavity will be outlined based either on clear visualization on CT, or if placed, with the help of surgical clips. If the excision cavity cannot be clearly delineated, the patient is not eligible for study participation. As the implanted catheters move with the target, compensation for variability of treatment setup and breathing motion is not needed and, therefore, the CTV equals both the PTV and the PTV_EVAL. The PTV_EVAL will be delineated as the breast tissue volume bounded by the uniform expansion of the lumpectomy cavity in all dimensions by 15 mm. The PTV_EVAL will be limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). (See Appendix F.)

03/07/11

12.1.4 *Determination of appropriateness for treatment*

Appropriateness for treatment with a multi-catheter approach will be dependant on the catheter configuration and the resultant dose homogeneity. Catheter number and location must allow the HDR 3D planning system to achieve dwell location and dwell time that results in dose delivery that satisfies the following requirements. Unlike the MammoSite[®] and other single-entry intracavitary devices, the dose to the skin can be more easily controlled and, therefore, tighter constraints are appropriate. With the multi-catheter system, the skin dose should not exceed prescription dose. To assure appropriate dose homogeneity throughout the implant two parameters will be used: the volume of tissue receiving higher doses and a Dose Homogeneity Index (DHI). The actual volume of tissue receiving 150% (V150) and 200% (V200) of the prescribed dose will be limited to ≤ 70 cc and ≤ 20 cc, respectively. The DHI, as represented by the volume ratio $(1 - V150/V100)$, will be $\geq .75$. (V150 will be the volume of tissue receiving 150% of the prescribed dose, and V100 will be the volume of tissue receiving the prescribed dose.)

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12.1.5 *Dose prescription and delivery*

- Treatment will begin within 9 weeks following lumpectomy or re-excision of margins and within 3 weeks of study entry.
- High Dose Rate treatment delivery only will be allowed. Low Dose Rate will not be allowed.
- The patient's position for treatment will be identical to the position in which the planning CT was obtained.
- A total of 34 Gy will be delivered as per all dose requirements of target coverage and dosimetric homogeneity. Two fractions per day, each of 3.4 Gy, separated by at least 6 hours, given on 5 treatment days (over a period of 5 to 10 days), will sum to 10 fractions and 34 Gy.

12.1.6 *Dose limitations for normal tissues*

Uninvolved normal breast: Ideally, < 60% of the whole breast reference volume should receive $\geq 50\%$ of the prescribed dose. For these calculations, the whole breast reference volume is defined as per Appendix F. The volume of the excision cavity will not be subtracted.

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12.1.7 *Treatment verification*

To assure proper catheter positioning for each treatment, proper patient positioning and catheter position will be evaluated by the treating physician prior to each HDR fraction. If a change in implant geometry is noted, this should be addressed prior to additional treatment (i.e., breast swelling, seroma cavity enlargement).

12.2 **Quality assurance of dose distribution**

The ITC will compare submitted DVHs for the PTV_EVAL, designated critical structures, and unspecified tissues.

Each treatment plan shall be judged as:

- Acceptable:
 - Dose volume histogram analysis of target coverage will confirm $\geq 90\%$ of the prescribed dose covering $\geq 90\%$ of the PTV_EVAL.
 - Dose homogeneity criteria, as described in Section 12.1.4 are met.
 - Critical normal tissue DVHs within 5% specified value (see Section 12.1.6).
 - Dose delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.

- Unacceptable:
 - Dose volume analysis of the target volume confirms < 90% of the prescribed dose and/or < 90% coverage of the PTV_EVAL.
 - Any of the criteria described in Section 12.1.4 are not met.
 - Critical normal structure DVH exceeds 5% of the specified value (see Section 12.1.6).
 - Dose delivered over a period of time extending greater than 10 days.

PARTIAL BREAST IRRADIATION (PBI) BY MAMMOSITE® OR SINGLE-ENTRY MULTI-LUMEN INTRACAVITARY DEVICE – GROUP 2

It is not within the purview of this study to provide instruction on the proper use of the MammoSite® or other single-entry intracavitary device. It is the responsibility of each participating radiation oncology facility to assure that the surgical and radiation oncology staff have a thorough understanding of the proper placement, management, and removal of the MammoSite® or other single-entry intracavitary device prior to study participation. Competency will be determined and monitored as per the Quality Assurance program outlined in Section 5.0 and will be based on the radiation oncology facility's ability to adhere to contouring requirements and to achieve dosimetric target coverage as outlined.

The following devices are options for intracavitary brachytherapy utilizing a single-entry approach:

- MammoSite® (balloon; single-lumen)
- MammoSite® ML (balloon; multi-lumen)
- Contura™ MLB (balloon; multi-lumen)
- SAVI® (Strut-Adjusted Volume Implant; multi-lumen)

13.1 PBI by MammoSite®/multi-lumen (single-entry) intracavitary device

Administer the PBI technique that was indicated at the time of patient registration. If a PBI technique is attempted but aborted prior to initiation of therapy because treatment cannot be delivered according to guidelines, then an alternative PBI technique may be attempted if the radiation oncology facility is credentialed for an alternative technique and if the substitute PBI treatment can be completed within time constraints. In the rare circumstance that treatment has been initiated but cannot be completed, further management of the patient is at the physician's discretion.

Please note that boosts are not permitted with any of the PBI techniques.

13.1.1 MammoSite®/multi-lumen (single-entry) intracavitary device placement and treatment planning

The MammoSite®/multi-lumen intracavitary device will be placed ***with closed cavity placement techniques only***. No surgical alterations to the cavity are allowed after the pre-randomization CT scan to accommodate the fit of the MammoSite®/multi-lumen intracavitary device. The use of space occupying devices in the lumpectomy cavity is not permitted in this trial. Device placement will be executed only after randomization and as soon after randomization as possible to increase success of proper placement and initiation of treatment within the time requirements. Radioactive source location, number of positions and dwell times are at the discretion of the physician and will be determined by High Dose Rate (HDR) CT-based 3D treatment planning to produce the optimal conformal plan in accordance with volume definition and dose requirements. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the planning target volume for evaluation (PTV_EVAL) and critical normal tissues.

13.1.2 *Imaging*

A treatment planning CT scan with the patient in a supine position with the MammoSite[®]/multi-lumen intracavitary device in place will be required. The CT should start at or above the mandible and extend several cm below the inframammary fold (including the entire lung). A CT scan thickness of ≤ 0.5 cm should be employed. The following structures will be contoured: the balloon surface (for the SAVI[®] device, a "device surface" is defined as a structure represented by a contour created by directly connecting each strut; see Appendix F, Figure 7b), the clinical target volume (CTV), the planning target volume (PTV) and the PTV_EVAL (see Section 13.1.3), trapped air and/or fluid (for the SAVI[®] device, this is air/fluid outside the device surface; see Appendix F, Figure 7b), and ipsilateral breast. The chin, shoulders, and entire ipsilateral breast should be included in the scan. The target and normal tissue structures must be outlined on all CT slices.

13.1.3 *Target volumes*

The excision cavity will be outlined based either on clear visualization on CT, or if placed, with the help of surgical clips. If the excision cavity cannot be clearly delineated, the patient is not eligible for study participation. As the implanted balloon/device moves with the target, compensation for variability of treatment set-up and breathing motion is not needed, and therefore, the CTV equals both the PTV and the PTV_EVAL. The targeted breast tissue immediately surrounds the balloon/device to a measured 10 mm distance from the balloon surface/device surface (see Appendix F, Figures 7a and 7b). The PTV_EVAL will be delineated as the breast tissue volume bounded by the uniform expansion of the balloon/device surface in all dimensions by 10 mm less the balloon/device surface volume. However, the PTV_EVAL will be limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). When determining dose coverage of the PTV_EVAL to assure compliance with dose requirements as outlined in Section 13.2, the volume of trapped air/fluid must be accounted for as it displaces a percentage of the target beyond 1 cm from the balloon/device surface. (For the SAVI[®] device, this is the volume of air/fluid outside the device surface.) The area of trapped air/fluid will be contoured at each level, a total volume obtained, and the percentage of the PTV_EVAL that is displaced will be calculated. This calculation is illustrated in the following equation:

$$(\% \text{ PTV_EVAL coverage}) - [(\text{vol trapped air/vol PTV_EVAL}) \times 100] = \geq 90\%$$

When determining the PTV_EVAL dose coverage, this displaced percentage must be subtracted. For example, if the percentage of PTV_EVAL displaced by trapped air/fluid is calculated to be 5%, then to comply with criteria, the dose coverage must be **at least** 95% of the PTV_EVAL receiving 90% of the prescribed dose. If the percentage of PTV_EVAL displaced by trapped air/fluid is $> 10\%$, then it is not possible to achieve acceptable dose coverage. (See Appendix F.)

13.1.4 *Determination of appropriateness for treatment*

Four parameters will be used for determining whether the placed MammoSite®/multi-lumen intracavitary device are appropriate for treatment: tissue-balloon/device conformance, balloon/device symmetry, minimal balloon/device surface-skin distance, and normal breast tissue dose volume parameters. All four parameters are essential for acceptable dosimetry.

- *Tissue-balloon/device conformance* – Ideally, the lumpectomy cavity surface should be in direct contact with the entire balloon/device surface assuring maximum prescription dose coverage of the PTV. Frequently air and/or fluid will be identified between the lumpectomy cavity and balloon/device surface. Whether as a result of an irregular cavity shape or because the air/fluid is trapped, this will result in less than ideal conformance as a percentage of the PTV will be beyond the prescription isodose line coverage. To determine the significance of the trapped air/fluid, these volumes will be contoured and used in calculating PTV_EVAL dose coverage (see Section 13.1.3). Typically when the volume of trapped air/fluid is < 10% of the PTV_EVAL, acceptable dose coverage can be achieved.
- *Balloon/device symmetry* – Disruption of the contour of the balloon/device surface or shifting of the central catheter will cause distortion of the balloon geometry and a negative effect on the dosimetric coverage of the PTV. The physical geometry of the MammoSite® single-lumen balloon device will not deviate > 2 mm of the expected dimensions. Device symmetry evaluation of the multi-lumen devices is complex, therefore, the ability to meet all dosimetric goals will serve to indirectly support sufficient device symmetry.
- *Minimal balloon/device surface-skin distance* – Ideally, the minimal balloon/device surface-skin distance should be ≥ 7 mm. However, if the balloon/device-skin thickness is 5 mm to 7 mm, then it will be considered acceptable for treatment after appropriate treatment planning documents that the maximum skin dose at any point is $\leq 145\%$ of prescription dose, assuring that the *skin dose does not exceed* acceptable limits. Despite the ability of the multi-lumen devices to dose shape, a minimum skin thickness of 5 mm is required for all intracavitary treatment devices.
- *Normal breast tissue dose volume parameters* – To assure that acceptable dose homogeneity is not exceeded while striving to achieve target coverage, the volume of tissue receiving higher doses will be limited. The actual volume of tissue receiving 150% (V150) and 200% (V200) of the prescribed dose will be limited to ≤ 50 cc and ≤ 10 cc, respectively. (V150 will be the volume of tissue receiving 150% of the prescribed dose, and V100 will be the volume of tissue receiving the prescribed dose.)

03/30/06

03/30/06

13.1.5 *Dose prescription and delivery*

- Treatment utilizing MammoSite®/multi-lumen intracavitary devices will begin within 9 weeks following lumpectomy or re-excision of margins and within 3 weeks of study entry.

- High Dose Rate treatment delivery only will be allowed. Low Dose Rate treatment delivery will not be allowed.
- The patient's position for treatment will be identical to the position in which the planning CT was obtained.
- The balloon/device will remain inflated/deployed throughout the treatment course.
- A total of 34 Gy will be prescribed to an approximate 1 cm radial distance from the balloon/device surface such that the dosimetric requirements in Section 13.2 are satisfied. Two fractions per day, each of 3.4 Gy, separated by at least 6 hours, given on 5 treatment days (over a period of 5 to 10 days), will sum to 10 fractions and 34 Gy.

13.1.6 *Dose limitations for normal tissues*

Uninvolved normal breast: Ideally, < 60% of the whole breast reference volume should receive $\geq 50\%$ of the prescribed dose. For these calculations, the whole breast reference volume is defined in Appendix F. The balloon/device volume should be subtracted from the whole breast volume for this calculation.

03/30/06

13.1.7 *Treatment verification*

To assure continued integrity of the balloon/device throughout treatment, an ultrasound or x-ray must be performed prior to each delivered fraction and evaluated for any change in balloon diameter/device orientation. These should be compared to a similar study performed at the time of treatment planning. If a change in balloon/device geometry is noted, this should be addressed prior to additional treatment. If the balloon deflates, it should be removed, a new balloon inserted and reinflated to previous volume, appropriateness for treatment confirmed, and treatment completed. With regard to replacement of a multi-lumen device, accurate rotation and inflation/strut deployment should be assured for accurate dose delivery. As with any radiation treatment approach, if set-up is uncertain, repeat CT scan and planning is recommended.

13.2 **Quality assurance of dose distribution**

The ITC will compare submitted DVHs for the PTV_EVAL, designated critical structures, and unspecified tissues.

Each treatment plan shall be judged as:

- Acceptable:
 - Dose volume histogram analysis of target coverage will confirm $\geq 90\%$ if the prescribed dose covering $\geq 90\%$ of the PTV_EVAL. The volume of trapped air/fluid will be accounted for using the methodology described in Section 13.1.3 of the protocol. (For the SAVI[®] device, this is any air/fluid outside the device volume.)
 - All four parameters must be met as described in Section 13.1.4.
 - Critical normal tissue DVHs within 5% specified value (see Section 13.1.6).
 - Dose delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.

- Unacceptable:
 - Dose volume analysis of the target volume confirms < 90% of the prescribed dose and/or < 90% coverage of the PTV_EVAL. The volume of tapped air/fluid will be accounted for using the methodology described in Section 13.1.3 of the protocol. (For the SAVI[®] device, this is any air/fluid outside the device volume.)
 - Any of the parameters not met as described in Section 13.1.4.
 - Critical normal structure DVH exceeds 5% of the specified value (see Section 13.1.6).
 - Dose delivered over a period of time extending greater than 10 days.

14.0 PARTIAL BREAST IRRADIATION (PBI) BY 3D CONFORMAL EXTERNAL BEAM RADIOTHERAPY – GROUP 2

It is not within the purview of this study to provide instruction on the proper use of 3D-CRT. It is the responsibility of each participating radiation oncology facility to assure that the staff have a thorough understanding of 3D-CRT techniques prior to study participation. Competency will be determined and monitored as per the Quality Assurance program outlined in Section 5.0 and will be based on the radiation oncology facility's ability to adhere to contouring requirements and to achieve dosimetric target coverage as outlined.

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14.1 PBI by 3D conformal external beam radiotherapy (3D-CRT)

Administer the PBI technique that was indicated at the time of patient registration. If a PBI technique is attempted but aborted prior to initiation of therapy because treatment cannot be delivered according to guidelines, then an alternative PBI technique may be attempted if the radiation oncology facility is credentialed for an alternative technique and if the substitute PBI treatment can be completed within time constraints. In the rare circumstance that treatment has been initiated but cannot be completed, further management of the patient is at the physician's discretion.

Please note:

- Boosts are not permitted with any of the PBI techniques.
- Electrons are not allowed.

14.1.1 3D-CRT treatment planning

The pre-randomization CT data set can be used for 3D-CRT treatment planning. Treatment will be delivered only to the planning target volume (PTV) using 3-dimensional conformal fields. Field within a field technique to improve dosimetric coverage can be utilized; however, the use of dynamic multi-leaf collimator (MLC) to facilitate the delivery of intensity-modulated distributions derived from constraints-based computer optimization (i.e., inverse planning) is excluded. Field arrangements are at the discretion of the physician and will be determined by 3D-CRT treatment planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the planning target volume for evaluation (PTV_EVAL) and critical normal tissues. **Dose calculations with tissue inhomogeneity correction must be used.**

14.1.2 Imaging

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

extent of normal tissue contouring is necessary with 3D-CRT to guide beam arrangement and normal tissue avoidance.

14.1.3 *Target volumes*

The excision cavity will be outlined based either on clear visualization on CT or, if placed, with the help of surgical clips. If the excision cavity cannot be clearly delineated, the patient is not eligible for study participation. The CTV will be defined by uniformly expanding the excision cavity volume by 15 mm. However, the CTV will be limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). The PTV, defined as a uniform 10 mm expansion of the CTV, will provide a margin around the CTV to compensate for the variability of treatment set-up and motion of the breast with breathing. The PTV is saved and is used to generate the beam aperture with an additional margin to take penumbra into account. Since a substantial part of the PTV often extends outside the patient (especially for superficial cavities), the PTV is then copied to a PTV_EVAL, which is edited. This PTV_EVAL is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding (if applicable) the PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung). This PTV_EVAL is the structure used for DVH constraints and analysis (see Section 14.2). This PTV_EVAL **CANNOT** be used for beam aperture generation. (See Appendix F.)

14.1.4 *Beam angles/treatment position*

The radiation oncology facility may choose whatever beam arrangement and number of beams they desire, as long as the necessary dose volume constraints mentioned above can be met. Typically, a 3, 4, or 5-field non-coplanar beam arrangement utilizing high-energy photons can be used. **No plan will be considered acceptable if any of the beams are directed towards critical normal structures: heart, lung, contralateral breast.** (See Appendix F for guidance on beam arrangement.) Patients should be treated in the supine position. Treatment in an alternative position (prone) will require pre-approval by one of the study chairs and will include a dry run case and rapid review of the case to be treated.

Bolus to improve anterior target coverage should not be used.

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14.1.5 *Dose prescription and delivery*

- 3D-CRT will begin within 9 weeks of lumpectomy or re-excision of margins and within 3 weeks of study entry.
- A total of 38.5 Gy will be prescribed to the ICRU 50 reference point dose (usually isocenter). Two fractions per day, each of 3.85 Gy, separated by at least 6 hours, given on 5 treatment days (over a period of 5 to 10 days), will sum to 10 fractions and 38.5 Gy.

