SUMMARY OF CHANGES - PROTOCOL

For Protocol Amendment #3 to: NSABP B-51/RTOG 1304

NCI Protocol #: NSABP B-51
Local Protocol #: NSABP B-51/RTOG 1304

NCI Version Data: February 24, 2016

Protocol Title: A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy

#	Section	Page(s)	Change
1.	**NSABP B-51/RTOG 1304 Cover Page**	1 2	ClinicalTrials.gov NCT#01872975 was added. NCTN Participating Organizations information revised to include NRG Oncology in the list and to correct the reference to ECOG-ACRIN. Address for NRG Oncology and NRG Oncology Statistics and Data Management Center were updated. The NCI Version Date was changed from August 29, 2014, to February 24, 2016. The Document History table was updated to include Amendment #3.
2.	**Protocol Revision Record**	5	The Protocol Revision Record has been updated and includes the changes made in Amendment #3.
3.	**Information Resources**	10	Row 1, columns 2 and 3, NRG Oncology mailing and website addresses were updated. Row 4, column 3, CCD NSABP e-mail address updated to NRG Oncology e-mail address. Row 5, column 2: Study entry questions should be referred to the NRG Oncology Support Desk. Row 5, column 3: The contact information for the Support Desk was added. Reference to Patient Entry Guidelines was deleted. Row 9, column 3: Instruction for location of B-51/1304 Pathology Instructions was revised to include the CTSU member Web site. Row 10, column 2: NSABP Division of Pathology changed to NRG Oncology Biospecimen Bank – Pittsburgh. Row 10, column 3: Pathology NSABP e-mail address updated to NRG Oncology e-mail address.
4.	**Information Resources**	11	Row 1, column 3: The phone number for the AE Reporting Nurse was updated and the SAE Reporting NSABP e-mail address was updated to the NRG Oncology e-mail address. Row 2, column 3: Instruction for location of B-51/1304 Forms and Supporting Documents was revised to include the CTSU Member Web site.

#	Section	Page(s)	Change
5.	**Cancer Trials Support Unit**	12	Row 4, CCD NSABP e-mail address updated to NRG Oncology e-mail address. Row 3: Information updated to match CTSU template text. Row 6 deleted from revised version of the protocol as requested by CTSU.
6.	**1.0** **Figure 1**	15 16	Paragraph 4: The minimum number of weeks of neoadjuvant chemotherapy was changed to 8 weeks to allow the use of other chemotherapy regimens. The protocol was revised to no longer indicate a type of anti-HER2 therapy to be used for HER2-positive patients. Paragraph 5: The protocol was revised to no longer indicate a type of anti-HER2 therapy to be used for HER2-positive patients. Box 2: The minimum number of weeks of neoadjuvant chemotherapy was changed to 8 weeks to expand the choice of chemotherapy regimens. Footnote **: The footnote was revised to no longer indicate a type of anti-HER2 therapy to be used for HER2-positive patients.
7.	**4.1**	29	Paragraph 2: The number of cases to be submitted for credentialing has been changed from 3 cases to 1 case if the institution is using one technique. Two cases are required if the institution intends to use both 3DCRT and IMRT. Credentialing for Arm 1/Group 1 is no longer required. Paragraph 3: Information about the Arm 1/Group 1 CT datasets deleted because credentialing is no longer required.
8.	**4.3.1**	30-31	Time frame for submission of treatment plans for Arm 1/Group 1A patients via TRIAD changed from within 30 days of treatment initiation to 21 days, and review of treatment plans was changed from 30 days to 21 days. The number of "Deviation Unacceptable" reviews on quality assurance review was added. Paragraph 2 from 08/29/14 version of the protocol was deleted because Pre-Treatment Reviews will no longer be done.
9.	**4.4**	31	Last sentence about Pre-Treatment Reviews was deleted because Pre-Treatment Reviews are no longer being performed.
10.	**4.4.1 from 08/29/14 version**	31	Section 4.4.1 from the 08/29/14 version of the protocol has been deleted because Pre-Treatment Reviews are no longer being done. Subsequent section was renumbered.
11.	**4.4.1**	31	All Arm 2/Groups 2A and 2B cases will be reviewed and feedback given to the institution on the radiation quality. The time frame for submission of treatment plans was changed from 30 days to 21 days, and review of treatment plans was changed from 30 days to 21 days. The number of "Deviation Unacceptable" reviews on quality assurance review was added.
12.	**5.2.9**	33	The minimum number of weeks of neoadjuvant chemotherapy was changed to 8 weeks to allow the use of other chemotherapy regimens.

#	Section	Page(s)	Change
13.	5.2.11	33	The eligibility criterion was revised to no longer indicate a type of anti-HER2 therapy to be used for HER2-positive patients.
14.	5.2.17	34	The interval between last surgery and randomization or last chemotherapy treatment and randomization was extended from 56 days to 70 days to allow for patients who need additional time to recover from surgery or chemotherapy treatment.
15.	6.0 Table 2	36	Footnote f: Scanning requirements to rule out metastatic disease were revised for Stage II patients to allow imaging studies to be performed as clinically indicated at the investigator's discretion.
16.	6.0 Table 3	36	A clarification was made to footnote b for timing of exams and assessments according to Group.
17.	7.1 Table 4	37	Row 5: Instruction for location of B-51/1304 Pathology Instructions was revised to include the CTSU Member Web site.
18.	7.3	37	Paragraph 1: Instruction for location of B-51/1304 Pathology Instructions was revised to include the CTSU Member Web site.
19.	8.3.2	43	Text deleted regarding instructions for administering questionnaires because they are no longer available on the NSABP legacy website.
20.	8.4	44	The description of the BAHO patient population was revised to clarify those patients in the BAHO study consist of patients consecutively enrolled on the study.
21.	9.1 9.2 9.3 9.4 9.7	45 46	The protocol was revised to no longer indicate a type of anti-HER2 therapy to be used for HER2-positive patients.
22.	10.4.1	48	The treatment modalities allowed was clarified.
23.	10.4.4	48	The megavoltage photon beams with energies was changed from ≥ 6 MV to ≥ 4 MV. Megavoltage electron beams are required was moved to be 10.4.5. Proton beams are not allowed was moved to 10.4.6.
24.	10.6	49-50	Heading revised to clarify information described in Section 10.6. The following text was added to paragraph 1: "Using these consensus definitions for a guideline, target volume contours may vary some to fit the individual, specific case according to the treating physician's judgement."
25.	10.6 Table 5	51	Note added for clarification. Throughout Table 5, references to "62-64 Gy" were changed to "62 or 64 Gy" to clarify that there is not a range.
26.	10.6.5.1	58	Grammatical edits were made in #4 and #7.
27.	10.6.5.2	59	Paragraph 1: The goals of treatment planning were clarified to include other normal tissue organs in addition to the heart and lung. Paragraph 4: Changes in patient positioning are now allowed but discouraged. Instructions for re-planning are provided.