14.1.6 *Dose limitations for normal tissues*

- *Uninvolved normal breast*: Ideally, < 60% of the whole breast reference volume should receive $\geq 50\%$ of the prescribed dose and < 35% of the whole breast reference volume should receive the prescribed dose. For these calculations, the whole breast reference volume is defined as per Appendix F.
- *Contralateral breast*: The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive < 3% of the prescribed dose to any point.
- *Ipsilateral lung*: < 15% of the lung can receive 30% of the prescribed dose.
- *Contralateral lung*: < 15% of the lung can receive 5% of the prescribed dose.
- *Heart (right-sided lesions)*: < 5% of the heart should receive 5% of the prescribed dose.
- *Heart (left-sided lesions)*: The volume of the heart receiving 5% of the prescribed dose (V5) should be less than the 40%.
- *Thyroid*: maximum point dose of 3% of the prescribed dose.

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14.1.7 *Treatment verification*

- Before first treatment
 - Portal films or images of each beam and an orthogonal pair (AP and lateral) must be obtained prior to initiation of treatment.
- Subsequent images or films
 - Subsequent orthogonal pair (AP and lateral) films or images must be obtained prior to fraction number 5. Additional images or films may be obtained at the investigator's discretion.

All films or images are to be maintained at the local facility. Do not submit to ITC unless requested.

14.2 **Quality assurance of dose distribution**

The ITC will compare submitted DVHs for the PTV_EVAL, designated critical structures, and unspecified tissues.

Each treatment plan shall be judged as:

- Acceptable:
 - Dose volume histogram analysis of the target volume confirms 90% of the prescribed dose covers $\geq 90\%$ of the PTV_EVAL.
 - Critical normal tissue DVHs within 5% specified value (see Section 14.1.6.).
 - Maximum dose does not exceed 120% of prescribed dose.
 - Dose delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.
- Unacceptable:
 - Dose volume histogram analysis of the target volume will confirm < 90% of the prescribed dose covers < 90% of the PTV_EVAL.
 - Critical normal structure DVH exceeds 5% of the specified value (see Section 14.1.6.).
 - Maximum dose exceeds 120% of prescribed dose.
 - Dose delivered over a period of time extending greater than 10 days.

15.0 **SYSTEMIC THERAPY**

15.1 **Chemotherapy**

Chemotherapy may be given at the discretion of the patient's medical oncologist. The use of chemotherapeutic agents during radiation therapy is not allowed.

15.1.1 ***Group 1 patients (WBI)***

Adjuvant chemotherapy will be given prior to WBI, as prescribed by the treating physician. Initiation of WBI should be at least 2 weeks after the last cycle of chemotherapy.

15.1.2 ***Group 2 patients (PBI)***

Adjuvant chemotherapy will be given following PBI. Chemotherapy will be initiated no sooner than 2 weeks after the completion of PBI.

15.2 **Hormonal therapy**

Patients with ER-positive and/or PgR-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).

15.2.1 ***Patients receiving chemotherapy***

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

15.2.2 ***Patients not receiving chemotherapy***

Hormonal therapy may be initiated before, during, or after completion of WBI or PBI at the discretion of the investigator.

01/08/07

15.3 **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.

16.0 **DIAGNOSIS OF BREAST CANCER RECURRENCE AND OTHER 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. 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.
- Please submit a copy of the clinic/office note summarizing the work-up and treatment plan for the recurrence/second primary cancer.
- 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.

16.1 **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)

16.2 **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)

16.3 **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

16.4 **Distant recurrence**

Defined as evidence of tumor in any area of the body, with the exception of those described in Sections 16.1 and 16.2.

16.4.1 ***Skin, subcutaneous tissue, and lymph nodes (other than local or regional) metastasis***

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

16.4.2 *Bone marrow metastasis*

Acceptable: positive cytology, histologic biopsy, or MRI scan.

16.4.3 *Lung metastasis*

Acceptable: (i) positive cytology, histologic biopsy or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases.

NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations such as biopsy or needle aspiration must be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

16.4.4 *Skeletal metastasis*

Acceptable: (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis; or (ii) biopsy proof of bone metastases; or (iii) bone scan that is clearly positive for bone metastases.

NOTE: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

16.4.5 *Liver metastasis*

Acceptable: (i) an abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases or (ii) liver biopsy confirmation of the metastatic disease.

NOTE: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

16.4.6 *Central nervous system metastasis*

Acceptable: (i) positive CT scan or MRI scan, usually in a patient with neurological symptoms or (ii) biopsy or cytology (for a diagnosis of meningeal involvement).

16.5 **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

16.6 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.

16.7 Documentation requested following death

- Autopsy reports should be secured whenever possible and should be submitted to the NSABP Biostatistical Center.
- A copy of the death certificate should be forwarded to the Biostatistical Center if it is readily available or if it contains important cause-of-death information not documented elsewhere.
- Please submit the last clinic/office note before the death or the physician's note summarizing the death.

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17.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

17.1 B-39/0413 definitions for adverse event reporting

Study therapy: In the B-39/0413 study, therapy is either WBI or PBI.

17.2 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 B-39/0413.

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17.3 Expedited reporting of adverse events

The NSABP follows procedures for centralized reporting of serious adverse events. These adverse events are to be reported to the NSABP Biostatistical Center. The NSABP forwards reports and documentation to the appropriate regulatory agencies involved in the trial. B-39/0413 utilizes the National Cancer Institute's (NCI) Adverse Event Expedited Reporting System (AdEERS) for all expedited reporting of adverse events. The NCI's guidelines for creating an AdEERS report can be found at <http://ctep.cancer.gov>.

The NSABP Biostatistical Center is identified in AdEERS as the Lead Group for NSABP protocols which require AdEERS reporting. Expedited AE reporting for this study must be submitted to the NSABP Lead Group using AdEERS, accessed via the CTEP home page: [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to the NCI by telephone at 301-897-7497. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

17.3.1 Expedited reporting methods

- **AdEERS 24-Hour Notification:** requires that an AdEERS 24-hour notification is electronically submitted to the NSABP Lead Group within 24 hours of learning of the adverse event. Each AdEERS 24-hour notification must be followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
- **AdEERS 5 Calendar Day Report:** requires that a complete AdEERS report is electronically submitted to the NSABP Lead Group within 5 calendar days of the investigator learning of the adverse event.
- Fax supporting documentation for all expedited reports to the NSABP Biostatistical Center at **(412) 622-2113**.

17.3.2 *Expedited reporting requirements*

- Expedited reporting requirements for all patients are provided in Table 4.
- Adverse events reported via AdEERS must also be reported on B-39 Form AE according to the instructions for form submission described in Section 17.4 and according to instructions on Form AE.

17.3.3 *Pregnancy occurring while patient is on study therapy*

If a patient becomes pregnant while receiving study therapy, notify the NSABP Clinical Coordinating Division (see Information Resources on page iv) as soon as possible.

17.3.4 *Other recipients of adverse event reports*

- The NSABP will forward reports and documentation to the appropriate regulatory agencies involved in this trial.
- 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.

TABLE 4. AdEERS Expedited Reporting Requirements For Adverse Events That Occur **Within 30 Days of the Last Treatment** of Study Therapy

03/30/06

Attribution	Grade 2	Grade 3		Grade 4 ^b		Grade 5 ^{a,b}		Protocol-Specific Requirements/ Exceptions
	<i>Unexpected</i>	<i>Unexpected</i>	<i>Expected</i>	<i>Unexpected</i>	<i>Expected</i>	<i>Unexpected</i>	<i>Expected</i>	
<i>Unrelated or Unlikely</i>				AdEERS		AdEERS		-See footnote (e) for other requirements -See footnote (d) for special requirements -See footnote (e) for special exceptions
<i>Possible, Probable, Definite</i>		AdEERS if hospitalized		AdEERS-24 and AdEERS	AdEERS	AdEERS-24 and AdEERS	AdEERS	
AdEERS-24:	Indicates an AdEERS 24-hour notification must be electronically submitted to the NSABP Lead Group <i>within 24 hours</i> of learning of the event.							
AdEERS:	Indicates a complete expedited report must be electronically submitted to the NSABP Lead Group <i>within 5 calendar days</i> of learning of the event.							
Hospitalization:	Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).							
All Reports:	On all reports, use the NCI protocol number, AdEERS ticket number, and the B-39/0413 patient ID provided during trial registration. <i>Fax supporting documentation to the NSABP Biostatistical Center.</i>							
a	All deaths within 30 days of the last treatment of study therapy require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a complete AdEERS report is required as outlined in the table.							
b	Adverse events that occur <u>greater than 30 days</u> after the last treatment of study therapy with attribution of possible, probable or definite to study therapy require reporting as follows:							
	<ul style="list-style-type: none"> • AdEERS 24-hour notification followed by a complete AdEERS report within 5 calendar days of learning of the event for: <ul style="list-style-type: none"> - grade 4 unexpected events - grade 5 unexpected events • AdEERS 5-calendar day report for: <ul style="list-style-type: none"> - grade 5 expected events 							
c	Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment.							
d Protocol-specific expedited reporting requirements:	For this study, the adverse events listed below, regardless of attribution, require expedited reporting via AdEERS to the NSABP Lead Group within 5 calendar days of learning of the event: <u>None</u>							
e Protocol-specific expedited reporting exceptions:	For this study, the adverse events listed below which occur, including hospitalizations for these events, do not require expedited reporting via AdEERS:							
	<ul style="list-style-type: none"> • Secondary malignancies 							

17.4 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 reported via AdEERS must also be reported on B-39 Form AE (Adverse Event Form) as described below and according to instructions on the Form AE.

17.4.1 *Reporting on Form AE*

- Report all grade 1, 2, 3, 4, and 5 adverse events resulting from either WBI or PBI therapy, including those adverse events previously reported via AdEERS.
- 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

17.4.2 *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
- Provide supporting documentation for all grade 3, 4 and 5 adverse events and any hospitalization ≥ 24 hours if documentation has not previously been submitted for that adverse event. Remove patient identifiers as described in Appendix G and submit to the NSABP Biostatistical Center (see Information Resources on page v).

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

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

18.0 NON-PROTOCOL THERAPY GUIDELINES

The following types of treatment, in addition to *any cancer therapy other than that specified in the protocol*, are prohibited until the time of development of the first breast cancer recurrence or second primary cancer.

18.1 Radiation therapy

03/30/06 18.1.1 *Intensity modulated radiotherapy (IMRT) is not allowed*

Segmental treatment techniques such as "field-in-field", that are intended to improve the uniformity of the dose distribution, are permitted. To be acceptable and clearly distinguished from IMRT, such techniques must meet the following criteria:

- The goal is improved dose uniformity and not to produce steep dose gradients to protect organs at risk (OARs).
- Optimization based on dose-volume constraints is not used.
- The majority of monitor units (> 50%) are given through one large field at each gantry angle.
- Individual QA dosimetry measurements are not routinely made.
- The number of segments is small.

18.1.2 *Boosts*

- Brachytherapy is not allowed to be used as a boost following whole breast irradiation.
- Boosts are not permitted with any of the PBI techniques.

03/07/11 18.1.3 *Low dose rate (LDR) brachytherapy*

LDR is not permitted for multi-catheter brachytherapy or for MammoSite® or other single-entry intracavitary brachytherapy.

18.2 Hormonal therapy for symptom management

- Patients may *not* receive any of the following:
 - Systemic sex hormones (e.g., hormone replacement therapy)
 - Femring®
- Patients may receive Vagifem® or Estring® for the management of vaginal or urinary symptoms.

19.0 PATIENT ENTRY AND WITHDRAWAL PROCEDURES

01/08/07

19.1 Closure of accrual to specific patient populations

The accrual targets for two low-risk patient populations have been reached sooner than anticipated (see Section 21.5). Therefore, to meet the aims of the NSABP B-39/RTOG 0413 study and to maintain the projected data analysis timeline described in Section 21.12, accrual was closed to the low-risk patient populations described below. To be enrolled in the study, patients who met the following criteria had to have signed a consent form by December 30, 2006.

- Patients who are ≥ 50 years of age with DCIS regardless of hormone-receptor status.
- Patients with invasive breast cancer who meet **ALL** of the following criteria:
 - ≥ 50 years of age *and*
 - Node-negative *and*
 - Hormone receptor-positive.

19.2 Registration procedures

- Only radiation oncology facilities that have been approved for accrual by meeting the radiation therapy technology requirements and providing the baseline physics information as described in Section 5.0 may enroll patients on this study.
- Once the radiation oncology facility has been approved, eligible patients can be registered in accordance with the Quality Assurance guidelines. Patients are registered as described in Section 19.4 prior to any protocol therapy.
- After the patient is registered, the institution will submit the required data within the necessary time constraints as outlined in Section 20.0.

19.3 Patient consent form

Before the patient is entered, the consent form (see Appendix H), including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

19.4 Entry

19.4.1 *Institutions with NSABP membership (and not RTOG membership)*

NSABP investigators must enter NSABP B-39/RTOG 0413 patients through the NSABP. Patient entry instructions can be found in the "Patient Entry Guidelines" section of the Members' Area of the NSABP Web site at <http://www.nsabp.pitt.edu>.

19.4.2 *Institutions with RTOG membership (and not NSABP membership)*

RTOG investigators must enter NSABP B-39/RTOG 0413 patients through the CTSU. (See Appendix D, Section 1.0, *Site Registration and Patient Entry for CTSU Investigators.*)

19.4.3 *Institutions with NSABP and RTOG membership*

For institutions with active NSABP and RTOG membership, the local NSABP and RTOG principal investigators should jointly decide whether all accrual to NSABP B-39/RTOG 0413 will be through the RTOG using the CTSU enrollment procedures or through the NSABP. This decision applies to all patients (**i.e., the option to select NSABP or RTOG at the time of each individual patient entry is not applicable**).

Please note: When the decision is made to enroll patients through the NSABP, full RTOG accrual credit will be awarded toward RTOG's accrual requirement. When the decision is made to enroll patients through the RTOG (using the CTSU enrollment procedures), full NSABP accrual credit will be awarded toward NSABP's accrual requirement.

19.5 **Patient study number**

After all of the faxed eligibility criteria have been completed, the institution will receive the patient's nine-digit study number.

03/30/06

19.6 **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. If she is in the QOL/cosmesis patient population (see Section 10.4), she 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 NSABP Biostatistical Center with written documentation of the patient's decision to fully withdraw from the study.

03/30/06

19.7 **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 who are in the QOL/cosmesis population (see Section 10.4) should be encouraged to complete the QOL/cosmesis assessments on schedule unless they have a second primary cancer or a breast recurrence.

20.0 REQUIRED FORMS AND MATERIALS

TABLE 5A. Required forms and materials for all B-39/0413 patients (see Table 5B for requirements for participants in the QOL/cosmesis patient population) 03/30/06, 01/08/07, 03/13/07

Form/material	Description	Submission
Radiation Oncology Facility Credentialing		
Digital data for credentialing	Radiation oncology facility assessment, knowledge assessment, and CT-based dry run case for each PBI technique. See Section 5.1.	Prior to enrolling patients; go to the RPC at http://rpc.mdanderson.org/rpc or ATC at http://atc.wustl.edu Web sites for instructions (click on “Credentialing”).
Pre-entry (see Table 5B for QOL/cosmesis)		
Eligibility checklist	Checklist to verify patient's eligibility BEFORE patient is randomized	Do NOT submit this checklist to the NSABP. Maintain it for review during site visit audit.
Form A (B-39)	Registration form	At the time of patient entry; consult the Patient Entry Guidelines section of the Members’ Area of the NSABP Web site, https://members.nsabp.pitt.edu .
Consent Form (B-39)	Signed/dated informed consent	
Entry (following randomization) (see Table 5B for QOL/cosmesis)		
Form ON (B-39)	On-study form – collects surgical and pathology information.	Submit forms and reports within 30 days following randomization to the NSABP Biostatistical Center.
Dictated operative reports	Typed operative report for each protocol-related operative procedure done prior to randomization.	
Dictated pathology reports	Typed pathology report for each protocol-related biopsy and operative procedure done prior to randomization.	
Pathology blocks with Form BLT	See Section 9.1 for details.	Submit to the NSABP Biostatistical Center within 3 months following randomization.
Baseline serum specimen with Form BNK	Serum specimen collected after randomization and prior to beginning study therapy (see Section 9.2).	Submit to the NSABP Serum Bank at Baylor. See Protocol Appendix C for instructions.
Treatment and follow-up (see Table 5B for QOL/cosmesis)		
PBI case review treatment data	QA review of <i>first 5 cases for each PBI technique</i> at each radiation oncology facility (see Section 5.2).	Submit digitally to ITC through http://atc.wustl.edu . First case – rapid review <i>before RT begins</i> . Accrual on hold until approval received. Next 4 cases submit within 1 week post-RT for timely review. (RT may begin and accrual continue before review feedback on timely review cases.) All PBI cases will be submitted digitally to ITC. See the ITC Web site for hardcopy items that also need to be submitted.
WBI case review treatment data	QA review of first 5 WBI cases at each radiation oncology facility (see Section 5.3).	As soon as possible (within 1 week), submit digitally to RTOG at http://www.rtog.org using the Site Tools section of the RTOG Web site. (RT may begin before review feedback.)
Patient treatment data for all Group 1 patients (WBI)	CT plan: <ul style="list-style-type: none"> • DRR of tangent field • Axial CT slice demonstrating lumpectomy cavity is included in 90% isodose line Fluoro plan: <ul style="list-style-type: none"> • Copy of tangent field (show inclusion of clips) 	Submit digitally to RTOG at http://www.rtog.org using the Site Tools section of the RTOG Web site within 1 week post-RT.