#	Section	Page(s)	Change
28.	**10.6.5.3**	59-60	Paragraph 1: The goals of treatment planning were clarified to include other normal tissue organs in addition to the heart and lung. Paragraph 2: PTV eval added for clarification. 60 Paragraph 1: Clarification made that boost radiation must be planned from the initial CT for radiation planning for Arm 2 cases. Compliance Criteria for Chestwall boost has been changed to Recommended Criteria. Some compliance criteria for chestwall boost have been deleted.
29.	**10.6.5.4**	60	Institutions may choose in some cases to combine the chestwall PTV and IMN PTV into one PTV.
30.	**10.7**	61	Paragraph 1: The dose-volume constraints for treatment plans have been divided into REQUIRED and RECOMMENDED. Treatment plans must meet the REQUIRED criteria while RECOMMENDED criteria should be used as a guide for treatment planning and will not be part of the scoring assessment of the data quality of the plans. Paragraph 3: Instructions on when institutions will be notified about plans whose DVH analysis does not meet Compliance Criteria were revised to delete information about Pre-Treatment Review.
31.	**10.10** **10.10 Tables 6A and 6B**	62 66-71	Paragraph 2: Information added to explain that there are REQIRED criteria for each target and normal tissue that will be used for scoring the radiation quality of the composite treatment plan. Information added to explain that there are RECOMMENDED guidelines for each target and organs at risk to assist with treatment planning and will not be used for scoring radiation quality. The information in Table 6 of the 08/29/14 version of the protocol has been split into Table 6A REQUIRED Compliance Criteria and Table 6B RECOMMENDED Compliance Criteria. Changes to the compliance criteria for each target and normal tissue listed in Sections 10.10.4 and 10.10.5 have been incorporated into the tables.
32.	**10.10.4** **10.10.5**	62-64 64-65	The compliance criteria for each target (new Section 10.10.4) and organ at risk (new Section 10.10.5) have been revised to include REQUIRED and RECOMMENDED. Please see the revised protocol for the details.
33.	**11.0**	72	Paragraph 1 deleted. Information required for AE reporting is included in Section 11.0.
34.	**11.3.5**	75	Bullet 2, hash mark 2: Location of the Pregnancy Information Form updated to include the CTEP Web site.
35.	**13.3.2**	81	Paragraph 1: Information added that permissions to view and download protocol and supporting documents are restricted based on information in CTSU RSS. Bullets 3-5: Bulleted instructions for obtaining the documents from the CTSU Web site have been revised.
36.	**13.7**	82	Paragraph 2: Information added that patient enrollment through OPEN initializes the patient in the Rave database.

#	Section	Page(s)	Change
37.	**14.2**	89	The Support Desk e-mail address updated to support@nrgoncology.org.
38.	**14.3**	89-90	Paragraphs 1and 2: RAVE information updated to text provided by CTSU.
		90	Bullet deleted. The Expected/Delinquency Report is no longer available on the NSABP website.
39.	**Sample Consent Form**		Consent form changes are outlined in the Summary of Changes for the consent form.

NRG ONCOLOGY
NSABP PROTOCOL B-51/RTOG PROTOCOL 1304

(ClinicalTrials.gov NCT#01872975)

A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG.

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Philadelphia, PA 19103
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NCI Version Date: February 24, 2016 (Replaces all other versions)

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NRG ONCOLOGY
NSABP PROTOCOL B-51/RTOG PROTOCOL 1304

A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy

Document History

	Version/Update Date	**Broadcast Date**
Amendment 3	February 24, 2016	June 30, 2016
Amendment 2	August 29, 2014	November 24, 2014
Update 1	April 16, 2014	June 12, 2014
Activation/Amendment 1	July 10, 2013	August 22, 2013
Pre-Activation	January 11, 2013	February 21, 2013

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PROTOCOL REVISION RECORD

Original Version: January 11, 2013

Amendment #1: July 10, 2013

NSABP B-51/RTOG 1304 Protocol amended prior to Protocol Activation.

Sections Changed/Deleted:

Cover Page
Information Resources
Section 3.0: 3.2.5
Section 10.0: 10.3.2, 10.3.3, 10.7, 10.10
Section 11.0: 11.5
Section 13.0: 13.5.1 and 13.5.2 have been deleted and subsequent sections renumbered
Section 15.0: 15.2
Appendix C: Pages 106-110
Sample Consent Form

Update #1: April 16, 2014

Sections Changed:

Throughout the protocol, the following have been changed:

- *The NSABP, RTOG, and the NSABP Operations Center were changed to NRG Oncology where appropriate.*
- *All references to NSABP Biostatistical Center have been changed to NRG Oncology Statistics and Data Management Center (SDMC).*
- *Division has been changed to Department throughout the protocol where appropriate.*
- *References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)."*

Cover Page
Information Resources
CTSU Address and Contact Information
Glossary of Selected Abbreviations and Acronyms
Section 4.0: 4.2, 4.5
Section 11.0: 11.3
Section 13.0: 13.1, 13.2, 13.3 were added; subsequent sections renumbered, 13.7
Section 14.0: 14.2, 14.3
Sample Consent Form

Amendment #2: August 25, 2014

Sections Changed/Deleted:

Cover Page
Information Resources
CTSU Address and Contact Information
Glossary of Selected Abbreviations and Acronyms
Section 1.0: 1.0
Section 4.0: 4.1, 4.2.1, 4.2.2, 4.3, 4.3.1, 4.4, 4.4.1, 4.4.2, 4.5
Section 5.0: 5.2.12, 5.2.14
Section 6.0: 6.0 (Tables 2 and 3)
Section 10.0: 10.0, 10.1.1, 10.1.2, 10.2.1, 10.2.2, 10.3.1, 10.3.2, 10.3.3, 10.3.4.1, 10.4.1, 10.6 (Table 5), 10.6.2.4, 10.6.3.4, 10.6.3.7, 10.6.4.2, 10.6.5, 10.6.5.2, 10.6.5.3, 10.6.5.4, 10.6.5.5 (deleted), 10.7, 10.9.1, 10.9.2, 10.9.3, 10.10 (Table 6)
Section 11.0: 11.2.3, 11.3, 11.3.5
Section 13.0: 13.1, 13.2, 13.3, 13.3.2, 13.3.3, 13.3.4, 13.3.5, 13.7
Section 14.0: 14.2, 14.3, 14.5.1, 14.5.2
Appendix B: 1.1 and 1.2 moved to Table 5, 2.1.1, 3.2.4, 3.3.3, 4.1.2, 4.1.4
Appendix C: Table deleted and moved to Section 10.10
Sample Consent Form