TABLE 5A. Required forms and materials for all B-39/0413 patients (continued) 03/30/06, 01/08/07, 03/13/07

Form/material	Description	Submission
Patient treatment data for all Group 2 patients (PBI)	<ul style="list-style-type: none"> • Treatment prescription • Dosimetric information Digital patient data (CT scans, critical normal structures, all target contours, doses, DVH's, etc.) • Final dosimetric information Any modified planning data Hard copy isodoses for total dose plan if changes made after initial submission. • Copies of dosimetric calculation 	Submit digitally to ITC through http://atc.wustl.edu immediately if rapid review case or within 1 week post-RT if timely review case. See the ITC Web Site for hardcopy items that must also be submitted.
Form RT1	RT Treatment form required for all <u>Group 1</u> patients – even those who did not start WBI.	Submit to the NSABP Biostatistical Center when RT has ended or if a Group 1 patient did not begin WBI.
Form RT2	RT Treatment form required for all <u>Group 2</u> patients – even those who did not start PBI.	Submit to the NSABP Biostatistical Center when RT has ended or if a Group 2 patient did not begin PBI.
Form C	Chemotherapy report is required for all patients, including those who did not receive adjuvant chemotherapy.	A computer-generated patient-specific form will be provided to the site at randomization. Complete and submit Form C according to the instructions printed on the form.
Form AE (B-39)	Report form for AEs possibly, probably or definitely related to RT. (Refer to the Form AE instruction page.)	Refer to the Reporting Period instructions on page 1 of Form AE.
Form F (B-39)	Collects information on protocol end point events.	Submit to the NSABP Biostatistical Center every 6 months for first 5 years; every 12 months thereafter; and when a protocol endpoint event occurs. (Submit documentation when indicated.)
Serum specimen with Form BNK	Serum sample collected at time of first breast cancer recurrence (see Section 9.2 for details).	Submit to the NSABP Serum Bank of Baylor; see Protocol Appendix C for instructions.
Form SPW	Withdrawal of permission for use of specimens in future research.	Submit to the NSABP Biostatistical Center when patient who previously consented to storage and use of her samples wishes to withdraw her consent for sample storage and use.
NSABP Biostatistical Center One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 Phone: (412) 624-2666 Fax for data forms submission: (412) 622-2111 Expedited AE Reporting Fax: (412) 622-2113		

TABLE 5B. Forms and materials only required for patients designated as participants in the QOL/cosmesis patient population (see Section 10.4)

Note: Accrual to the BAHO substudy was closed on May 27, 2009. All BAHO substudy related requirements listed in Table 3 (the QOL questionnaires, MD-reported cosmesis assessments, and digital images) continue to be required for women who are currently participating in the BAHO substudy. 03/30/06, 01/08/07, 11/02/09

Form/material	Description	Submission
Pre-entry		
Form QLB (B-39)	Baseline quality of life and patient-reported cosmesis assessment	Complete prior to randomization <i>after consent is signed</i> . Submit to the NSABP Biostatistical Center within 30 days following randomization if the patient is in the QOL/cosmesis population. (If patient is not designated as being in the QOL/cosmesis population at randomization, do not submit the form). See Section 10.4 for QOL and cosmesis patient population.
Form COS (B-39)	Radiation oncologist (or surgeon)-reported cosmesis assessment	
Entry (following randomization)		
Digital images of patient's breasts	See Section 7.2	If the patient is in the QOL/cosmesis population, complete before randomization or after randomization but prior to start of therapy. Submit as JPEG files to the RTOG-provided Web-based Image Management System (http://www.rtog.org) within 30 days.
Years 1-3		
Form QLT (B-39)	End of treatment quality of life and patient-reported cosmesis assessment	Administer at last office visit during non-hormonal adjuvant therapy treatment (radiation or chemotherapy, whichever is last); submit to the NSABP Biostatistical Center.
Form QLP (B-39)	Post-treatment quality of life and patient-reported cosmesis assessment	Administer 4 weeks after end of non-hormonal adjuvant therapy (RT or chemotherapy, whichever is last); submit to the NSABP Biostatistical Center
Form QLF (B-39)	Follow-up quality of life and patient-reported cosmesis assessment	Administer at 6 months following completion of RT (if no chemotherapy) or from end of both RT and chemotherapy (if chemotherapy is given). Also administer at 1, 2, and 3 years post-treatment for all patients. Submit to the NSABP Biostatistical Center
Form QMD (B-39)	Missing data form for use with Forms QLT, QLP, and QLF	Whenever a scheduled QOL questionnaire (Form QLT, QLP, QLF) is not filled out by, or not given to, the patient and assessment could not be obtained by phone or mail. (Not required for partially completed forms or after a documented cancer recurrence, second primary cancer, or death.) Submit to the NSABP Biostatistical Center.
Digital images of patient's breasts	See Section 7.2	If the patient is in the QOL/cosmesis population, submit as JPEG files to the RTOG-provided Web-based Image Management System (http://www.rtog.org) at 1 and 3 years following completion of therapy.
Form COS (B-39)	Radiation oncologist (or surgeon)-reported cosmesis assessment	Complete at 1 and 3 years post-treatment by the radiation oncologist or surgeon completing the baseline assessment, if possible; submit to the NSABP Biostatistical Center.
Form CMD (B-39)	Missing data form for use with digital images and Form COS	Submit when a scheduled Form COS is not completed by the radiation oncologist or surgeon or when digital images can not be obtained at the scheduled time point. Submit to the NSABP Biostatistical Center.
NSABP Biostatistical Center One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 Phone: (412) 624-2666 Fax for data forms submission: (412) 622-2111 Expedited AE Reporting Fax: (412) 622-2113		

21.0 STATISTICAL CONSIDERATIONS

21.1 Randomization and treatment assignments

Assignment of treatments to patients will be balanced with respect to disease stage (DCIS only, invasive disease with no positive nodes on pathological examination, invasive disease with 1-3 positive nodes on pathological examination), menopausal status, hormone receptor status (ER-positive and/or PgR-positive vs ER-negative and PgR-negative), intention to receive chemotherapy and institution, using a biased-coin minimization algorithm.⁵⁷

21.2 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.

21.3 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 from randomization 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 randomization 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.

01/08/07

21.4 Estimates of event rates

Table 6 shows the cumulative incidence of IBTR in selected sub-populations of patients accrued to NSABP protocols B-13, B-14, B-15, B-16, B-18, B-19, B-20, B-22, B-23, B-24 and B-25.

TABLE 6. Incidence of IBTR in selected populations of NSABP patients

01/08/07

#	Group	Age	ER	CTS	# Pats	Chemo?	Tam?	# IBTRs	10 Yr Cum Inc (%)	% in B-39
D1	DCIS	≤ 49	±	0-3	208	No	Yes	27	13.6 (9.4 to 19.5)	5.45
D2	DCIS	≥ 50	±	0-3	442	No	Yes	24	5.7 (3.8 to 8.4)	20.39
11	N0	≤ 49	-	0-3	898	Yes	B-23 Only	58	6.5 (5.0 to 8.6)	2.09
12	N0	≤ 49	+	0-3	788	B-20 Only	Yes	87	9.0 (7.2 to 11.4)	10.07
13	N0	≥ 50	-	0-3	607	Yes	B-23 Only	20	4.0 (2.6 to 6.4)	6.62
14	N0	≥ 50	+	0-3	1139	B-20 Only	Yes	33	1.8 (1.2 to 2.8)	50.71
15	N1, 1-3	≤ 49	-	0-3	353	Yes	No	41	12.8 (9.4 to 17.3)	0.39
16	N1, 1-3	≤ 49	+	0-3	491	Yes	No	54	11.1 (8.4 to 14.5)	0.78
17	N1, 1-3	≥ 50	-	0-3	159	Yes	All but 26	18	11.4 (7.4 to 17.7)	0.24
18	N1, 1-3	≥ 50	+	0-3	350	Yes	All but 20	14	3.7 (2.0 to 6.2)	3.26
All DCIS								51	8.2 (6.2 to 10.7)	
All Invasive								325	6.4 (5.7 to 7.2)	

All node-positive patients in Table 6 were treated with fairly standard chemotherapy regimens (AC, CMF, AC→CMF), as were all node-negative ER-negative patients (AC, CMF, M→F). All node-negative ER-positive patients received at least five years of tamoxifen, and some also received chemotherapy (CMF, M→F). Almost all node-positive ER-positive patients received tamoxifen in addition to chemotherapy, except in cohort 16 (node-positive patients aged ≤ 49 who were ER-positive). For this group, it is reasonable to suppose that the 10-year cumulative incidence of IBTR might have been reduced by as much as 40% (i.e. to $6 \times 11.1\% = 6.7\%$) had tamoxifen been given. All other groups have been more or less "optimally" treated according to standards in force in the late 1990s.

To estimate the 10-year cumulative incidence of IBTR in the control arm of the current protocol, we assumed the patient mix indicated in the last column of Table 6. This is the observed distribution as of October 4, 2006. We also reduced the 10-year cumulative incidence of IBTR in cohort 16 to 6.7%, as explained above. Finally, we reduced the 10-year cumulative incidence of IBTR in all node-positive cohorts by 20% to account for the possibility that many of these patients will receive taxane-containing adjuvant regimens that may reduce rates of local recurrence. Applying these proportions to the cohort-specific cumulative incidences of Table 6 results in an overall 10-year cumulative incidence of IBTR equal to 4.3%.

03/30/06
01/08/07

21.5 Accrual rate and total sample size

We originally estimated that in the first year of accrual we would average 75 patients per month, and that the rate would increase to 125/month in subsequent years. As of October 4, 2006, the average rate of accrual was 162 patients per month. Investigators were informed in December 2006 that only patients in cohorts D2 and 14 who signed a consent form by December 30, 2006, would be permitted to join the study. We assume that the observed rate of accrual to the higher risk cohorts in Table 6 will continue (at an average of 49 patients per month) until the accrual goal is achieved.

Effective with Amendment #2, the total accrual to the trial was increased from 3000 patients to 4300 patients. The projected time to reach this accrual goal was thus increased from 2 years and 5 months to 4.6 years.

The quality of life study will be performed in a subset of 964 protocol participants. The subset will include 482 enrolled patients who have indicated the intention to receive chemotherapy, and 482 patients who have indicated the intention not to receive chemotherapy. Patients must also read English, Spanish, or French. Patients will be excluded from the QOL and cosmesis population if the baseline QOL and COS questionnaires are not both completed before randomization.

21.6 Statistical Analysis - primary endpoint

The analysis will take the form of an equivalence test. Let R = risk of IBTR following partial breast irradiation relative to the risk of IBTR following whole breast irradiation.

Formally, we define PBI to be inferior to WBI if the hypothesis

$$H_{\text{PBI Inferior}} : R \geq 1.5$$

is true. Similarly, we define WBI to be inferior to PBI if the hypothesis

$$H_{\text{WBI Inferior}} : R \leq 1/1.5 = 0.667$$

is true. Finally, we define PBI to be equivalent to WBI if neither $H_{\text{PBI Inferior}}$ nor $H_{\text{WBI Inferior}}$ is true.

First, we will test the hypothesis $H_{\text{PBI Inferior}}: R \geq 1.5$ against the one-sided alternative $R < 1.5$ at a significance level determined by the alpha spending approach, as indicated in Section 21.12. The test will be powered such that if the two procedures are exactly equivalent (i.e. if $R=1$), then the probability that we will fail to reject the inferiority hypothesis will be $\beta=.15$. If we reject $H_{\text{PBI Inferior}}$, we will conclude that the true relative risk is less than 1.5; otherwise our conclusion will be that we have been “unable to rule out that PBI causes a 50% increase in the crude hazard of IBTR relative to WBI.” The test will be conducted by estimating R using a Cox proportional hazards model, stratified on disease stage (DCIS, N0, N1 1-3), age at randomization ($\leq 49, \geq 50$) and hormone receptor status (ER-negative, ER-positive). This will provide a partial maximum likelihood estimate for the log-relative risk $\hat{\theta} = \log(\hat{R})$ and its estimated standard error $s(\hat{\theta})$. $H_{\text{PBI Inferior}}$ is rejected if

$$\frac{\hat{\theta} - \log(1.5)}{s(\hat{\theta})} < -z_{\alpha}$$

Next we will test the $H_{\text{WBI Inferior}}: R \leq 1/1.5 = 0.667$ against the one-sided alternative $R > 0.667$ at the significance level determined by alpha spending. The test will be powered such that if $R=1$, then the probability that we will fail to reject $H_{\text{WBI Inferior}}$ will be $\beta=.15$. If we reject $H_{\text{WBI Inferior}}$ we will conclude that the true relative risk is greater than 0.667; otherwise our conclusion will be that we have been “unable to rule out that WBI causes a 50% increase in the crude hazard of IBTR relative to PBI.” $H_{\text{WBI Inferior}}$ is rejected if

$$\frac{\hat{\theta} - \log(0.667)}{s(\hat{\theta})} > z_{\alpha}$$

PBI and WBI will be declared to be equivalent if we reject both $H_{\text{PBI Inferior}}$ and $H_{\text{WBI Inferior}}$. This will be the case if a $(1-2\alpha)\%$ confidence interval for R lies entirely between 0.667 and 1.5.

In order to have sufficient power to reject either inferiority hypothesis if $R=1$, we will defer the definitive analysis until in total 175 IBTRs have been reported on both treatment arms among eligible patients who have received their assigned treatments.

Using the approximation $s(\hat{\theta}) \approx 2/\sqrt{175} = .151$, it follows that that equivalence will be claimed if the estimated relative risk falls between about 0.86 and 1.17. If the relative risk exceeds 1.17, we will not be able to rule out the hypothesis that $R \geq 1.5$, while if the relative risk is less than 0.86, we will not be able to rule out the hypothesis that $R \leq 0.667$.

We will also provide estimates and confidence intervals for the crude hazards and cumulative incidence curves for IBTR in either treatment arm.

21.7 Power considerations - primary analysis

Table 7 shows the operating characteristics of the primary analysis for various values of the relative risk:

TABLE 7. Operating characteristics of the primary analysis

True Relative Risk R	Probability of concluding WBI is inferior (Accepting H_{WBI} Inferior)	Probability of concluding WBI is not inferior (Rejecting H_{WBI} Inferior)	Probability of concluding equivalence (Rejecting both H_{PBI} Inferior and H_{WBI} Inferior)	Probability of concluding PBI is not inferior (Rejecting H_{PBI} Inferior)	Probability of concluding PBI is inferior (Accepting H_{PBI} Inferior)
1/1.5=0.667	.95	.05	.05	1.000	.000
1/1.4=0.714	.88	.12	.12	.999	.001
1/1.3=0.769	.76	.24	.24	.997	.003
1/1.2=0.833	.57	.43	.42	.99	.01
1/1.1=0.909	.34	.66	.61	.95	.05
1	.15	.85	.70	.85	.15
1.1	.05	.95	.61	.66	.34
1.2	.01	.99	.42	.43	.57
1.3	.003	.997	.24	.24	.76
1.4	.001	.999	.12	.12	.88
1.5	.000	1.000	.05	.05	.95

21.8 Interpretation of relative risk

Although R is defined as the ratio of the crude hazard for IBTR following partial breast irradiation compared to the crude hazard for IBTR following whole breast irradiation, for the rates of IBTR and competing risks applicable in the population under consideration, it is also very nearly the ratio of the corresponding 10-year cumulative incidences, assuming that the treatments do not differentially impact the crude hazards of the competing risks. (In any case the ratio of cumulative incidences will never exceed R). Thus, for a patient whose 10-year probability of IBTR is 6.0% with whole breast irradiation, a relative risk of $R=1.5$ would imply an increased 10-year probability of IBTR with partial breast irradiation equal to almost $1.5 * 6.0\% = 9.0\%$, or an absolute increase in risk of 3.0%. For a patient at increased risk of IBTR, the absolute increase in risk would be greater than this: For example, for a patient whose 10-year probability of IBTR is 10.0% with whole breast irradiation, a relative risk of $R=1.5$ would imply an increased 10-year probability of IBTR with partial breast irradiation equal to almost $1.5 * 10.0\% = 15\%$, or an absolute increase in risk of 5%. For patients who are at low risk, the absolute difference would be small.

21.9 Statistical analysis - secondary endpoints

A site of first treatment failure table will be constructed, summarizing the frequency and crude hazards of IBTRs, regional failures, distant recurrence and deaths prior to recurrence. Confidence intervals will be calculated for relative risks, and cumulative incidence plots will be drawn showing how the complement of disease-free survival is partitioned into the various competing risks for each treatment group.

Overall survival, recurrence-free survival, and distant disease-free survival will be compared using the log-rank test, stratified on disease stage (DCIS, N0, N1, 1-3), menopausal status and hormone receptor status (ER-positive and/or PgR-positive vs ER-negative and PgR-negative). The hypotheses of identical distant disease-free and recurrence-free intervals and of identical survival curves will be tested against a two-sided alternative at the .05 level.

21.9.1 *Quality of life and cosmesis*

The primary endpoints for the quality of life evaluation are self-reported cosmesis (as measured by the BCTOS cosmesis scale) and fatigue (as measured by the SF-36 vitality scale). As a preliminary step, we will verify our expectations that the stage of disease does not directly impact fatigue or cosmesis (apart from the effects of treatment). The primary analysis plan is based on that assumption.

The primary quality of life analysis will employ analysis of variance (ANOVA) to determine whether the radiation therapy group (whole versus partial breast irradiation) impacts the change in fatigue from baseline to the end of adjuvant therapy (including both radiation therapies and, if applicable, chemotherapy) and the change in self-reported cosmesis from baseline to 3 years after randomization. The analyses will also control for axillary dissection. There will be four such comparisons because patients who receive chemotherapy will be analyzed separately from patients who do not receive chemotherapy. Separate analyses are preferable because chemotherapy is expected to impact the cosmesis and fatigue outcomes directly, and it also necessitates a change in the timing of the assessments. Each comparison will be performed at significance level 0.0125. For fatigue, we will test the null hypothesis of equal fatigue against a two-sided alternative. For cosmesis, we will seek to establish that the two radiation therapies are equivalent. Specifically, we will perform one-sided tests against each of these null hypotheses: a) the mean change in the cosmesis score in the PBI arm is at least 0.4 standard deviations greater than in the WBI arm, and b) the mean change in the cosmesis score in the PBI arm is at least 0.4 standard deviations less than in the WBI arm.