Amendment #3: February 24, 2016

Sections Changed/Deleted:

Cover Page
Information Resources
CTSU Address and Contact Information
Section 1.0: 1.0 (Figure 1)
Section 4.0: 4.1, 4.3.1, 4.4, 4.4.1
Section 5.0: 5.2.9, 5.2.11, 5.2.17
Section 6.0: 6.0 (Table 2 and Table 3)
Section 7.0: 7.1 (Table 4), 7.3
Section 8.0: 8.3.2, 8.4
Section 9.0: 9.1, 9.2, 9.3, 9.4, 9.7
Section 10.0: 10.4.1, 10.4.4, 10.6 (Table 5), 10.6.5.1, 10.6.5.2, 10.6.5.3, 10.6.5.4, 10.7, 10.10 (Tables 6A and 6B), 10.10.4, 10.10.5
Section 11.0: 11.0, 11.3.5
Section 13.0: 13.3.2, 13.7
Section 14.0: 14.2, 14.3
Sample Consent Form

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INFORMATION RESOURCES

Cooperative Group contact information	**NRG Oncology** Nova Tower 2 Two Allegheny Center – Suite 1200 Pittsburgh, PA 15212-5402 Phone: 412-339-5300 **NRG Oncology SDMC** One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 Phone: 412-624-2666 Fax: 412-624-1082 (General office) **http://www.nrgoncology.org**	**NRG Oncology** 1818 Market Street, Suite 1720 Philadelphia, PA 19103 Phone: 215-574-3189 (Web support) Phone: 215-574-3203 (Statistics) Fax: 215-928-0153 **http://www.nrgoncology.org**
Questions/problems regarding IRB review & informed consent	NRG Oncology Department of Regulatory Affairs	Phone: 412-339-5300 E-mail: regulatory@nsabp.org
Submission of IRB approval	CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103	Phone: 1-866-651-2878 Fax: 215-569-0206 E-mail: CTSURegulatory@ctsu.coccg.org
Questions concerning eligibility and clinical aspects of the trial	NRG Oncology Clinical Coordinating Department	Phone: 1-800-477-7227 E-mail: ccdpgh@nrgoncology.org
Study entry information (see Section 13.0)	NRG Oncology Support Desk	E-mail: support@nrgoncology.org
Questions regarding radiation therapy treatment planning	NRG Oncology RT Quality Assurance	Phone: 215-574-3219
Radiation therapy credentialing	IROC Houston QA Center	http://irochouston.mdanderson.org E-mail: irochouston@mdanderson.org Phone: 713-745-8989
Submission of electronic data for credentialing and case reviews and treatment data	TRIAD Support	http://www.rtog.org/CoreLab/TRIAD.aspx E-mail: TRIAD-Support@acr.org Phone: 703-390-9858
Submission of tumor blocks (see Section 7.1)	NRG Oncology SDMC One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 ***Note: When sending blocks, or other materials, please indicate on the package "Pathology specimens Enclosed."***	*Questions regarding receipt of specimens:* Phone: 412-624-2666 *For all other questions:* Phone: 412-697-6611 *Refer to the B-51/1304 Pathology and Correlative Science Instructions in the Members' Area of the NSABP Web site or the CTSU Member Web site.*
Arrangement for return of blocks that are not to be stored or to request kits for 2 mm core sampling of existing tumor/lymph node block(s)	NRG Oncology Biospecimen Bank-Pittsburgh	Phone: 412-697-6611 E-mail: nrgbiobankpgh@nrgoncology.org

INFORMATION RESOURCES (continued)

Questions concerning expedited adverse event reporting (see Section 11.3)	NRG Oncology SDMC B-51/1304 AE Reporting Nurse	Phone: 412-383-2557 Fax: 412-622-2113 E-mail: SAEReportingpgh@nrgoncology.org
Submission of patient-completed questionnaires (see Section 14.0)	NRG Oncology SDMC B-51/1304 Data Manager	Phone: 412-624-2666 Fax: 412-622-2115 *Refer to the B-51/1304 Forms and Supporting Documents page in the Members' Area of the NSABP Web site or the CTSU Member Web site.*
Questions concerning data management and Medidata Rave	NRG Oncology SDMC B-51/1304 Data Manager	Phone: 412-624-2666

CANCER TRIALS SUPPORT UNIT (CTSU)
ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data through Medidata Rave unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-2878 Fax: 215-569-0206 E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)	Patient enrollments will be conducted through the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Online Data Submission: B-51/1304 will use Medidata Rave for electronic data submission. Access Rave using your active CTEP-IAM user id and password at the following url: https://login.imedidata.com/selectlogin. Refer to Section 14.3 for specific instructions. Submit patient-completed questionnaires to NRG Oncology SDMC as directed on the worksheet. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submission.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility and treatment-related questions, contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccdpgh@nrgoncology.org. **For data submission questions**, contact the B-51/1304 Data Manager at the NRG Oncology SDMC by calling 412-624-2666.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or email: 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 Web site is located at https://www.ctsu.org.		

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS

3DCRT	three-dimensional conformal radiation therapy
AC	doxorubicin and cyclophosphamide
AE	adverse event
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
ATC	Advanced Technology Consortium
BAHO	Behavioral and Health Outcomes
BCTOS	Breast Cancer Treatment Outcome Scale
BID	twice a day
CAP	College of American Pathologists
CI	confidence interval
CPK	creatine phosphokinase
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTSU	Cancer Trials Support Unit
CTV	clinical target volume
DCIS	ductal carcinoma in situ
DFS-DCIS	disease-free survival-ductal carcinoma in situ
DRFI	distant recurrence-free interval
DVA	dose-volume analysis
DVH	dose-volume histogram
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
FNA	fine needle aspiration
FQ	Facility Questionnaire
GTV	gross tumor volume
H&E	hematoxylin and eosin
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IAM	Identity and Access Management
IBC-RFI	invasive breast cancer recurrence-free interval
IHC	immunohistochemistry
IMN	internal mammary node
IMRT	intensity modulated radiation therapy
IRB	Institutional Review Board
IROC	Imaging and Radiation Oncology Core
LCIS	lobular carcinoma in situ
LRR	loco-regional recurrence
LRRFI	loco-regional recurrence-free interval
MOS SF-36	Medical Outcomes Study Short-Form 36
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NCTN	National Clinical Trials Network

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS (continued)

NSABP	National Surgical Adjuvant Breast and Bowel Project
NTCP	normal tissue complication probability
OAR	organs at risk
OPEN	Oncology Patient Enrollment Network
OR	overall response
OS	overall survival
p	probability
pCR	pathologic complete response
PET	positron emission tomography
PgR	progesterone receptor
PO	by mouth
PRO	patient-reported outcome
PTV	planning target volume
PTV EVAL	planning target volume for evaluation
QA	quality assurance
QOL	quality of life
RTOG	Radiation Therapy Oncology Group
RTQA	Radiation Therapy-Quality Assurance
SAE	serious adverse event
SDMC	Statistics and Data Management Center
SFTP	Secure File Transfer Protocol
SPC	second primary cancer
WBI	whole breast irradiation
XRT	external radiation therapy

1.0 SUMMARY OF STUDY DESIGN

NSABP B-51/RTOG 1304, a Phase III, multicenter, randomized post neoadjuvant therapy trial, will evaluate whether the addition of chestwall and regional nodal external radiation therapy (XRT) after mastectomy or breast and regional nodal XRT after breast conserving surgery will significantly reduce the rate of events for invasive breast cancer recurrence-free interval in patients who present with histologically positive axillary nodes but convert to histologically negative axillary nodes following neoadjuvant chemotherapy.