Cosmesis will also be evaluated based on assessments made by the radiation oncologist. As in the primary QOL analyses, ANOVA will be used to determine if there is an impact on physician evaluated cosmesis due to the radiotherapy group (whole breast vs. partial breast) at 2 time points: end of adjuvant (non-hormonal) therapy and at 3 years. For the same reasons as it is being done in the primary QOL analyses, separate analyses will be done for patients who do and not receive chemotherapy. The objective is to test for equivalence between the radiotherapy groups using the same null hypotheses as in the primary QOL,

namely a) the mean change in the cosmesis score in the PBI arm is at least 0.4 standard deviations greater than the WBI arm, and b) the mean change in the cosmesis score in the PBI arm is at least 0.4 standard deviations less than the WBI arm.

In addition, cosmesis will be evaluated by an independent panel based on photographs using the same reporting scale as the physicians and the same null hypotheses as stated above. This analysis will be looking at the impact of the radiotherapy group on change in cosmesis from baseline to 3 years and will be done separately for patients who do and do not receive chemotherapy.

As a secondary analysis, cosmesis ratings across source (patient, physician, and photographic review panel) will be evaluated for comparability. Secondary longitudinal analyses will be performed including all assessment time points and including the convenience of care. Exploratory comparisons among PBI modalities will also be performed.

All secondary and exploratory QOL and cosmesis analyses will be performed at significance level 0.05, without adjustment for multiple comparisons, and reported as secondary or exploratory.

- *Evaluable data for quality of life analyses*

All analyses will be performed including patients with the relevant questionnaire items completed at baseline and at least one follow-up time point.

- *Missing quality of life data*

Completion of all scheduled QOL forms is part of the routine delinquency assessment for centers collaborating in B-39/0413. Adherence to the QOL assessment schedule will be encouraged by means of proactive reminders to the participating institutions. The NSABP Biostatistical Center staff will continue to monitor proportions of missing QOL information occurring in each treatment arm at different assessment points. If a decline in QOL follow-up assessments is observed in specific centers or specific trial arms, interventions will be developed in order to correct problems in the data collection process and to bring delinquent centers back in line with the B-39/0413 protocol. If all efforts to collect at a scheduled questionnaire fail, the center will be required to submit a QOL Missing Data Form (QMD).

Despite these precautions, a certain amount of missing data is expected. The information from patients with missing data will be reviewed in order to determine whether the data analytic procedures will be biased. Subjects with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, collaborating center, and reasons for non-adherence. Mean scores on the primary QOL measures will be compared for patients with or without missing data at different assessment points in order to investigate whether missing data was preceded by a significant decline in QOL scores. In addition, we will investigate whether questionnaires are more likely to have missing items if other items on the same questionnaire

have high scores. If no missing data mechanism can be detected following this review, the data will be analyzed assuming the missing data are at random. In the case of item non-response, summed scores will be computed using the mean from the other items in the analysis. If a missing data mechanism appears to be present, we will undertake to develop an appropriate analytic strategy to control for the potential bias and, if possible, to impute the missing values. The appropriateness of alternative strategies will depend upon both the pattern (e.g., item non-response versus intermittent missing forms versus complete dropouts) and the severity of the missing data problem.⁵⁸⁻⁶⁰ For example, an appropriate strategy could involve the stratification of the patients in the study in terms of the completeness of their data for key time periods (e.g., 6 months or 1 year) and the comparison of results from separate analyses for each group or it could involve the implementation of more sophisticated imputation procedures designed to model a missing data mechanism within the framework of a repeated measure analysis.^{61,62} We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

21.10 Power considerations - cosmesis and fatigue analyses

The quality of life sub-study sample size of 964 (482 receiving chemotherapy; 482 not receiving chemotherapy) affords 85% power to detect a difference (at significance level 0.0125) in the fatigue outcome between radiotherapy treatment groups of 0.35 standard deviations. For the SF-36 vitality scale, a difference of 0.35 standard deviations corresponds to a change of one response level (e.g., from “some of the time” to “a little of the time”) on 1-2 of the 4 items. The sample size also provides 88% power to detect equivalence in the primary patient-reported cosmesis outcome when the two treatments have the same mean cosmesis. When the difference in patient-reported is actually 0.07 standard deviations, the power to detect equivalence in the primary cosmesis outcome is 80%. With this sample size, there is 90% power to detect equivalence (at significance level 0.05) in the secondary cosmesis scores as evaluated either by the physician or the panel, when the mean cosmesis scores are truly the same.

This analysis assumes that up to 15% of patients will not be evaluable for the fatigue analyses because the post-treatment assessment will not be performed, and up to 25% of patients will not be evaluable for the primary self-reported cosmesis analysis because the 3-year assessment will not be performed.

21.11 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 17.0. In addition, summaries of adverse events and toxicities will be prepared monthly and reviewed by the B-39/0413 Protocol Chairs, Officers, and Statisticians. Information will also be reviewed by NSABP and RTOG internal staff at periodic meetings.

Throughout the accrual and active treatment periods of the trial, progress reports will be prepared and presented to the B-39/0413 Data Monitoring Committee (DMC) at 6-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 DMC, together with interim analysis results.

01/08/07
11/02/09

21.12 Analysis schedule

The definitive analysis of the primary endpoint will take place after 175 IBTRs have been reported among patients receiving their randomized treatment assignment. Assuming that accrual continues as it has been observed, a 5% ineligibility/treatment refusal rate, and control arm failure rates as described above, definitive analysis will take place about 10 years following the initiation of the trial.

Three interim analyses will be performed before the final analysis when 175 events are observed. The first interim analysis will be held when 44 events are observed. The second and third interim analyses will be held when 88 and 132 events are observed. For all interim analyses, each one-sided hypothesis described in Section 21.6 will be performed with $\alpha=0.001$. The final analysis will be performed with $\alpha=0.0493$. Under the NSABP data management system, summary files are locked every 3 months, so in practice the numbers of events at each interim analysis may differ slightly from the numbers cited above. If significant deviations occur, the p-values will be adjusted by alpha-spending to ensure that the type I error control criteria are maintained.⁶³ This approach guarantees that the type I error of the study, including the interim analyses, is less than 0.05.

A possible schedule of interim analyses is given in Table 8. The actual number of events at the time of each interim analysis will depend on the observed event rate (except at the first analysis and the final analysis, which will occur at fixed numbers of events as indicated).

Table 8. Number of events and p-values for interim and final analyses 01/08/07, 11/02/09

Analysis	Number of Events	P-value
1	44	0.001
2	88	0.001
3	132	0.001
Final Analysis	175	0.0493

21.13 Issues related to racial and ethnic differences

Possible racial and ethnic variation in response to the treatments under consideration is of most concern in African-Americans. Many researchers have noted less favorable survival rates for African-American breast cancer patients compared to Caucasians.^{64,65} This observation has been attributed to many factors, including more advanced disease at the time of treatment,⁶⁶ social and economic factors,⁶⁷ and specific tumor characteristics such as ER positivity.^{68,69} Although outcomes in general tend to be less favorable for African-Americans, significant interaction between race and treatment response has not been reported, suggesting that, where treatment efficacy is noted, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.^{70,71}

Potential for the enrollment of minority patients in this protocol is enhanced by the NSABP's recognition of the importance of increasing minority accrual. To this end, we provide opportunities for greater participation by underrepresented racial and ethnic groups. In similar studies, the racial/ethnic composition for the study population is approximately 87% white, < 1% American Indian or Alaskan Native, 2% Asian or Pacific Islander, 8% black (not of Hispanic origin), 3% Hispanic, and < 1% other. It is anticipated that this distribution will be maintained for Protocol B-39/0413. The prognostic effect of race/ethnicity will be evaluated using statistical models. Because of sample size limitations, we will not be able to compare effects separately for the different cultural or racial groups.

TABLE 9. Expected racial and ethnic composition of NSABP B-39/RTOG 0413

01/08/07

Ethnic Category	Total
Hispanic or Latino	107
Not Hispanic or Latino	4193
Ethnic Category: Total of all subjects	4300
Racial Category	
American Indian or Alaskan Native	7
Asian	108
Black or African American	251
Native Hawaiian or other Pacific Islander	14
White	3920
Racial Category: Total of all subjects	4300
Ethnic Categories:	Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
	Not Hispanic or Latino
Racial Categories:	American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
	Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
	Black or African American – a person having origins in any of the black racial groups of Africa.
	Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

22.0 **PUBLICATION INFORMATION AND ADMINISTRATIVE AGREEMENTS**

The publication or citation of study results will be made in accordance with the publication policy of the NSABP that is in effect at the time the information is to be made publicly available.

23.0 REFERENCES

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APPENDIX A
TNM NOMENCLATURE AND STAGING FOR BREAST CANCER

TNM Nomenclature

Primary Tumor (T)

T ₀	No evidence of primary tumor
T _{is}	Carcinoma in situ
T ₁	≤ 2 cm
	T _{1mic} ≤ 0.1 cm
	T _{1a} > 0.1 cm but not > 0.5 cm
	T _{1b} > 0.5 cm but not > 1.0 cm
	T _{1c} > 1.0 cm but not > 2.0 cm
T ₂	> 2 cm- but not > 5 cm
T ₃	> 5 cm
T ₄	Any size, with direct extension to chest wall or skin (only as described below)
	T _{4a} Extension to chest wall (excluding pectoral muscle)
	T _{4b} Edema (including peau d'orange) or ulceration of skin or presence of satellite skin nodules (confined to the same breast)
	T _{4c} Both T _{4a} and T _{4b}
	T _{4d} Inflammatory carcinoma

Important notes:

Inflammatory Carcinoma

Inflammatory carcinoma 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 clinical findings. 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.

Skin of Breast

Dimpling of the skin, nipple retraction, or any other skin change, except those described under T_{4b} and T_{4d} may occur in T₁, T₂, or T₃ without changing classification.

Regional Lymph Nodes (N)

Clinical

N ₀	No regional lymph node metastasis
N ₁	Metastasis to movable ipsilateral axillary lymph node or nodes
N ₂	Metastasis to ipsilateral axillary lymph nodes fixed or matted to one another or to other structures; or in clinically apparent* ipsilateral mammary nodes in the absence of clinically evident axillary lymph node metastasis
	N _{2a} Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
	N _{2b} Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N ₃	Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.
	N _{3a} Metastasis in ipsilateral infraclavicular lymph node(s)
	N _{3b} Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N _{3c} Metastasis in ipsilateral supraclavicular lymph node(s)

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

APPENDIX A (continued)

TNM nomenclature (continued)

03/30/06

Pathologic (pN)^a

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
 pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction

pN0 (i -) No regional lymph node metastasis histologically, negative IHC
*[pN0(i -) No regional lymph node metastases identified on H&E and/or IHC]**
 pN0 (i +) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
*[pN0(i +) Isolated tumor cells or clusters identified, no cluster larger than 0.2 mm identified by H&E or IHC]**

pN0 (mol -) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)^b
 pN0 (mol +) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)^b

pN₁ Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
 pN_{1mi} Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
 pN_{1a} Metastasis in 1 to 3 axillary lymph nodes
 pN_{1b} Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
 pN_{1c} Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN_{3b} to reflect increased tumor burden)

pN₂ Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent*** internal mammary lymph nodes in the absence of axillary lymph node metastasis.
 pN_{2a} Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm.)
 pN_{2b} Metastasis in clinically apparent*** internal mammary lymph nodes in the absence of axillary lymph node metastasis

pN₃ Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent*** ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
 pN_{3a} Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
 pN_{3b} Metastasis in clinically apparent*** ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
 pN_{3c} Metastasis in ipsilateral supraclavicular lymph nodes

Metastasis (M)

M₀ No distant metastases

M₁ Distant metastasis

^a Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i +) (sn)

^b RT-PCR: reverse transcriptase/polymerase chain reaction.

* The following clarification has been made to the AJCC classification: the identifier (i+) will be used to indicate "isolated tumor cells." All metastatic lesions no larger than 0.2 mm, whether detected by H&E or IHC, will be designated pN0(i+), while a designation of pN0(i-) will be used to indicate no detectable tumor cells by either H&E or IHC. Singletary SA, Greene FL, Sobin LH. Classification of Isolated Tumor Cells: Clarification of the 6th Edition of the American Joint Committee on Cancer Staging Manual. Cancer 2003; 98:2740-2741.

** Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

***Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

APPENDIX A (continued)

Staging

03/30/06

	<i>T</i>	<i>N</i>	<i>M</i>
Stage 0	T _{is}	N ₀	M ₀
Stage I	T ₁	N ₀	M ₀
Stage IIA	T ₀	N ₁	M ₀
	T ₁	N ₁	M ₀
	T ₂	N ₀	M ₀
Stage IIB	T ₂	N ₁	M ₀
	T ₃	N ₀	M ₀
Stage IIIA	T ₀	N ₂	M ₀
	T ₁	N ₂	M ₀
	T ₂	N ₂	M ₀
	T ₃	N _{1,N2}	M ₀
Stage IIIB	T ₄	N _{0,N1,N2}	M ₀
Stage IIIC	Any T	N ₃	M ₀
Stage IV	Any T	Any N	M ₁

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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.

APPENDIX C

**PROCEDURE FOR COLLECTING, PROCESSING,
AND SHIPPING SERUM SPECIMENS**

A. Supplies, equipment, and facilities

The following supplies will be provided for each patient to each clinical site by the NSABP Serum Bank at Baylor:	The clinical sites must have on hand the following supplies and equipment:
<ul style="list-style-type: none"> • 10 ml evacuated red-top vacutainer tubes (3) • 10 ml yellow-top vacutainer tube (1) (containing 3 ml ACD) • 7 ml polypropylene Sarstedt sample vials (3) • polyfoam container including ziplock bags, foam pad, absorbent material, and U-Tek cold pack • patient identification labels • preprinted airbills for specimen shipment • corrugated cardboard boxes – must be used with each shipment • diagnostic specimen envelope 	<ul style="list-style-type: none"> • disposable gloves • alcohol swabs • sterile gauze pads or cotton swabs • 21-gauge vacutainer needle, 1-1/2" (multiple-sampling) • pipets and pipeting system • vacutainer holder • tourniquet • refrigerator or ice bucket with crushed ice • centrifuge capable of accommodating 10-ml vacutainer tubes • needle disposal containers • biohazard containers • waterproof black markers • Ziplock bags • Package tape • NSABP Form BNK <i>(specimen documentation form)</i>

For problems with supplies or requests for additional supplies, please contact the NSABP Serum Bank at Baylor at the telephone or fax number provided under “Information Resources,” page v.

B. Timing of specimen collections

Blood specimens are to be collected at the following time points:

- baseline (following randomization but before study therapy begins); and
- at the time of first locoregional or distant recurrence.

Please note: The baseline collection will be collected before therapy begins. Subsequent specimens should be collected as soon as possible following diagnosis regardless of whether new therapy has started.

APPENDIX C (continued)

C. Sample collection procedures

Four vacutainer tubes of blood are to be drawn for these specimens. Tubes will be provided by the NSABP Serum Bank for this purpose.

Procedures:

Please refer to your institutional policies and procedures for drawing blood specimens. The following are specific procedures related to the collection of specimens for transport to the NSABP Serum Bank.

1. Assemble the vacutainer tubes and vials required for the collection. These include:
 - three 10-ml red top vacutainer tubes (plain, without silica or polymer)
 - one 10-ml yellow top ACD vacutainer tube
 - three 7-ml polypropylene Sarstedt sample vials
2. Label the above tubes and vials with patient identification labels provided by the NSABP Serum Bank.
3. Completely fill the three red top vacutainer tubes and the yellow top ACD vacutainer tube with blood, according to your institutional procedure for blood specimen collection.
4. Place the yellow top tube on ice or in the refrigerator.
5. Place the three red top tubes upright in the test tube rack; allow to sit at room temperature for approximately 1 hour for clot to form before the tubes are centrifuged. The blood from patients with abnormal clotting due to disease or from those receiving anticoagulant therapy will require a longer time for complete clot formation. *Do not refrigerate tubes before centrifugation.*
6. If using a refrigerated centrifuge, set temperature of centrifuge to 25°C. Balance centrifuge carriers containing the vacutainer tubes using a top loading balance. Fill a fourth reusable tube with distilled water to serve as a balance tube. Make sure that tubes are properly seated in the carriers.
7. Load the carriers onto the centrifuge rotor. If either a swinging bucket rotor or a fixed angle bucket rotor is used, **centrifuge tubes at 1000-1200 g for 15 minutes**. *Do not exceed 1300 g in a fixed angle bucket rotor or 2200 g in a swinging head bucket rotor when centrifuging glass vacutainer tubes.*
8. While tubes are being centrifuged, sort the empty labeled Sarstedt vials in a row of a test tube rack.
9. Allow the centrifuge to come to a complete stop. Carefully open the centrifuge, taking care to avert your face from the opening. (Avoid inhaling escaping air.) Inspect carriers for tube breakage. Remove carriers from centrifuge and place on table. Carefully remove vacutainer tubes from carriers and sort into the test tube rack, matching each red top tube with the appropriately labeled Sarstedt vial.
10. Pick up the first red top tube, verifying identification against the labeled Sarstedt vial. Hold the tube so the stopper is pointing away from your face. Gently pry the stopper out,

APPENDIX C (continued)

using a pulling force with the forefinger and a pushing force with the thumb. Discard stopper in a biohazard container.

11. Using a transfer pipet, carefully transfer serum from the first tube into the Sarstedt vial. The clot/serum interface will be very tight so that serum can be carefully pipetted off to within a few millimeters of the interface. Remove as much of the serum as possible. Cap the Sarstedt vial and return it to the test tube rack. Discard the tube with remaining clot and the transfer pipet into a biohazard container. Repeat this procedure with the two additional red top tubes.
12. The yellow top tube does not require any processing before shipping.

D. Shipping procedures

Both serum and blood specimens should be shipped the same day as collected to the NSABP Serum Bank. To ensure the integrity of the specimens, the mailers must contain a refrigerant pack to maintain a cool temperature during shipping.

In the event that a blood sample needs to be collected on a Friday, process the blood and store the serum in the refrigerator until Monday when it should be shipped. For the yellow-top ACD tube, refrigerate the sample unprocessed; the ACD tube will support blood cells.

Polyfoam containers are provided with a foam insert to cushion the vials/tubes. Cold packs are provided; these must be frozen at -20°C overnight before shipping. One cold pack must be placed in the lid of the polyfoam container; the polyfoam container lid is designed to accommodate this. The vials/tubes must be placed in a Ziplock bag, along with the absorbent material, before inclusion in the polyfoam container. Fold and place the Form BNK in a second Ziplock bag. Be sure that the bags are securely closed before placing in the polyfoam container. The polyfoam container **must** be sealed completely, placed inside a cardboard box **and** then in a diagnostic lab pack or it **will not** be accepted for shipment. A completed Form BNK must be included in the polyfoam container.

An account has been established with an overnight carrier for priority "Overnight Air Shipment" of specimens to this laboratory. ***Clinics should ship on Monday through Thursday*** so that shipments do not arrive on the weekend.

As shipments are received in the NSABP laboratory, the mailers will be opened, emptied, and returned with the cold packs to the clinic from which they were sent. Shipping containers will be returned by surface mail and may require a week to arrive at the clinic from which they were sent.

Since overnight carriers may vary and the specific details required for specimen shipment could change over the course of the study, the NSABP Serum Bank will provide more detailed instructions with specimen kits when they are shipped to the institutions. Please review those instructions carefully before mailing specimens.

Stepwise procedures:

1. Place a frozen U Tek cold pack in the cover of the insulated polyfoam container. Place the foam pad in the polyfoam container.

APPENDIX C (continued)

2. Carefully place the three Sarstedt vials in a Ziplock bag; wipe any moisture from the outside of the yellow top tube and place this in the Ziplock bag. Seal the bag and place in the polyfoam container next to the ice pack. (The tube should be “sandwiched” between the refrigerant pack and the foam pad.)
3. ***Complete the NSABP Form BNK, place in a Ziplock bag, and enclose in the polyfoam container.*** Seal the polyfoam container. Place the polyfoam container inside the cardboard box and seal the cardboard box. Place the cardboard box inside the diagnostic lab pack. Close the lab pack and seal.
4. Fill out the overnight carrier airbill; check all information for accuracy.
5. Arrange for priority overnight shipping. Specify that these are diagnostic specimens.
6. Ship the package immediately. Please note that blood and serum should be shipped on Monday through Thursdays ***only*** so that delivery is made to the NSABP Specimen Bank on a weekday.

CANADIAN SITES PLEASE NOTE: If you are shipping on a Thursday, please contact the NSABP Serum Bank by fax at (713) 798-1642 and provide the tracking number of your shipment. Serum Bank personnel can then arrange for Saturday delivery if your shipment is delayed in Customs and does not arrive on Friday as scheduled.

Shipments must be sent to the following address, using the preprinted airbill.

03/30/06

Baylor College of Medicine Breast Center NSABP Serum Bank Room N1220 One Baylor Plaza Houston, TX 77030

APPENDIX D

CANCER TRIALS SUPPORT UNIT (CTSU) INSTRUCTIONS

These instructions supplement the protocol for CTSU participants. The protocol is to be followed in areas not described in this appendix.

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1.0 SITE REGISTRATION AND PATIENT ENTRY FOR CTSU INVESTIGATORS

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site (<https://members.ctsu.org>) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the NSABP B-39 Web page on the CTSU Member Web site (<https://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as "approved" in the CTSU RSS.

Requirements for NSABPB-39/RTOG 0413 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Radiation oncology facility credentialing approval (see Section 5.0 of the protocol)

Requirements for patient enrollment on NSABPB-39/RTOG 0413:

- Patient must meet all inclusion criteria and no exclusion criteria should apply
- Patient has signed and dated the consent
- All baseline laboratory tests and pre-study evaluations performed

CTSU Procedures for Patient Enrollment: Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voice mail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e., within one hour, call the Registrar cell phone at 1-301-704-2376. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Form A (Registration Form) with necessary attachments
- Properly signed and dated NSABP B-39/RTOG 0413 consent form

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Monday-Friday, Eastern time (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

APPENDIX D (continued)

Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will access the NSABP on-line registration system to obtain assignment of a treatment arm and a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Eligible patients can be registered in accordance with the Quality Assurance Guidelines outlined in Sections 5.2 and 5.3 of the protocol. The first case for each PBI technique must be submitted, reviewed, and approved prior to treatment start. *Additional patients may not be enrolled for the specific PBI technique that is undergoing the rapid review process until approval for the rapid review case is received.*

01/08/07

2.0 SPECIAL MATERIALS AND SUBSTUDIES

2.1 Submission of pathology materials

Investigators must submit pathology specimens along with the completed Form BLT directly to the **NSABP Biostatistical Center**. This should be done after the patient is randomized but within 3 months of randomization (see protocol Section 9.1).

2.2 Serum collection

CTSU will ship supplies for serum collection to the CTSU site at the time of patient registration. Subsequent serum collection kits will be sent to the CTSU site by the NSABP Serum Bank. CTSU investigators should follow protocol directions for collection of serum and blood (see Section 9.2 and Appendix C). Specimens should be shipped the same day as collected to the **NSABP Serum Bank**. Clinics should schedule specimen shipments to occur on Monday – Thursday so as not to be received on the weekend. See Appendix C for the NSABP Serum Bank address. A completed NSABP Form BNK transmittal form must accompany all shipments.

2.3 Quality of life and cosmesis study

Note: Accrual to the BAHO substudy was closed on May 27, 2009. All BAHO substudy related requirements listed in Table 3 (the QOL questionnaires, MD-reported cosmesis assessments, and digital images) continue to be required for women who are currently participating in the BAHO substudy.

B-39 patients who are in the QOL and cosmesis patient population should be discouraged from participating in other QOL or symptom management studies.

The QOL and cosmesis population will include 964 patients enrolled on NSABP B-39 (i.e., 482 enrolled patients who have indicated the intention to receive chemotherapy, and 482 patients who have indicated the intention not to receive chemotherapy). Form QLB will be collected following patient consent but prior to randomization. Form QLT will be administered at the last office visit during non-hormonal adjuvant therapy (radiation or chemotherapy, whichever is last). Form QLP will be administered 4 weeks after the end of non-hormonal adjuvant therapy (RT or chemotherapy, whichever is last). Form QLF will be administered at 6 months, and at 1, 2, and 3 years following completion of RT (if no chemotherapy) or from the end of both RT and chemotherapy (if chemotherapy given). All QOL forms must be submitted to the NSABP Biostatistical Center.

Radiation oncologist (or surgeon)-reported cosmesis (Form COS) assessments will be completed before randomization and at years 1 and 3 after completion of therapy. If the

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APPENDIX D (continued)

radiation oncologist will not be available to make these assessments, they may be made by the surgeon. We strongly urge that all three assessments be performed by the same individual.

If, for any reason, a QOL form is not filled out by the patient, a Missing Data Form (QMD) must be submitted to the NSABP Biostatistical Center. If for any reason a radiation oncologist (or surgeon)-reported cosmesis form or digital images are not completed, a Cosmesis Missing Data form (CMD) must be submitted to the NSABP Biostatistical Center.

The photographs will be taken at the same time points as Form COS: baseline, 1 year and 3 years after therapy. However, the baseline photographs may be taken after randomization (but prior to the start of chemotherapy and radiation therapy), whereas Forms QLB and COS must be completed prior to randomization.

For a patient to be included in the QOL and cosmesis population, the baseline QOL and COS questionnaires must be completed before randomization and submitted to the NSABP Biostatistical Center, and the cosmesis digital photographs must be submitted to the designated RTOG Web site in a timely manner.

Consult Section 10.0 of the protocol for further details.

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3.0 DATA SUBMISSION FOR CTSU INVESTIGATORS

All case report forms (CRFs) associated with this study must be downloaded from the NSABP B-39 Web page located on the CTSU Registered Member Web site (<https://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the NSABP Biostatistical Center. The preferred method of sending data is via fax at 412-622-2111. Do not include a cover sheet for faxed data.

The NSABP Biostatistical Center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the NSABP Biostatistical Center and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.

Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the NSABP Biostatistical Center.

- Transmittals and reports associated with pathology and blood specimen submission should be sent to the address listed in the protocol. Final pathology and operative reports should be attached to Form ON as detailed in Section 20.0, Table 5A of the Protocol.
- Submit electronic data for credentialing and for PBI case reviews and treatment data to the ITC (see Information Resources, page iv).
- Submit CT images for patients randomized to WBI using the Site Tools section of the RTOG Web site (see Information Resources, page iv).

APPENDIX D (continued)

- Submit digital images for cosmesis assessments, if patient is in the QOL population, using the Site Tools section of the RTOG Web site (see Information Resources, page v).

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4.0 **ADVERSE EVENT (AE) REPORTING BY CTSU INVESTIGATORS**

This study will utilize the CTCAE Version 3.0 for Toxicity and Adverse Event (AE) reporting. A link to the CTC guidelines is available on the CTSU member Web site. CTSU investigators should employ definitions of adverse events as described in Section 17.0, Table 4, and Appendix G. All reporting should be conducted within the time frames specified in Section 17.0 and on Table 4 and completed forms should be submitted as outlined below. Refer to Appendix G for basic information for adverse event reporting.

Your local Institutional Review Board must be informed of all reportable serious adverse reactions.

4.1 **Routine reporting**

CTSU institutions should refer to Section 17.4 of the protocol and the B-39 Form AE for specific instructions regarding routine adverse event reporting. Supporting documentation must be included when indicated in the form instructions. Form AE is to be completed by the CTSU institution and sent to the NSABP Biostatistical Center. Include on Form AE those events that have been reported via AdEERS.

4.2 **Expedited reporting**

- Refer to Section 17.3 and Table 4 for instructions regarding expedited adverse event reporting.
- Contact the B-39/0413 Research Nurse Specialist at the NSABP Biostatistical Center (refer to Information Resources, page v) for questions regarding completion of reports, the need for supporting documentation, and submission time constraints.
- Follow the instructions in Section 17.3 of the protocol when AdEERS reporting is required. Access the AdEERS electronic web-based application and complete it fully and accurately. AdEERS reports are submitted electronically to the NSABP Lead Group, and available supporting documentation is faxed to the NSABP Biostatistical Center at **(412) 622-2113** at the time of AdEERS submission. Include the patient's study number and the AdEERS ticket number on each page of supporting documentation.
- The NSABP Lead Group submits the AdEERS report to the NCI.
- Events that have been reported via AdEERS must also be reported on Form AE.

4.3 **Reporting breast cancer recurrence and second primary malignancies**

Breast cancer recurrence and all second primary malignancies are to be reported on NSABP follow-up form (Form F). Submit supporting documentation that confirms the breast cancer recurrence or second primary malignancy. Form F is to be completed by the CTSU institution and sent with the supporting documentation to the NSABP Biostatistical Center.

APPENDIX D (continued)

4.4 **Pregnancy occurring while the patient is on study therapy**

If a patient becomes pregnant while receiving study therapy, notify the NSABP Clinical Coordinating Division.

01/08/07 5.0 **REGULATORY AND MONITORING**

5.1 **Study audit**

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol, (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Registered Member Web site.

5.2. **Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-US HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU Web site.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

5.3 **Clinical Data Update System (CDUS) monitoring**

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

APPENDIX E

WHOLE BREAST IRRADIATION

03/30/06 1.0 CT-BASED RADIATION

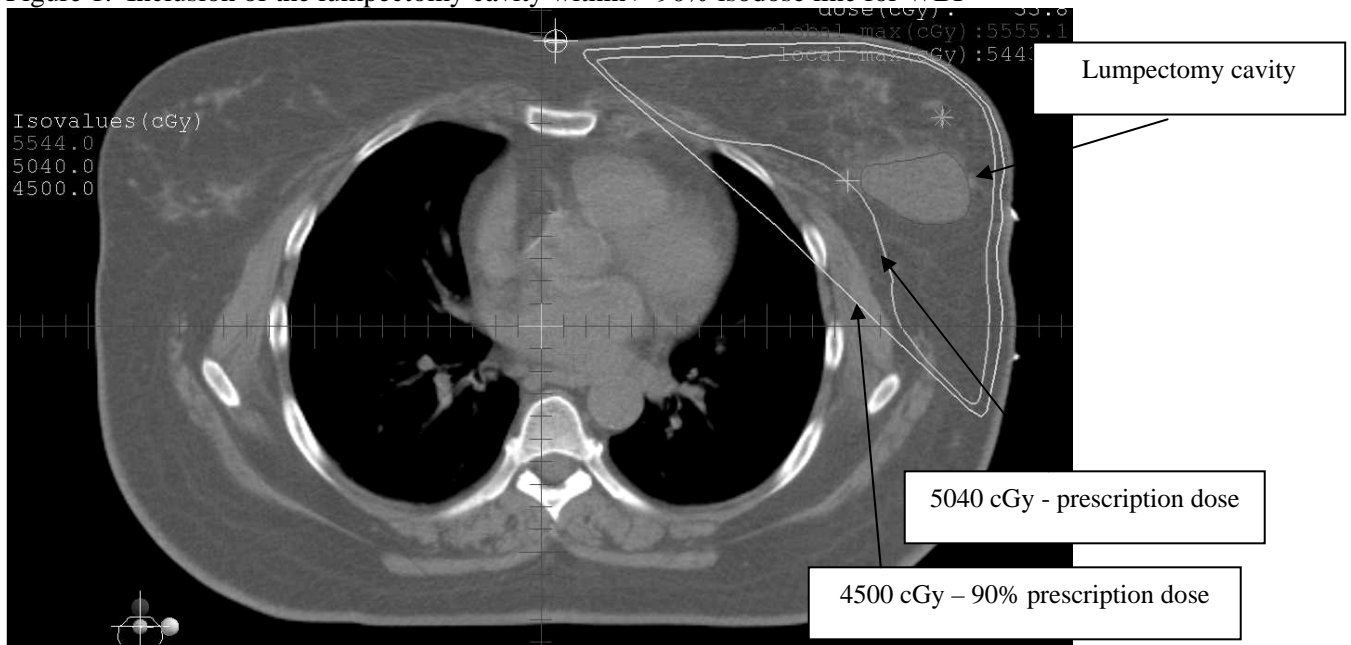
Verification of lumpectomy cavity coverage within the prescription isodose for WBI:

The radiation oncology facility is to submit one axial CT slice demonstrating that the identified lumpectomy cavity is covered by $> 90\%$ isodose line and a DRR of the tangent field. An example of this is seen below in Figure 1.

Verification process when the lumpectomy cavity cannot be identified on CT:

For some patients the lumpectomy cavity may no longer be visible at the time of CT radiation planning. When the cavity is not identifiable on CT at time of radiation planning and there are no surgical clips to identify the location of the lumpectomy cavity, the post-op CT submitted for registration to this study (see Section 7.0) can be used. The radiation oncologist can identify a representative axial CT slice with the cavity present on the post-op registration CT. A comparable anatomic axial slice from the radiation planning CT with the isodoses present should be found and verify that the $\geq 90\%$ isodose line is covering the region where the lumpectomy cavity was previously visible. Both the CT slice from the registration scan demonstrating the lumpectomy cavity location and the radiation planning scan documenting the isodose coverage are to be submitted. A DRR of the WBI tangent fields should also be submitted.

Figure 1. Inclusion of the lumpectomy cavity within $> 90\%$ isodose line for WBI



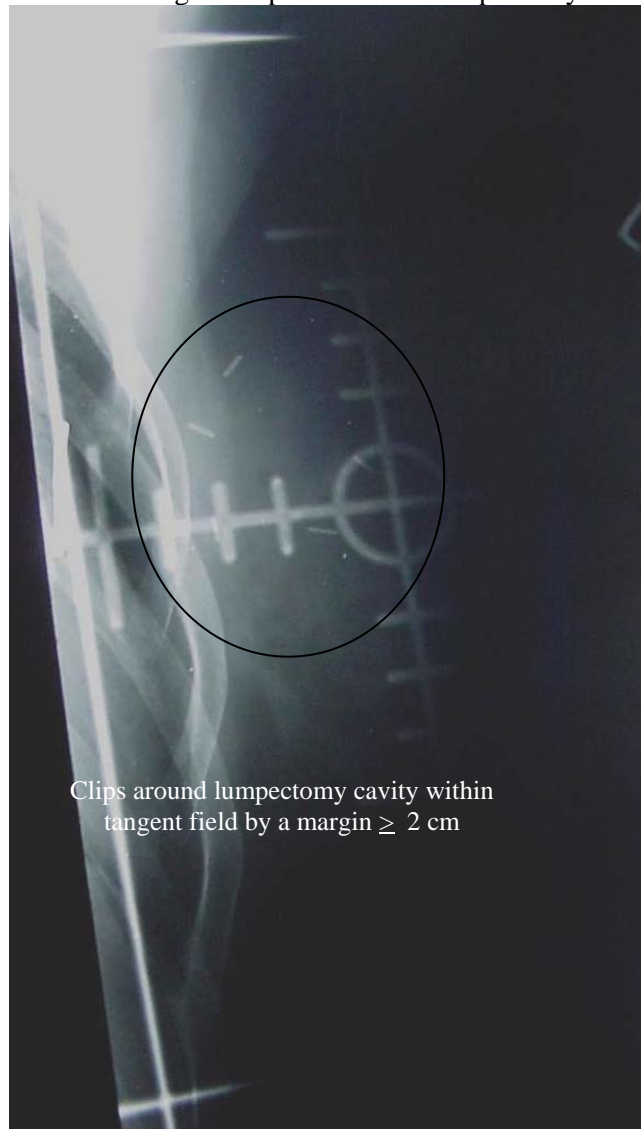
APPENDIX E (continued)

2.0 FLUOROSCOPIC SIMULATION

Verification of the lumpectomy cavity coverage within the whole breast tangent field

The tangent fields must include the clips that demarcate the lumpectomy cavity with a 2 cm margin. The institution must submit a scanned copy or digital picture of one of the tangent films demonstrating the inclusion of the clips around the lumpectomy cavity. An example of this is seen in Figure 2.