Secondary aims include overall survival, loco-regional recurrence-free interval, distant recurrence-free interval, disease-free survival-ductal carcinoma in situ, and second primary cancer. The study will also look at quality of life issues related to arm function, arm and breast edema, cosmesis, pain, fatigue, and restricted work and social activity.

Patient must have clinically T1-3, N1 breast cancer at the time of diagnosis and must have had pathologic confirmation of axillary nodal involvement at presentation (before neoadjuvant therapy) based on either a positive FNA (demonstrating malignant cells) or positive core needle biopsy (demonstrating invasive adenocarcinoma).

Patients must have completed a minimum of 8 weeks of standard neoadjuvant chemotherapy consisting of an anthracycline and/or taxane-based regimen. Patients with HER2-positive tumors must have received neoadjuvant anti-HER2 therapy (either with all or with a portion of the neoadjuvant chemotherapy regimen), unless medically contraindicated.

After patients complete their neoadjuvant chemotherapy, they will have either a lumpectomy or a mastectomy. At the time of definitive surgery, all removed axillary nodes must be histologically free from cancer. ***Note: Patients found to be pathologically node positive by sentinel node biopsy alone should be approached regarding participation in the Alliance in Oncology study A011202 if the study is open at the investigator's institution.*** All patients will receive additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

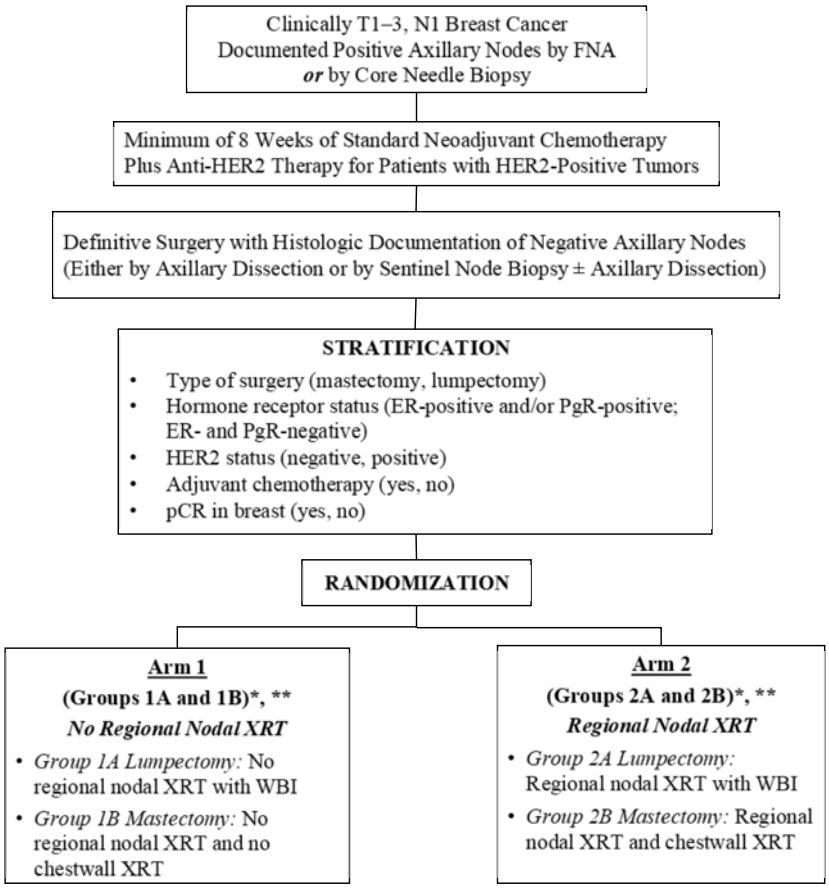
Mastectomy patients will be randomized to no XRT or to receive comprehensive XRT, which is radiation to the chestwall plus regional nodal areas. Lumpectomy patients will be randomized to receive standard whole breast XRT (no regional nodal XRT) or to receive comprehensive XRT, which is radiation to the breast plus regional nodal areas.

Tumor blocks must be submitted for correlative science studies, which will include examining the role of proliferation measures as a prognosticator for patients with residual disease after neoadjuvant chemotherapy and the development of predictors of the degree of reduction in loco-regional recurrence. Submission of a tumor sample from the primary breast tumor is a study requirement for all patients. A tumor block from any gross residual disease (**>** 0.5 cm) at the time of surgery is also required.

The Behavioral and Health Outcomes population will include 736 enrolled patients. Targeted patient-reported outcome instruments for arm function, arm and breast edema, cosmesis, pain, and fatigue will be used. In addition, disruption in everyday function (work, childcare, disability time) will be tracked, along with overall quality of life. Patients will complete assessments prior to randomization and at 3, 6, 12, and 24 months from randomization.

The B-51/1304 study will enroll 1636 patients over a period of 5 years. It is anticipated that the definitive analysis will be carried out approximately 7.5 years after study initiation.

Figure 1.
NSABP B-51/RTOG 1304 Schema



* Patients will be randomized to one of the following:

- **Arm 1**
  - **Radiation therapy for Group 1A**
    Whole breast irradiation + boost
  - **No radiation therapy for Group 1B**
- **Arm 2**
  - **Radiation therapy for Group 2A**
    Whole breast irradiation + boost and regional nodal irradiation
  - **Radiation therapy for Group 2B**
    Chest wall and regional nodal irradiation

** All patients will receive additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

2.0 BACKGROUND

2.1 Introduction

Decisions on the use of adjuvant chestwall + regional nodal radiotherapy (XRT) after mastectomy or regional nodal XRT after breast conserving surgery + breast XRT (WBI) are generally based on the pathologic nodal status at the time of surgical staging. Patients who have involved axillary nodes are generally recommended to receive XRT to the chestwall + regional nodal basins (after mastectomy) or to the breast + regional nodal basins (after lumpectomy). On the other hand, XRT for patients with negative axillary nodes is not typically recommended after mastectomy, and it is confined to the breast after breast conserving surgery.