Figure 2. Digital photo of a tangent field demonstrating inclusion of the surgical clips around the lumpectomy



APPENDIX F

CONTOURING GUIDELINES

03/07/11 1.0 NORMAL STRUCTURE AND TARGET CONTOURING

Contouring accurately and consistently is essential for the case evaluation and data comparison in this protocol. The definitions are consistent between the 3 PBI techniques. The following structures will be contoured in all cases: excision cavity, balloon surface/device surface, clinical target volume (CTV) and planning target volume (PTV), the planning target for evaluation (PTV_EVAL), skin, and ipsilateral breast. If treating with MammoSite®/multi-lumen intracavitary device or multicatheter brachytherapy, it may be possible to auto-contour the ipsilateral breast in the available 3D external beam planning software and import the CT and contour into the HDR planning system, alternatively, manual entry of the ipsilateral breast volume, as per guidelines below, is necessary and acceptable to assure complete data set can be electronically submitted. Contact the appropriate software vendor for guidance. If treating with 3D-CRT technique, additional required contouring will include the contralateral breast, thyroid, ipsilateral and contralateral lung, and heart. The chin, shoulders and contralateral breast should be included in the scan. The target structures and normal tissue structures must be outlined on all CT slices.

1.1 Thyroid

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

1.2 Heart

The heart should be contoured beginning just below the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart’s 4 chambers are present. All the mediastinal tissue below this level should be contoured, including the great vessels (ascending and descending aorta, inferior vena cava). The heart should be contoured on every contiguous slice thereafter to its inferior-most extent near the diaphragm. If one can identify the esophagus, this structure should be excluded. One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

03/30/06 2.0 WHOLE BREAST REFERENCE VOLUME CONTOURING

Delineation of breast tissue extent remains difficult and free-handed CT interpretation by each individual investigator will yield significant variability. **For the purposes of this protocol, the whole breast volume will be referred to as the whole breast reference volume and defined as all tissue volume, excluding lung, within the boundaries of standard whole breast tangential fields (See Figures 1 and 2). 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. The methodology of contouring, free-handed or automated, is at the discretion of the individual investigator assuming the contour represents the defined volume. To facilitate, the patient should

APPENDIX F (continued)

be positioned in standard whole breast external beam treatment position. It is recommended that external marker wires be placed to indicate the clinical expectations of the external beam tangential field borders as a guide. The CT should be obtained from the mandible to the base of the lungs with a slice thickness of ≤ 5 mm.

2.1 Free-handed contouring

Although it requires additional time, free-handed contouring can be easily completed if an auto-contouring method is not available within the 3D planning system. Within a 3D treatment planning system, standard virtual whole breast medial and lateral tangential fields should be designed and used to guide free-handed contouring. The superior, inferior, medial and lateral borders are defined by the borders of the simulated whole breast tangential beams. The skin will be the anterior/superficial boundary while the base of the simulated tangential fields and the lung/chest wall interface will delineate the posterior boundary of the breast tissue volume, thereby, including chest wall and excluding the lung (See Figures 1 and 2). The contours will be entered on all CT slices within the boundaries of the simulated tangential fields.

2.2 Automated contouring

Each 3D planning system has available different contouring functions and the specific methods may vary from system to system. Institutions are encouraged to investigate the capabilities of their planning system in regards to these contouring functions. Within the Pinnacle 3D planning system, auto-contouring the whole breast reference volume, as defined above, is easily accomplished and can be completed in several ways. Outlined below is an example of one of these methods:

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

APPENDIX F (continued)

designate the lung and field borders limiting ROI's. Highlight "contract" as the function and designate the destination of the newly created ROI (simply create a new ROI which will then be listed in the destination list). Click on Proceed with Contraction to complete the process.

3.0 3D-CRT BEAM ARRANGEMENT

Suggested beam arrangements include noncoplanar 3-, 4- and 5-field beam arrangements using 6-MV photons. These arrangements use fields that approximate breast tangents within a 10°-20° steeper gantry angle for the medial beams to maximally spare breast tissue and couch angles of 15°-70°. The beam arrangement is arrived at in a similar manner for both. First, the isocenter is placed in the center of the PTV. The procedure used to set up the 4-field technique, consisting of a left anterior superior-to-inferior oblique (Lt ASIO), left anterior inferior-to-superior oblique (Lt AISO), right anterior inferior-to-superior oblique (Rt AISO), and right posterior superior-to-inferior oblique (Rt PSIO) for a right breast lesion is described. First, 3 medial tangents (couch angle of 0° for 2 beams and 180° for 1 beam) and 1 lateral tangent (couch angle of 0°) are constructed. Typically, the medial tangents have a 10°-20° steeper gantry angle than whole-breast tangents to spare more breast tissue. The lateral tangent may also have a slightly shallower gantry angle to spare breast tissue, provided that it does not exit through the contralateral breast. Next, couch angles are applied to each beam. Typical couch angles for the 3 anterior oblique fields are 35°-45° from a transverse plane. However, for the Rt AISO beam, particular care should be taken to ensure that the field exited superior to the heart. The couch angle used for the posterior oblique field is usually only 10°-20° to avoid entering through the ipsilateral arm, as well as collision problems with the gantry head and treatment couch. The 5-field technique is usually used for left-sided lesions and consists of Rt ASIO, Rt lateral, Rt AISO, Lt PSIO, and Lt PISO beams. The primary difference that makes this technique better suited for left-sided lesions is the elimination of the Lt AISO beam that would exit through the heart. The tradeoff is a larger volume of normal breast tissue irradiated. Each field typically has a universal 60° wedge in place for part of the treatment time. The heel of the wedge was directed anteriorly for all fields. The field edge is 5 mm beyond the PTV to account for penumbra. (Baglan KL, Sharpe SB, Jaffray D, et al. Accelerated partial breast irradiation using 3D conformal radiation therapy [3D-CRT]. *Int J Radiat Oncol Biol Phys.* 55:302-311, 2003.)

4.0 TARGET CONTOURING

Target definitions are outlined in the protocol and are listed here with figure depictions.

03/30/06

4.1 3D-CRT

- CTV – 1.5 cm beyond excision cavity. Volume expansion limited to exclude pectoralis muscles, chest wall, and the first 5 mm beneath the skin (See Figure 4).
- PTV – 1.0 cm beyond CTV (See Figure 5).
- PTV_EVAL – the PTV excluding pectoralis muscles, chest wall and the first 5 mm beneath the skin (See Figure 6).

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4.2 MammoSite®/multi-lumen intracavitary devices

CTV equals PTV equals PTV_EVAL – 1.0 cm expansion beyond balloon/device surface. Volume expansion limited to exclude pectoralis muscles, chest wall and the first 5 mm beneath the skin. (See Figures 7a and 7b.)

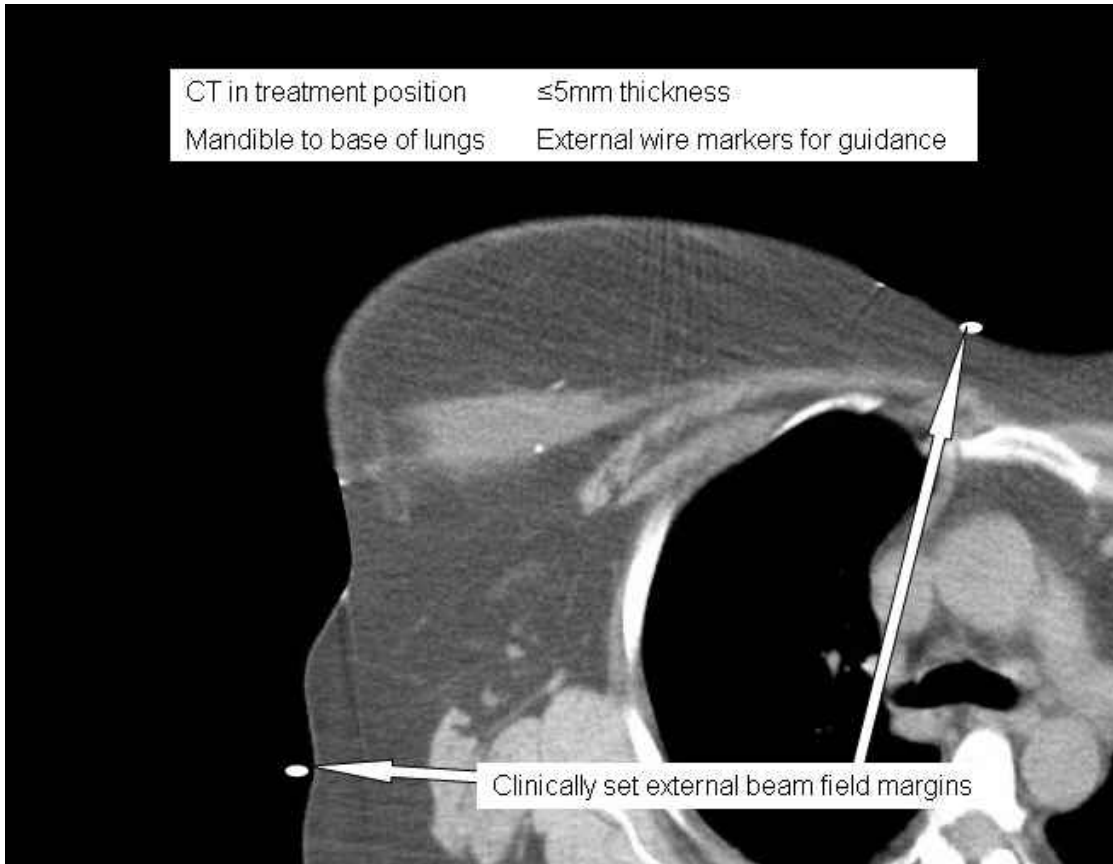
APPENDIX F (continued)

4.3 Multi-catheter

CTV equals PTV equals PTV_EVAL – 1.5 cm expansion of excision cavity. Volume expansion limited to exclude pectoralis muscles, chest wall and the first 5 mm beneath the skin. (See Figure 8.)

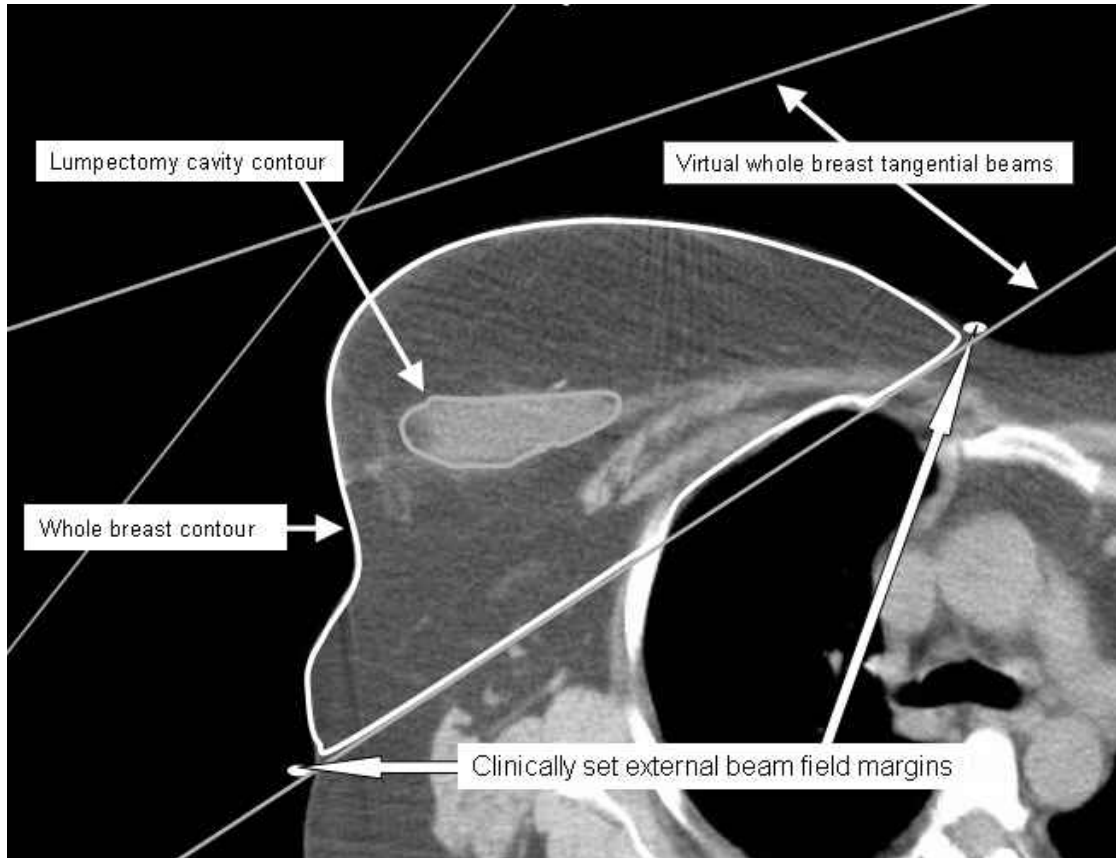
APPENDIX F (continued)

Figure 1. CT guidelines



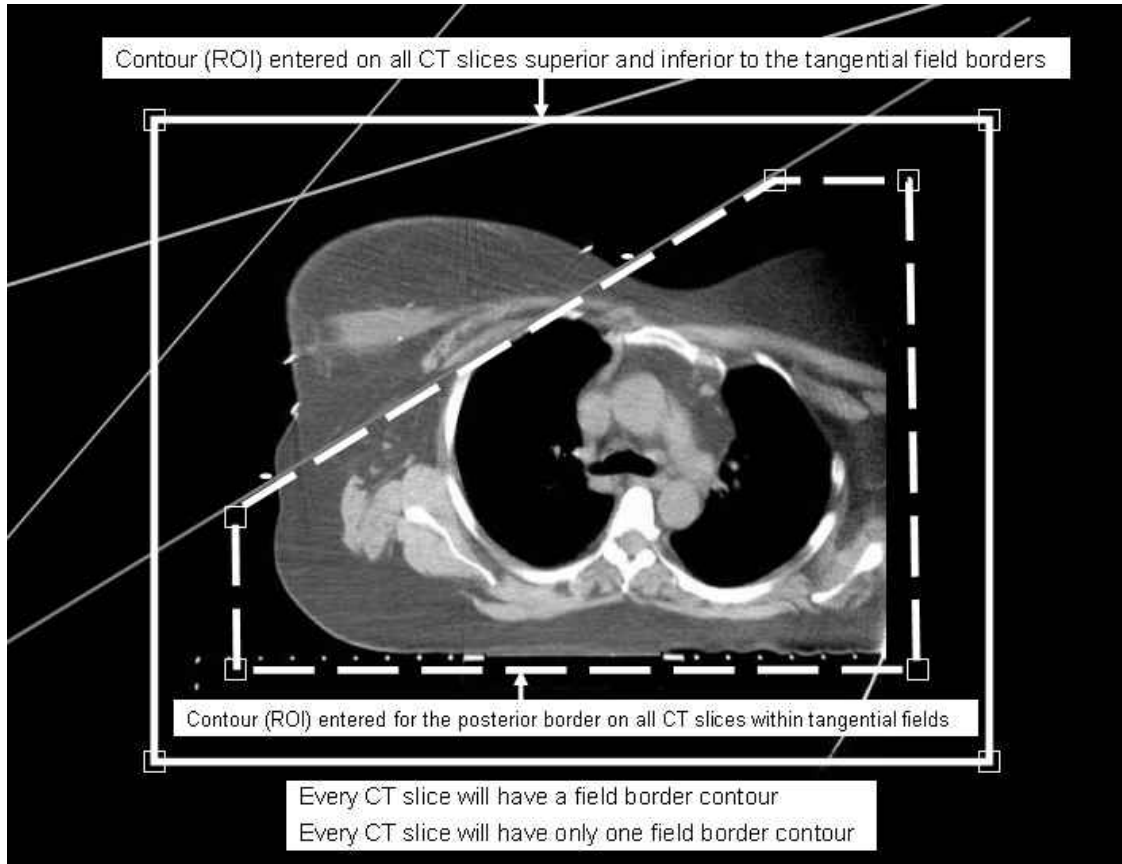
APPENDIX F (continued)

Figure 2. Whole breast contour



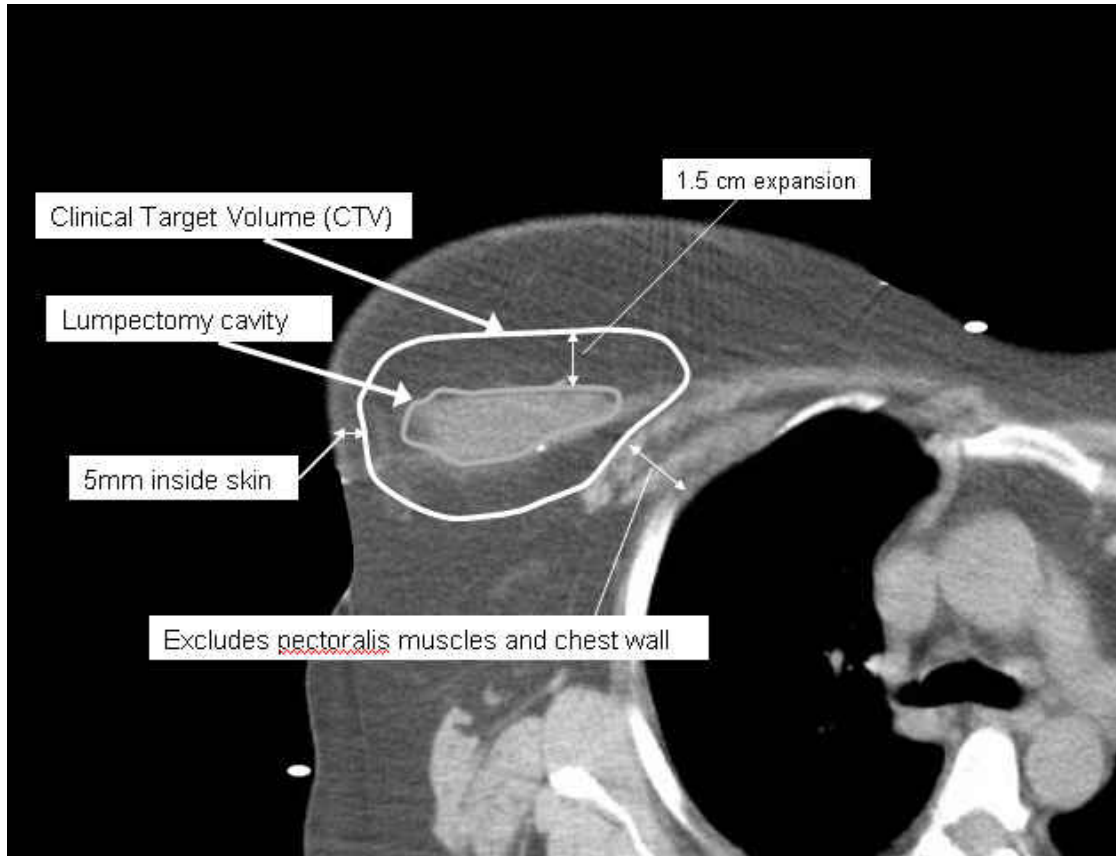
APPENDIX F (continued)