In patients with large operable breast cancer, neoadjuvant chemotherapy has been consistently shown to down-stage primary breast tumors allowing for conversion of mastectomy candidates to candidates for breast conserving surgery. In addition, neoadjuvant chemotherapy has been shown to down-stage involved axillary nodes. With modern chemotherapy regimens (anthracycline- and taxane-containing regimens), it is estimated that about 40% of patients with involved axillary nodes at presentation would have pathologically negative axillary nodes at the time of surgery.[1] This proportion is estimated to be even higher in patients with triple-negative breast cancers and in those with HER-2 neu positive tumors who receive neoadjuvant chemotherapy + trastuzumab.[2,3]

Several randomized clinical trials and non-randomized studies have consistently shown that achievement of pathologic complete response (pCR) in the breast with negative axillary nodes is associated with excellent long-term outcomes both in terms of loco-regional recurrence (LRR) as well as distant recurrence.[4–6] With the increasing use of neoadjuvant chemotherapy, a commonly encountered clinical scenario involves patients who present with pathologically involved axillary nodes, receive neoadjuvant chemotherapy, and are found to be pathologically node-negative at the time of definitive surgery. For such patients, there is an active debate on the appropriate use (and extent) of loco-regional XRT after mastectomy or breast conserving surgery. On one hand, since these patients presented with known positive axillary nodes, they are at high-risk for LRR and should receive XRT to the chestwall and regional nodal basins (after mastectomy) or to regional nodal basins in addition to breast XRT (after lumpectomy). On the other hand, sterilization of involved axillary nodes by neoadjuvant chemotherapy lowers the risk for LRR making the need for XRT to the chestwall and regional nodal basins after mastectomy and to regional nodal basins (after lumpectomy) questionable. The decision of whether to add chestwall + regional nodal XRT in patients who have undergone mastectomy is further complicated by the desire of most patients to undergo immediate reconstruction at the time of mastectomy.

This active debate in the use of XRT is clearly shown in more recent NSABP neoadjuvant trials (NSABP B-40/B-41) where the use of XRT was left at the discretion of the treating physician. When we examined the rates of comprehensive loco-regional XRT used in these two NSABP protocols, we found that only 60% of lumpectomy patients who presented with clinically positive nodes and were found to have histologically negative nodes at the time of surgery received comprehensive breast and regional nodal XRT. Similarly, only 50% of mastectomy patients who presented with clinically positive nodes and were found to have histologically negative nodes at the time of surgery received comprehensive chestwall and regional nodal XRT. These data clearly highlight that there is no established standard of care for the use/extent of XRT in these patients.

The proposed clinical trial formally tests the hypothesis of whether the addition of chest wall + regional nodal XRT (after mastectomy) or regional nodal XRT (after lumpectomy), will improve outcomes in patients with operable breast cancer and positive axillary nodes at presentation whose axillary nodes convert to negative after neoadjuvant chemotherapy.

2.2 Evidence for using adjuvant XRT in patients with early-stage breast cancer

For patients with early-stage breast cancer who receive surgery as their initial treatment, there is abundant information on rates and predictors of LRR, with or without adjuvant systemic therapy.[7–10] This information has been used for decisions about the use of loco-regional XRT following mastectomy or the addition of regional nodal XRT following breast conserving surgery.

For patients treated with mastectomy, based on the available evidence from several randomized clinical trials and overview analyses,[11–15] chestwall and regional XRT has been shown to significantly reduce LRR and to significantly prolong overall survival for patients with positive axillary nodes. However, for patients with negative axillary nodes, the absolute reduction in LLR from post-mastectomy XRT was small, and there was no significant improvement in overall survival (OS).

For patients treated with breast conserving surgery, the addition of post-lumpectomy breast XRT has been shown to significantly reduce rates of breast cancer recurrence and to significantly reduce breast cancer specific mortality.[16] The effect of adding regional nodal XRT to breast XRT has not been formally tested (until more recently). By extrapolation from the post-mastectomy XRT trials, most clinicians would recommend adding regional nodal XRT to breast XRT for patients with 4 or more positive nodes but not in those with negative nodes. Debate exists on the need to add regional nodal XRT for patients with 1−3 positive nodes, although more recently, results from the NCIC MA.20 trial demonstrated that in lumpectomy patients with 1–3 positive nodes (some high-risk node-negative patients were also included), the addition of regional nodal XRT to breast XRT significantly reduced regional nodal recurrence and significantly prolonged disease-free survival (DFS) and distant disease-free survival (DDFS). Also, a non-significant trend in prolonging OS was shown with the addition of regional nodal XRT.[17] On the basis of the above results, chestwall and regional nodal XRT are commonly prescribed for mastectomy patients with positive axillary nodes, and regional nodal XRT in addition to breast XRT is rapidly gaining momentum for the majority of node-positive patients treated with lumpectomy.

The outcome data from the MA.20 trial challenge the traditional wisdom (as established by the Oxford Overview analyses) of a 4:1 ratio between the reduction in LRR and the reduction in distant recurrence. In the MA.20 trial, the addition of regional nodal radiation to breast radiation significantly lowered the risk of LRR and the risk of distant recurrence. However, the number of distant recurrence events prevented with the addition of regional nodal radiation (116-77=39) was larger than the number of LRR events prevented by the use of regional nodal radiation (48-29=19).[17] This can be the result of the fact that at times LRR may go undetected or can be detected only after distant recurrence has been diagnosed. The results of the MA.20 trial support our approach of using invasive breast cancer recurrence-free interval as our primary endpoint for the B-51/1304 trial.

2.3 Rationale for neoadjuvant chemotherapy

Neoadjuvant chemotherapy is the gold standard for patients with locally advanced breast cancer and a reasonable alternative to adjuvant chemotherapy in those with large operable disease. In randomized clinical trials, neoadjuvant chemotherapy has been found to be equally effective to adjuvant chemotherapy in prolonging DFS and OS and has some potential clinical advantages such as the conversion of mastectomy candidates to candidates for breast conserving surgery and the improvement in cosmesis by reducing the size of lumpectomy in patients who are breast conserving surgery candidates but present with large tumors. In addition, the consistent observation that achievement of pCR to neoadjuvant chemotherapy is associated with excellent long-term outcomes has brought forward the hypothesis that neoadjuvant chemotherapy can be used to reduce the extent of surgery in the axilla by down-staging involved axillary nodes and performing sentinel node biopsy alone and to reduce the extent of (or need for) loco-regional XRT by down-staging primary tumors and sterilizing involved axillary nodes. However, in contrast to the abundant information on LRR rates for patients treated with surgery first followed by adjuvant systemic therapy, there is limited information on rates and predictors of LRR in patients who receive neoadjuvant chemotherapy. The reason for this paucity of data is two-fold. First, considerably fewer patients with operable breast cancer are being treated with neoadjuvant vs. adjuvant chemotherapy. Second, by the time neoadjuvant chemotherapy became established as an alternative to adjuvant chemotherapy, the role of loco-regional XRT in patients with positive nodes was well-established. Thus, most available databases of patients treated with neoadjuvant chemotherapy include those who, at the discretion of the treating physician, were treated with postoperative XRT (because they either had pathologically positive nodes at surgery or because they were presumed to be node-positive before neoadjuvant chemotherapy). As a result of this paucity of data on patterns and rates of LRR, there is considerable debate on how to best treat with loco-regional XRT those patients who present with involved axillary nodes before neoadjuvant chemotherapy, and who are found to have negative axillary nodes after the neoadjuvant treatment.