Figure 3. Example of auto-contouring whole breast



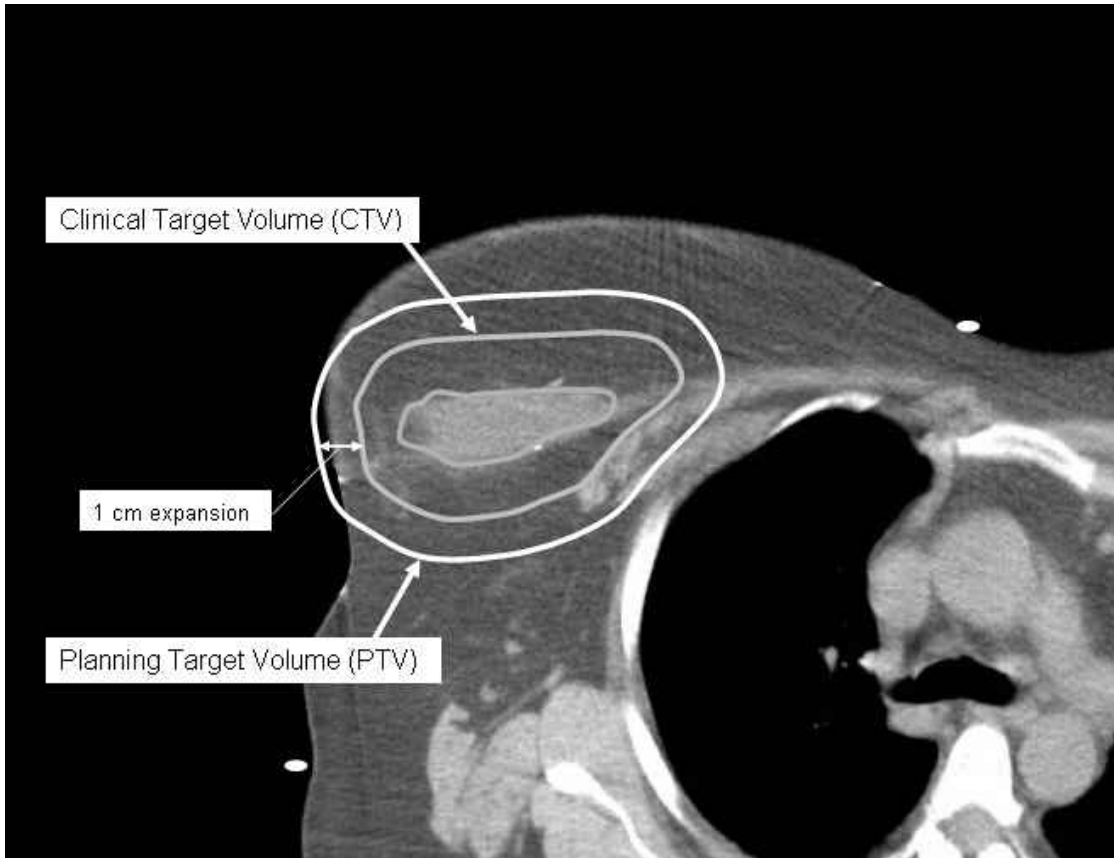
APPENDIX F (continued)

Figure 4. 3D-CRT excision cavity and CTV



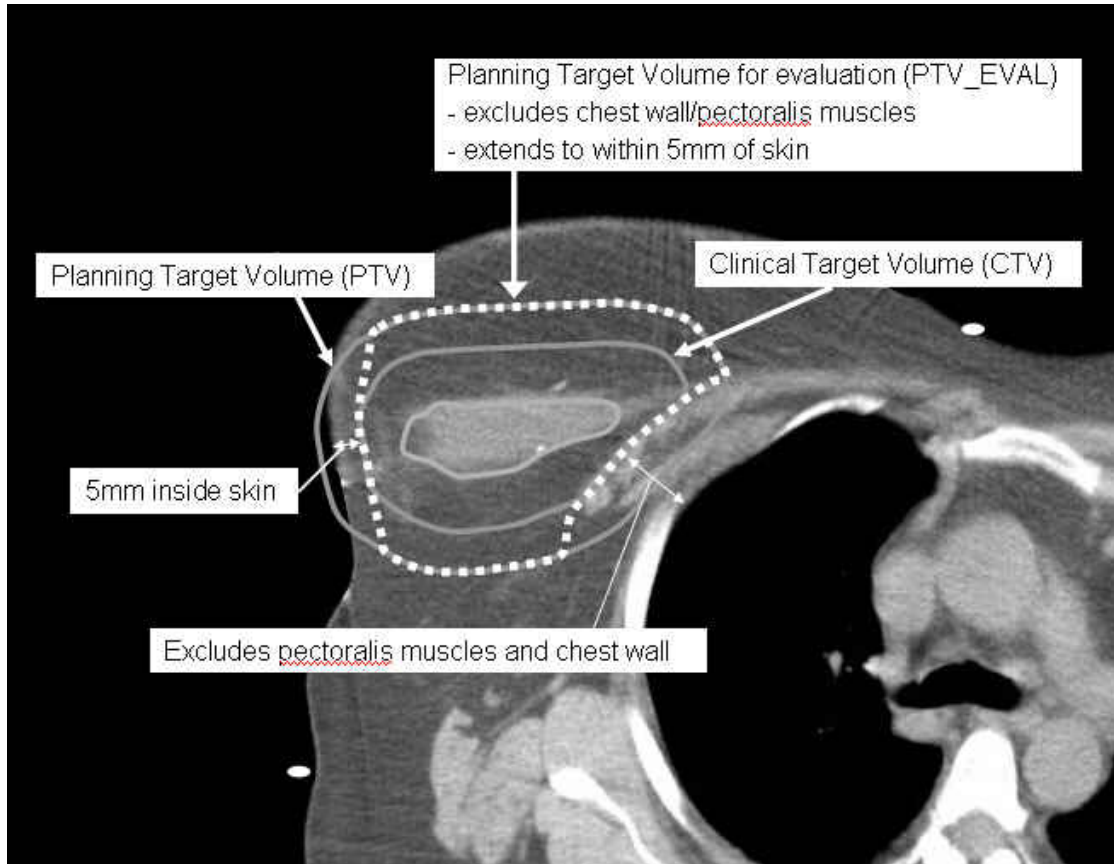
APPENDIX F (continued)

Figure 5. 3D-CRT



APPENDIX F (continued)

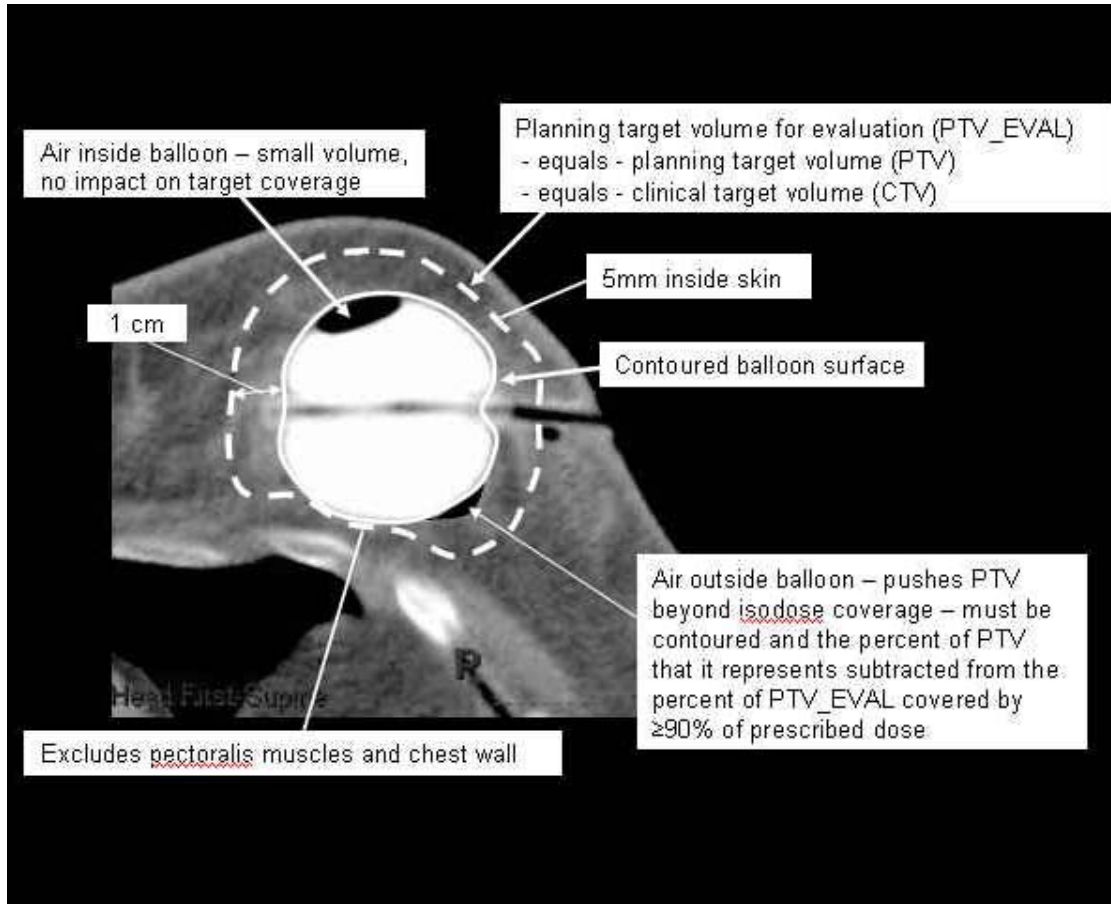
Figure 6. 3D-CRT



APPENDIX F (continued)

03/07/11

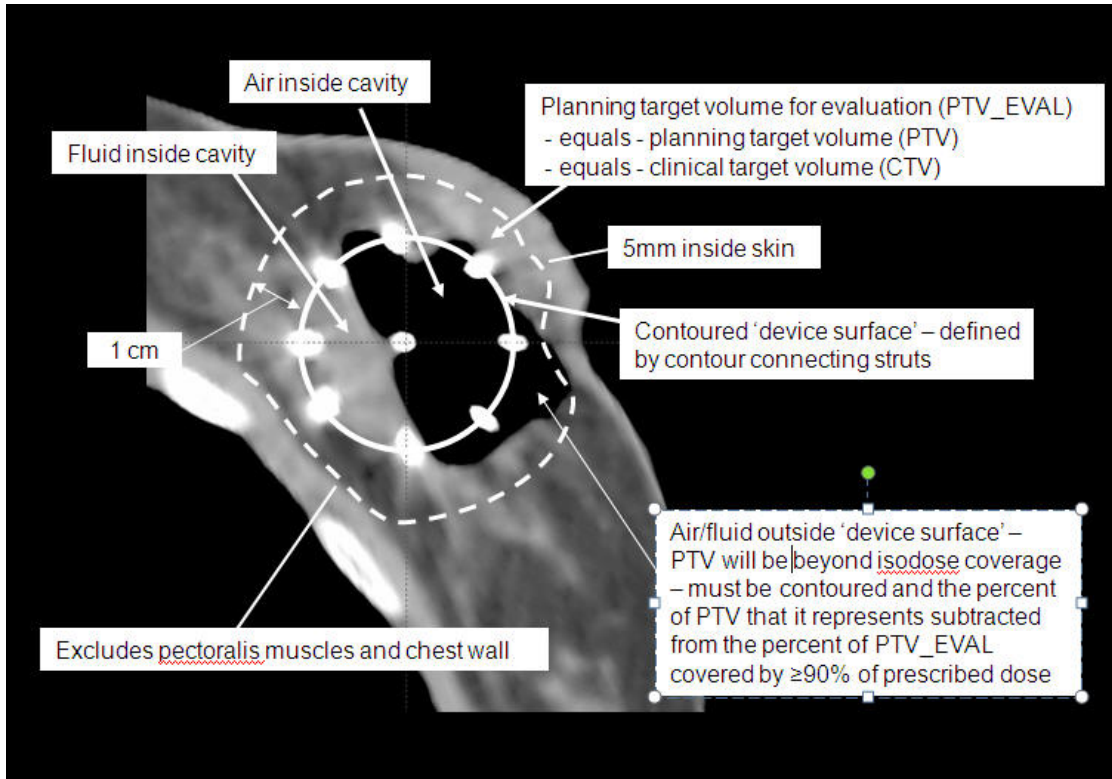
Figure 7a. MammoSite®/multi-lumen intracavitary devices



APPENDIX F (continued)

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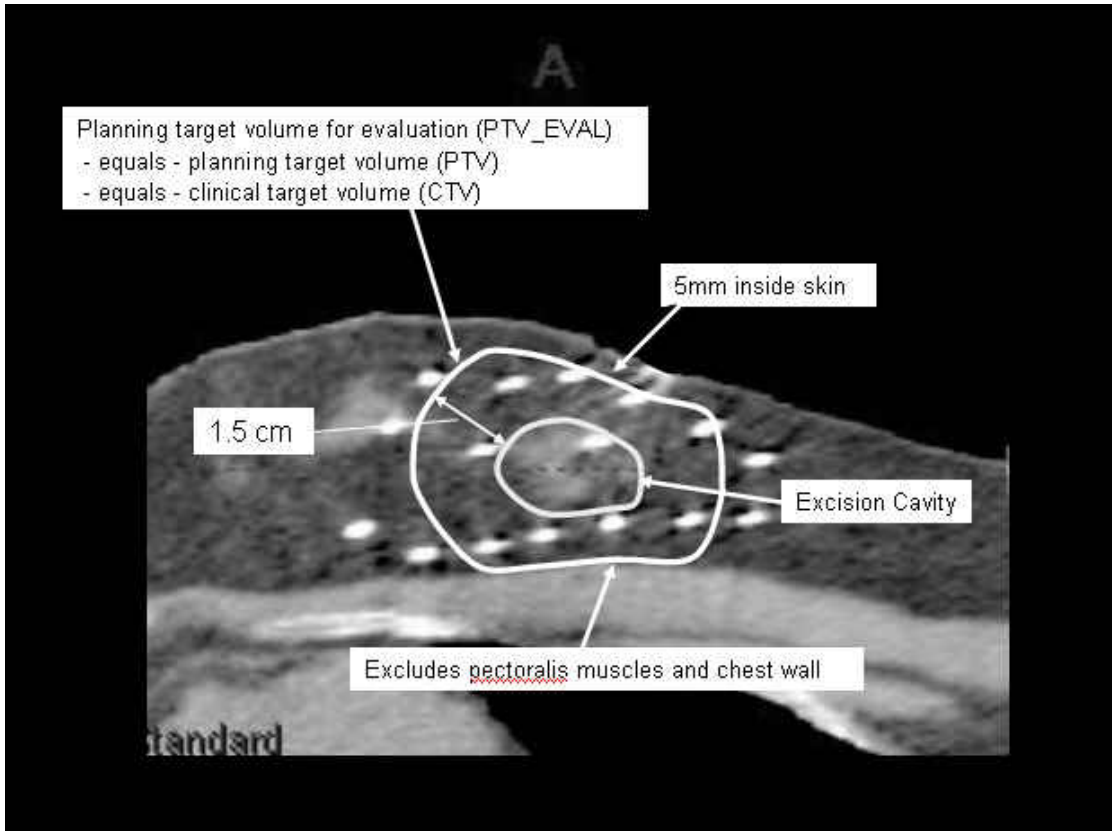
Figure 7b. SAVI® intracavitary device



APPENDIX F (continued)

03/07/11

Figure 8. Multi-catheter brachytherapy target contouring



APPENDIX G

INFORMATION BASICS FOR ADVERSE EVENT REPORTING

1.0 PURPOSE

Included in this appendix is general information required for adverse event reporting. Please refer to Section 17.0 of this protocol "Adverse Event Reporting Requirements" for specific instructions regarding expedited and routine adverse event reporting.

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. Additionally, the timely reporting of serious adverse events is required by FDA regulations and is addressed in the investigator registration form FDA-1572. Because of the medical importance of serious and/or unexpected adverse events, the responsible physician should review any expedited report prior to submission to the NSABP.

2.0 DEFINITIONS FOR ADVERSE EVENT REPORTING

03/30/06

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:

03/30/06

- *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>). If assistance is needed, contact the NSABP Clinical Coordinating Division or the Research Nurse Specialist at the NSABP Biostatistical Center. All appropriate treatment locations should have access to a copy of the CTCAE Version 3.0.

03/30/06

- *Determine whether the adverse event is related to the study therapy.* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

APPENDIX G (continued)

- *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.

03/30/06 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, and when associated with an AdEERS report, the AdEERS ticket number.

APPENDIX H

NSABP B-39/RTOG 0413 Sample Consent Form

NSABP PROTOCOL B-39/RTOG 0413: A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

Consent Version: March 7, 2011

To be attached to Protocol Version: March 7, 2011

03/30/06

Instructions to Local Institutional Review Boards Regarding Local IRB Review of Multicenter Clinical Trials

In order to conform to OHRP guidelines (effective November 9, 1992) regarding local IRB review of multicenter clinical trials, and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial.