2.4 The NSABP experience on rates and patterns of loco-regional recurrence in patients treated with neoadjuvant chemotherapy

Until the late 1990s, all National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant and neoadjuvant breast cancer clinical trials did not allow chestwall/regional nodal XRT after mastectomy or regional nodal XRT after breast-conserving surgery. This was because up until that time, there was no convincing evidence that XRT to those areas significantly improved OS, while it did increase morbidity. In fact, as late as 1995, a systematic review of randomized trials of XRT plus surgery vs. surgery alone for early breast cancer demonstrated that despite a three times lower rate of LRR with XRT plus surgery compared to surgery alone, there was no significant difference in 10-year survival.[11] Similar results were demonstrated in the 2000 update of the overview in which the long-term (10-year and 20-year) favorable and unfavorable effects of XRT were examined.[12] Only after a significant overall survival benefit with the addition of post-mastectomy XRT was demonstrated in the late 1990s for patients with positive nodes receiving adjuvant chemotherapy[13–15] was the addition of chestwall and regional nodal XRT after mastectomy and regional nodal XRT after breast conserving therapy allowed in subsequent NSABP trials. Before this change, the NSABP conducted two trials of neoadjuvant chemotherapy (NSABP B-18 and NSABP B-27). Data from these two trials provide us with the opportunity to examine the rates and patterns of LRR in patients treated with neoadjuvant chemotherapy as well as to identify independent predictors of LRR in this setting.

Between October 1988 and April 1993, 1523 patients in NSABP B-18 were randomized to receive either 4 cycles of neoadjuvant doxorubicin and cyclophosphamide (AC x 4) or the same chemotherapy given after surgery. Eligible patients had operable, palpable breast cancer (T1–3, N0–1, M0) diagnosed by fine needle aspiration (FNA) or core needle biopsy. Between December 1995 and December 2000, 2411 patients in NSABP B-27 were randomized to receive either 4 cycles of neoadjuvant AC or 4 cycles of neoadjuvant AC followed by 4 cycles of either neoadjuvant or adjuvant docetaxel. Eligible women had primary operable breast cancer (T1c–3, N0, M0 or T1–3, N1, M0) diagnosed by core biopsy or FNA. Stratification variables for both studies were age, clinical tumor size, and clinical nodal status. FNA results were used to establish eligibility; hormone receptor status was not available at randomization and was not used for stratification. In B-18, patients who were ≥ 50 years of age received tamoxifen (10 mg PO BID for 5 years) starting after chemotherapy, regardless of hormone receptor status. In B-27, all patients received tamoxifen (20 mg/day for 5 years) starting on the first day of chemotherapy regardless of hormone receptor status. In both studies, patients undergoing lumpectomy received breast XRT, but patients undergoing mastectomy received no XRT.

2.4.1 ***Incidence of LRR by protocol arm and in the B-18 and B-27 combined dataset***

The 10-year cumulative incidence of LRR was 14.3% and 12.2% in the neoadjuvant AC arms of B-18 and B-27, respectively (p=0.05). There was a significant reduction in the 10-year cumulative incidence of LRR with the addition of neoadjuvant docetaxel (8.5%, p=0.02 vs. the AC alone arm of B-27) and a nearly significant reduction with adjuvant docetaxel (9.5%, p=0.08 vs. the AC alone arm of B-27).[18]

In the combined dataset, the 10-year cumulative incidence of LRR was 11.1% for the entire cohort of patients (8.4% local and 2.7% regional). LRR incidence was 12.6% among 1947 patients treated with mastectomy (9.0% local and 3.6% regional) and 10.3% among 1100 patients treated with lumpectomy plus breast XRT (8.1% local and 2.2% regional). Thus, local recurrences accounted for 71% of 10-year LRR in patients treated with mastectomy and for 79% of 10-year LRR in patients treated with lumpectomy plus breast XRT.

2.4.2 ***Multivariate analyses of predictors of LRR in the B-18 and B-27 combined dataset***

Of the 3088 eligible patients with follow-up in the combined dataset, information on surgery type and all covariates was known in 2961 patients. In this cohort, age at randomization, clinical tumor size before neoadjuvant chemotherapy, clinical nodal status before neoadjuvant chemotherapy, and pathologic nodal status/pCR in the breast following neoadjuvant chemotherapy and surgery were significant independent predictors of LRR by multivariate analysis: age at randomization (≥ 50 yrs vs. < 50 yrs; HR=0.78 [0.63–0.98], p=0.03), clinical tumor size before neoadjuvant chemotherapy (> 5 cm vs. ≤ 5 cm; HR=1.51 [1.19–1.91], p=0.0007), clinical nodal status before neoadjuvant chemotherapy (positive vs. negative; HR=1.61 [1.28–2.02], p<0.0001), and pathologic breast tumor response/pathologic nodal status (node-negative/no Breast pCR vs. node-negative/Breast pCR; HR=1.55 [1.01–2.39] and node-positive vs. node-negative/Breast pCR (HR=2.71 [1.79–4.09], p<0.0001).[18]

Independent predictors of LRR were also evaluated separately for patients treated with mastectomy and for those treated with lumpectomy plus breast XRT. In the multivariate Cox proportional hazards model for patients treated with mastectomy, age was not a significant independent predictor of LRR, but clinical tumor size, clinical nodal status,

and pathologic breast tumor response/pathologic nodal status were significant predictors (Table 1). In the multivariate Cox proportional hazards model for patients treated with lumpectomy plus breast XRT, clinical tumor size was not a significant independent predictor of LRR, but age, clinical nodal status, and pathologic breast tumor response/pathologic nodal tumor response were significant independent predictors (Table 1).[18]

Table 1. Multivariate analysis of independent predictors of 10-year locoregional recurrence (LRR) according to type of surgery

Patients Treated with Mastectomy (1071 patients, 131 LRR Events)*		
Variable	**Hazard Ratio (95% CI)**	**P**
Clinical tumor size: > 5 vs. ≤ 5 cm†	1.58 (1.12–2.23)	0.0095
Clinical nodal status: cNode(+) vs. cNode(-)†	1.53 (1.08–2.18)	0.017
Breast/nodal pathologic status: ypNode(-)/No Breast pCR vs. ypNode(-)/Breast pCR†	2.21 (0.77–6.30)	
		0.0002
ypNode(+) vs. ypNode(-)/Breast pCR†	4.48 (1.64–12.21)	
Patients Treated with Lumpectomy Plus Breast XRT (1890 patients, 189 LRR Events)*		
Age: ≥ 50 vs. age < 50†	0.71 (0.53–0.96)	0.025
Clinical nodal status: cNode(+) vs. cNode(-)†	1.70 (1.26–2.31)	0.0005
Breast/nodal pathologic status: ypNode(-)/No Breast pCR vs. ypNode(-)/Breast pCR†	1.44 (0.90–2.33)	
		0.0006
ypNode(+) vs. ypNode(-)/Breast pCR†	2.25 (1.41–3.59)	

* Includes only patients for whom all covariates are known.
† Category used as baseline for comparison of risk.

2.4.3 ***Incidence of local and regional recurrence according to independent predictors***

The incidence of local, regional, and LRR was examined separately in patients treated with breast conserving surgery + breast XRT and in those treated with mastectomy, according to the independent predictors of LRR (Figures 2, 3, 4, and 5)

- *Patients treated with lumpectomy plus breast XRT*
  - *Ipsilateral breast tumor recurrence:* For patients treated with lumpectomy plus breast XRT, the majority of LRR were ipsilateral breast tumor recurrences (IBTR) with rates ranging from 5.2% to 8.7% in those ≥ 50 years of age and from 6.9% to 13.6% in those < 50 years (Figures 2 and 3). In patients ≥ 50 years of age, IBTR rates did not appear to be influenced by pathologic breast tumor response/pathologic nodal status or initial clinical nodal status (Figure 2) However, in patients < 50 years of age, there was a trend of increasing IBTR rates with decreasing pathologic breast tumor response and positive pathologic nodal status (Figure 3). For clinically node-negative patients, IBTR rates were 6.9%, 8%, and 10.5% for those with negative nodes/Breast pCR, negative nodes/no Breast pCR, and positive nodes, respectively.

For clinically node-positive patients, the respective IBTR rates were 7%, 10%, and 13.6% (Figure 3).[18]

- *Regional nodal recurrence:* Rates of regional nodal recurrence in patients treated with lumpectomy plus breast XRT were very low for patients with clinically negative nodes (0.5%–2.3%) and for those with clinically positive nodes but pathologically negative nodes at surgery (0–2.4%) (Figures 2 and 3). Pathologic breast tumor response/pathologic nodal status did not seem to influence rates of regional nodal recurrence in clinically node-negative patients, but in clinically node-positive patients the rates of regional recurrence were higher in patients who remained pathologically node-positive after neoadjuvant chemotherapy (7.5%–8.7%) (Figures 2 and 3).

Figure 2. 10-year cumulative incidence of LRR in patients ≥ 50 years of age treated with lumpectomy plus breast XRT

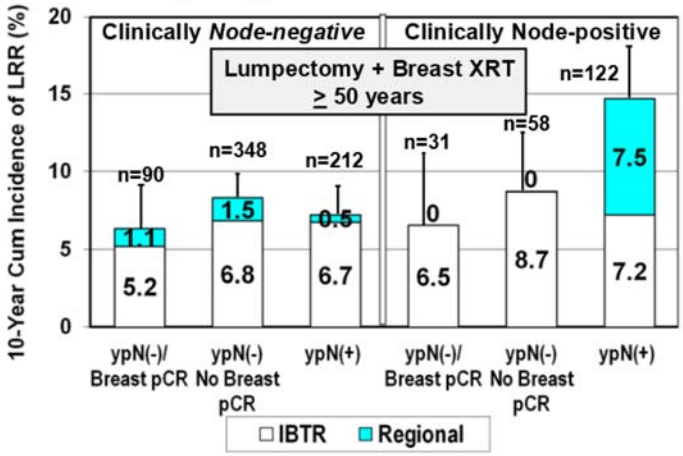
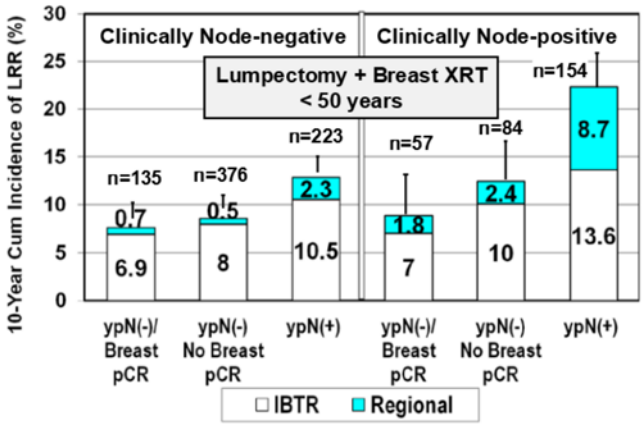


Figure 3. 10-year cumulative incidence of LRR in patients < 50 years of age treated with lumpectomy plus breast XRT



- *Patients treated with mastectomy*
  - *Chestwall recurrence:* Rates of chestwall recurrence generally increased with decreasing pathologic breast tumor response and positive pathologic nodal status, and this increase was more pronounced in patients with tumors > 5 cm compared to those ≤ 5 cm and in patients with clinically positive nodes compared to those with clinically negative nodes (Figures 4 and 5). Although the number of patients is low, chestwall recurrences after mastectomy were very infrequent in patients who achieved breast pCR with pathologic negative nodes irrespective of tumor size and clinical nodal status (1 local recurrence in 94 patients) (Figures 4 and 5).[18]
  - *Regional nodal recurrence:* Regional nodal recurrence rates were generally low in clinically node-negative patients irrespective of clinical tumor size (2.3%–4.3% in patients with tumors ≤ 5 cm and 2.3%–6.2% in those with tumors > 5 cm). Rates were higher for clinically node-positive patients, particularly if they remained pathologically node-positive at surgery (Figures 4 and 5).