The protocol and sample consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the sample consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. Also, the NSABP Operations Center requires that, similarly, the NSABP also be notified of substantive changes in the consent form section regarding consent to collect and store samples for possible future testing. Of primary concern are text changes that could potentially affect the future usage of the banked samples. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. **The investigator is responsible for forwarding copies of substantive IRB-approved changes with their justifications to the NSABP Operations Center Division of Regulatory Affairs immediately.** It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff and government agencies.

NSABP SAMPLE CONSENT

**Consent Form
for
A Randomized Phase III Study of Conventional Whole Breast
Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for
Women with Stage 0, I, or II Breast Cancer**

11/02/09 *Note: Centers outside of the U.S. and Canada must insert the applicable country and government oversight agencies in place of the FDA and Health Canada where appropriate throughout this consent form.*

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Why have I been asked to take part in this research study?

You are being asked to take part in this study because you have breast cancer and have had a lumpectomy to remove the cancer.

Who is conducting the study?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) are conducting this study.

(The NSABP institution must supply appropriate information about who is conducting the trial locally.)

Why is this research study being done?

Studies have shown that giving radiation therapy to the breast after lumpectomy helps keep cancer from coming back in the breast. The purpose of this study is to see if partial breast irradiation (PBI) is as good as or better than whole breast irradiation (WBI) in keeping cancer from coming back in the breast. WBI is a standard treatment after a lumpectomy. WBI is radiation therapy given 5 days a week for 5 to 7 weeks to the whole breast. PBI is radiation therapy given only to the area of the breast where the cancer was removed. PBI is given 2 times a day on 5 days. PBI may be given over a period of 5 to 10 days.

03/07/11 There are 3 different methods of PBI that are being used in this study: multi-catheter brachytherapy (bray-key-THAIR-uh-pee), single-catheter brachytherapy (MammoSite[®], MammoSite[®] ML, Contura[™] MLB, and SAVI[®]), and 3D conformal external beam irradiation.

- 3-D conformal external beam irradiation uses a beam of radiation to deliver the radiation therapy dose. It is pointed to the place in your breast where the cancer was removed.

- Multi-catheter brachytherapy uses a small bead (seed) of radioactive material. The seed is passed through catheters (small, thin tubes) that are placed in the lumpectomy area. The number of tubes will depend on the size of your breast and the size of the area where the tumor had been. You will see the ends of the tubes extending from the side of your breast. The tubes will be connected to a special machine for your treatments. The radiation therapy dose is delivered by a radioactive seed as it travels through each tube. The seed will be removed at the end of each treatment. The tubes will stay in your breast until the 10 radiation therapy treatments are done.

- 03/07/11
- The MammoSite[®], MammoSite[®] ML, and Contura[™] MLB are balloon methods that use one tube with a small balloon on the end. The balloon is put in the place where the tumor had been. The balloon is filled with salt water so it fits this space. The SAVI[®] device uses a tube that has a bundle of smaller tubes inside of it that are spread open so that they fit inside the place where the tumor had been. For all of these methods, the end of the tube will extend from the side of your breast. The tube will be connected to a special machine for your treatments. The radiation therapy dose is delivered by a radioactive seed that travels through the tube into the device that has been placed in your breast. The seed will be removed at the end of each treatment. The device will stay in your breast until the 10 radiation therapy treatments are done.

These 3 PBI methods have a shorter treatment time than WBI. Early studies show that PBI may work as well as WBI. However, there has not been a study that directly compares PBI to WBI. This study will determine if the shorter PBI treatment time results in cancer returning in the breast more often than with WBI. It is also important to be sure that the way the breast looks after PBI is as good as or better than WBI.

- 03/30/06 *(The local consent form must include this information related to the three different PBI techniques since patients must understand what the primary aim of the trial is. Only after this section may text in the consent form be omitted or changed, when noted, regarding the technique(s) not available at the local institution.)*

This study will learn about the good and bad effects of radiation therapy. The study also will learn about the feelings women have about how their breast looks after surgery and radiation therapy.

- 01/08/07 **How many people will take part in the study?**

About 4,300 women will take part in the study.

What will happen if I take part in this research study?

Before you begin the study: You will need to have the following exams, tests and procedures to find out if you can be in the study. These exams, tests and procedures are part of regular cancer care and may be done even if you do not join this study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- history and physical exam
- chest x-ray or chest CT scan

- bone scan, bone x-rays, or bone tests (only if you have bone pain or if certain blood test results are not normal)
- CT scan of your abdomen (only if the blood tests related to your liver are abnormal)
- mammogram
- breast exam
- CT scan of the breast that had the cancer to help plan the radiation therapy
- blood tests (including a pregnancy test for women of childbearing potential)

During the study: If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be "randomized" into one of the two study groups: Group 1 or Group 2. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either of the two groups. Patients in Group 1 will receive WBI. Patients in Group 2 will receive PBI. Patients in both groups may receive chemotherapy and hormonal therapy if their doctor decides it is necessary.

If you are in Group 1: WBI will start soon after you join the study, if you do not need chemotherapy. If you need chemotherapy, it will be given before your radiation. Your doctor will decide which chemotherapy treatment is best for you. Your doctor will tell you about the possible side effects of the chemotherapy. After your chemotherapy is finished, you will receive WBI once a day for 5 days a week. WBI will last 5 to 7 weeks. Each treatment lasts for 10 to 15 minutes. You will visit the radiation oncology office once a day for your radiation therapy. You should be able to do most or all of your daily activities between treatments. Radiation does not stay in your body between treatments or after the final treatment.

If you are in Group 2: You will start PBI soon after you join the study. Your treatment will be given 2 times a day, about 6 hours apart, on 5 days. The treatments may be given over a period of 5 to 10 days. Each treatment lasts for 10 to 15 minutes. You will visit the radiation oncology office twice a day for your radiation therapy. You are free to leave the office and should be able to do most or all of your daily activities between treatments. Radiation does not stay in your body between treatments or after the final treatment.

03/07/11 There are 3 types of PBI but you will only receive one type. Your doctor will decide which type you can receive. If you can receive more than one type of PBI, you and your doctor will choose which type is best for you. Very rarely, treatment with single-catheter or multi-catheter brachytherapy cannot be finished. If this happens, the device will be removed. Your doctor will discuss other treatment decisions with you.

03/30/06 ***(Sites may alter the treatment description section to indicate the number and techniques of PBI that are available at their radiation oncology facility. For example, if only two techniques are available, the consent can be modified as follows:***

There are two types of PBI at this site, but you will only receive one type. Your doctor will decide which type you can receive. If you can receive more than one type of PBI, you and your doctor will choose which type is best for you.)

If you need chemotherapy, it will start after your PBI treatment is finished. Your doctor will decide which chemotherapy treatment is best for you and will tell you about the possible side effects of the chemotherapy treatment.

For both Groups 1 and 2: If your breast cancer is affected by hormones (estrogen or progesterone), your doctor will also give you at least 5 years of hormonal therapy. If you are going to receive chemotherapy, the hormonal therapy will begin after chemotherapy has ended. If chemotherapy is not going to be part of your treatment, your hormonal therapy can begin before, during, or after your radiation therapy.

03/07/11

Group 1 Standard Treatment	Group 2 Test Treatment
<p>Whole Breast Irradiation (WBI) Chemotherapy, if needed</p> <p><i>Followed by</i></p> <p>Whole Breast Irradiation (1 treatment a day, 5 days a week for 5-7 weeks)</p>	<p>Partial Breast Irradiation (PBI)</p> <p>Multi-catheter Brachytherapy (2 treatments a day, about 6 hours apart on 5 days)*</p> <p><i>or</i></p> <p>MammoSite®, MammoSite® ML, or Contura™ MLB Balloon Catheter or SAVI® Device (2 treatments a day, about 6 hours apart on 5 days)*</p> <p><i>or</i></p> <p>3-D Conformal External Beam Irradiation (2 treatments a day, about 6 hours apart on 5 days)*</p> <p><i>Followed by</i> Chemotherapy, if needed</p> <p>* The treatments will be given on 5 days over a period of 5 to 10 days.</p>
Group 1 and Group 2	
<p>Hormonal therapy (only if your tumor has a positive hormone receptor test) will be chosen by your doctor and will continue for at least 5 years. The timing for when the hormonal therapy will begin depends on whether or not you will receive chemotherapy.</p>	

You will need the following tests and procedures. They are part of regular cancer care unless noted otherwise.

During the first year after entering the study, you will have the following tests and procedures performed:

- a *brief history and physical exam* at the end of radiation therapy, and about 1, 6, and 12 months after finishing radiation therapy, or after finishing radiation therapy and chemotherapy, if received.
- a *mammogram and an examination of your breasts* will be performed at 6 months and 12 months after finishing radiation therapy, or after finishing radiation therapy and chemotherapy, if received.

During 2-5 years after entering the study, you will have the following tests and procedures performed:

- *a brief history and physical exam and an examination of your breasts* will be performed every 6 months after finishing radiation therapy, or after finishing radiation therapy and chemotherapy, if received.
- *a mammogram* will be performed every 12 months after finishing radiation therapy, or after finishing radiation therapy and chemotherapy, if received.

After the 5th year on the study, a brief history and physical exam, a mammogram, and an examination of your breasts will be required yearly.

How long will I be in the study?

You will be asked to visit your study doctor for follow-up exams for at least 5 years and to have yearly mammograms for the rest of your life.

We would like to keep track of your medical condition for the rest of your life. Keeping in touch with you and checking on your condition yearly helps us to look at the long-term effects of the study.

Can I stop being in the study?

Yes, you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

You can choose to withdraw one of two ways. In the first, you can stop your study treatment but still allow the study doctor to follow your care. In the second, you can stop your study treatment and not have any further contact with the study staff.

Can anyone else stop me from being in the study?

The study doctor may stop you from taking part in this study at any time if he or she believes it is in the best interest for your health, if you do not follow the study rules, or if the study is stopped by the NSABP.

What side effects or risks can I expect from being in the study?

03/30/06 You may have side effects while on this study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Everyone taking part in the study will be carefully watched for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen some of the side effects. Many side effects go away soon after your radiation therapy. In some cases, side effects may be very serious, long-lasting, or may never go away.

You should talk with your study doctor about any side effects that you may have while taking part in the study.

03/30/06 *(Risks associated with a technique may be omitted if it will not be available locally to patients.)*

Risks and side effects related to multi-catheter brachytherapy PBI***Likely effects***

These side effects occur in **10% or more** of patients receiving multi-catheter brachytherapy:

- mild redness of the skin over the treatment area
- mild scar tissue
- flaking or peeling of dry skin over the treatment area
- slightly smaller breast size or change in the way the breast looks
- swelling of the breast
- bruising
- mild breast pain

Less likely effects

These side effects occur in **3-9%** of patients receiving multi-catheter brachytherapy:

- infection
- small visible blood vessels on the skin surface over the treatment area
- increased firmness of the breast tissue
- slight change in color of the skin over the treatment area
- thickening of the skin over the treatment area
- 03/30/06 • damaged fat cells in the breast that cause a red, swollen, or tender area in the breast (These damaged cells can look like a tumor and a biopsy may be needed.)

Rare but serious effects

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving multi-catheter brachytherapy:

- severe scar tissue
- breast pain lasting a long time
- severe infection
- punctured lung
- 03/30/06 • another cancer due to radiation therapy

03/07/11 ***Risks and side effects related to single-catheter brachytherapy methods of PBI (MammoSite[®], MammoSite[®] ML, Contura[™] MLB, SAVI[®])***

Likely effects

03/07/11 These side effects occur in **10% or more** of patients receiving radiation therapy with single-catheter brachytherapy methods:

- mild redness of the skin over the area of the balloon
- mild scar tissue
- flaking or peeling of dry skin over the area of the balloon
- slightly smaller breast size or change in the way the breast looks
- swelling of the breast
- bruising
- mild breast pain

Less likely effects

03/07/11 These side effects occur in **3-9%** of patients receiving radiation therapy with the single-catheter brachytherapy methods:

- infection
- small visible blood vessels on the skin surface over the area of the balloon
- increased firmness of the breast tissue
- slight change in color of the skin over the area of the balloon
- thickening of the skin over the area of the balloon

03/30/06 • damaged fat cells in the breast that cause a red, swollen, or tender area in the breast (These damaged cells may look like a tumor and a biopsy may be needed.)

03/30/06 • catheter may have to be reinserted under local anesthesia

Rare but serious effects

03/07/11 These side effects are **rare but serious**, occurring in less than **3%** of patients receiving radiation therapy with single-catheter brachytherapy methods:

- severe scar tissue
- severe infection
- breast pain lasting a long time

03/30/06 • another cancer due to radiation therapy

Risks and side effects related to whole breast irradiation (WBI) or 3-D conformal external beam PBI*Likely effects*

These side effects occur in **10% or more** of patients receiving whole breast or 3-D conformal external beam radiation therapy:

- reddening of the skin during treatment and for several weeks following treatment
- tanning of the skin lasting months and may be permanent
- slightly smaller breast size or change in the way the breast looks
- tiredness and weakness during treatment and for several weeks following treatment
- muscles in chest wall under treated breast may feel tight or sore
- swelling of breast

Less likely effects

These side effects occur in **3-9%** of patients receiving whole breast or 3-D conformal external beam radiation therapy:

- peeling of the skin in the area treated with radiation
- pain at the site of radiation treatment

Rare but serious effects

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving whole breast or 3-D conformal external beam radiation therapy:

- cough
- difficulty breathing
- irritation of the sac surrounding the heart
- inflammation of the heart muscle
- rib fracture
- another cancer due to radiation therapy

03/30/06

Risk related to fertility and pregnancy: If you are pregnant, you should not take part in this study. You should not become pregnant if you decide to take part because the radiation can affect an unborn baby. Ask for more information about preventing pregnancy if this applies to you. Also, you should not nurse your baby while on this study. Ask your doctor for more information.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. While doctors hope that PBI will be at least as effective in preventing breast cancer from returning as WBI, there is no proof of this yet. We do know that the information from this study will help doctors learn more about PBI as a treatment for breast cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- 03/30/06
- Receiving WBI or PBI without being in this study
 - Getting treatment or care for your cancer without being in this study
 - Taking part in another study
 - Getting no treatment

Please talk with your doctor about your choices before you decide if you will take part in this study.

11/02/09 **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, for quality assurance, and data analysis include:

- the National Surgical Adjuvant Breast and Bowel Project (NSABP);
- the Radiation Therapy Oncology Group (RTOG);
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights;
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials; and
- government agencies, including the NCI or its authorized representatives, the FDA, the Office for Human Research Protections (OHRP), Health Canada, and the Irish Medicines Board. These agencies may review the research to see that it is being done safely and correctly.

03/30/06 **What are the costs of taking part in this study?**

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for.

Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ (*insert doctor's name*), if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or her at _____ (*insert doctor's phone number*).

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

(Canadian Sites must insert the following paragraph in place of the one above:

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not waive any of your legal rights for compensation by signing this form.)

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

The Data Monitoring Committee (DMC), an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. You may be asked to sign another consent form in response to new information.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any question or concerns you may have about this study. Contact your study doctor _____ (*insert doctor's name and phone number*).

For questions about your rights while taking part in this study, call the _____ (*insert the institution's name*) Institutional Review Board (IRB) (a group of people who review the research to protect your rights) at _____ (*insert IRB phone number*).

(If your institution is using the NCI Central IRB, insert the following text: You may also call the Operations Office of the NCI Central Institutional Review Board [CIRB] at 1-888-657-3711 [from the continental U.S. only].)

Additional tests for the NSABP B-39/RTOG 0413 study

The following section of the informed consent form is about additional research studies that may be done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you say "no" to taking part in these additional studies.

Consent for use of blood and tissue for future research

About using blood and tissue for future research: The NSABP would like to keep some of the blood and tissue that is taken during the study but is not used for other tests. If you agree, the blood and tissue samples will be kept and may be used in future research to learn more about cancer and other diseases. The blood and tissue samples will be given only to researchers approved by the NSABP. Any research study using your samples must also be approved by an IRB. The research that is done with your blood and tissue samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your blood and tissue samples will not affect your care.

Things to think about: The choice to let the NSABP keep the blood and tissue samples for future research is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood and tissue samples can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want the NSABP to use your blood and tissue samples and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the NSABP decides to destroy them.

In the future, people who do research with your blood and tissue samples and people who do other types of health-related research may need to know more about your health. While the NSABP may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue samples are used for genetic research (about diseases that are passed on in families). Even if your blood and tissue samples are used for this kind of research, the results will not be told to you and will not be put in your health records.

Your blood and tissue samples will only be used for research and will not be sold. The research done with your samples may help to develop new products in the future, but you will not get paid.

Benefits and risks: The possible benefits of research from your blood and tissue include learning more about what causes cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of information from your health records. The NSABP will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood and tissue collected and stored by the NSABP.

Making your choice: Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and use of your blood and tissue samples, you may still take part in the B-39/0413 study.

Indicate your choices by circling "Yes" or "No" after each statement.

1. My blood and tissue samples may be kept by the NSABP for use in future research to learn about, prevent, detect, or treat cancer.

YES

NO

2. My blood and tissue samples may be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

YES

NO

3. My study doctor (or someone he or she chooses) may contact me in the future to ask me to take part in more research.

YES

NO

Where can I get more information?

- You may call the National Cancer Institute's (NCI's) Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web Site at <http://cancer.gov>

For the NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials>

For the NCI's general information about cancer, go to: <http://cancer.gov/cancerinfo>

You may also visit the NSABP Web site at <http://www.nsabp.pitt.edu>

You will receive a copy of this form. If you want more information about this study, ask your study doctor.

(NSABP institutions may insert or attach a list of materials that they can provide locally to patients regarding clinical trials, radiation therapy information, the institution/investigator, and/or the NSABP.)

Signatures

I have been given a copy of all 13 pages of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this research study.

Date

Patient's signature

Date

Signature of person conducting the
informed consent discussion