Figure 4. 10-year cumulative incidence of LRR in patients with ≤ 5 cm tumors treated with mastectomy

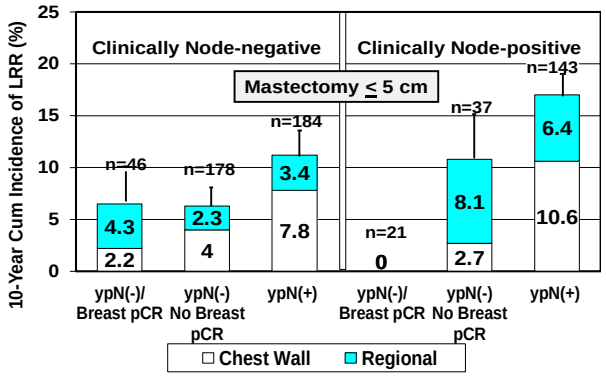
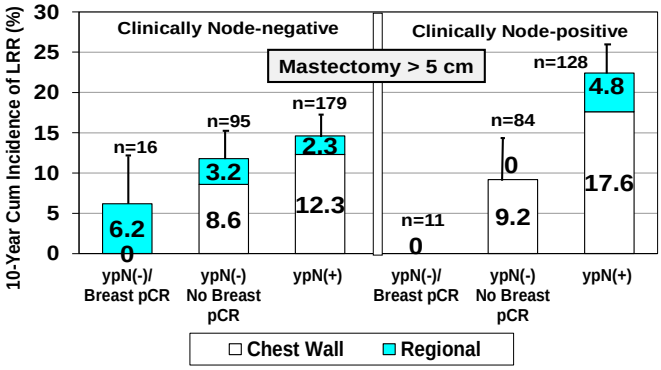


Figure 5. 10-year cumulative incidence of LRR in patients with > 5 cm tumors treated with mastectomy



2.4.4 *Rates of LRR according to number of pathologically positive nodes at surgery*

When rates of LRR for patients with pathologically positive nodes at surgery were examined according to the number of positive nodes (1–3 vs. ≥ 4), the rates were generally higher for those with ≥ 4 positive nodes vs. those with 1–3 positive nodes. However, based on the independent predictors of LRR, the rates of LRR were consistently above 10% for all subsets of patients with 1–3 positive nodes (with the exception of clinically node-negative patients ≥ 50 years of age treated with breast conserving surgery + XRT).[18]

The report of the B-18 and B-27 combined dataset describes the largest prospectively collected cohort of patients with operable breast cancer treated with neoadjuvant chemotherapy for which information of rates and patterns of LRR is available. Patients met predefined eligibility criteria and were uniformly monitored as part of the B-18 and B-27 neoadjuvant chemotherapy trials. The major strength of the data, however, is that the use of XRT was legislated by protocol and was not left to the discretion of the treating physician. Thus, patients undergoing mastectomy were not permitted to be treated with chestwall or regional nodal XRT, and patients treated with lumpectomy were required to receive breast XRT but were not permitted to receive additional regional nodal XRT, irrespective of the number of residual positive nodes at surgery or the original clinical nodal status or clinical tumor size before neoadjuvant chemotherapy. To that extent, the two trials provide us with a large cohort of patients for whom the natural history of LRR can be assessed without the confounding effects of non-uniform post-mastectomy chestwall radiation or radiation to regional nodal basins. One significant limitation of the study is the lack of information on ER, PgR, and HER2 neu status since the majority of these patients were diagnosed by FNA. Thus, it is still not clear to what extent pCR in the breast and sterilization of axillary nodes will influence the effect of subtypes on rates of LRR.

2.5 **Using neoadjuvant chemotherapy in order to tailor the use of loco-regional XRT**

The results of the combined analysis of B-18 and B-27 clearly demonstrate that in addition to age and clinical factors available before neoadjuvant chemotherapy (such as clinical tumor size and clinical nodal status), pathologic response in the breast and pathologic axillary nodal status have a major impact on the rates and patterns of LRR. The results further suggest that pCR in the breast with pathologically negative axillary nodes minimizes the effect of age, clinical tumor size, and clinical nodal status on the rates of LRR. Since clinical nodal status is a strong surrogate of pathologic nodal status, these results indicate that in patients treated with neoadjuvant chemotherapy, rates of LRR in patients who have positive nodes before neoadjuvant chemotherapy can be modified downwards if the nodes become pathologically node-negative after neoadjuvant chemotherapy (particularly if there is also pCR in the breast). Thus, patients who have positive axillary nodes at presentation (who would be candidates for post-mastectomy chestwall and regional nodal XRT or post-lumpectomy regional nodal XRT in addition to breast XRT) can potentially avoid XRT if they become pathologically node-negative after neoadjuvant chemotherapy. As there is active debate on the standard of care for such patients before either strategy becomes the standard of care, randomized clinical trial data are needed to demonstrate that the use of XRT (chestwall and regional nodal XRT for mastectomy patients and regional nodal XRT for lumpectomy patients) would significantly improve patient outcomes. The results of this proposed clinical trial have the potential to produce a major paradigm shift in the loco-regional management of early-stage breast cancer assuming the data demonstrate that the addition of XRT would not significantly improve outcomes in this originally high-risk group of

patients who significantly lower their risk of LRR by achieving pathologic down-staging of their axillary nodes by neoadjuvant chemotherapy. For this reason (to determine if the addition of XRT would significantly improve outcome and potentially lead to a paradigm shift), this study has been designed as a superiority trial.

2.6 Issues with post-mastectomy breast reconstruction and the use of post-mastectomy chestwall XRT

A major concern for patients who present with pathologically involved axillary nodes is that decisions for immediate breast reconstruction can be complicated by the need for chestwall and regional nodal XRT. Thus, for those patients the decision of whether to offer implant-based or autologous tissue breast reconstruction is one that requires careful consideration. The approach of a two-stage reconstruction with a tissue expander followed by a permanent breast implant after post-mastectomy XRT, consistently reveals high rates of acute and chronic complications and poor aesthetic outcomes (capsular contraction, pain, asymmetry, and need for implant replacement).[19] Also, placement of an autologous tissue flap at the time of primary surgery has the potential of flap contraction following the use of XRT. The approach of immediate-delayed reconstruction where an expander is placed at the time of surgery followed by deflation of the expander, chestwall XRT, and then, replacement of the expander with autologous flap reconstruction offers an acceptable solution to the problem but requires a second major surgical procedure. Thus, if one can avoid the need for XRT in a proportion of these node-positive patients by down-staging their nodes with neoadjuvant chemotherapy, it could possibly lead to a considerable improvement in the cosmetic outcome and quality of life of such patients.

The presence of a breast reconstruction has also been reported to compromise the planning of post-mastectomy radiation. Investigators at MD Anderson Cancer Center analyzed the adequacy of radiation dose delivery to women who had undergone immediate reconstruction versus those without reconstruction present post-mastectomy. It was demonstrated that almost half of the radiation plans were sub-optimal in the presence of an immediate reconstruction compared to when there was not a reconstruction present in terms of dose delivery to the chestwall and internal mammary nodes, and for minimization of dose to the lung and avoidance of the heart.[20] To avoid delivery of radiation that is potentially less effective and more toxic in reconstructed patients, it is important to identify sub-optimal radiation treatment plans. This requires the development of acceptance criteria for judging the adequacy of any given radiation treatment plan. Dose volume analysis (DVA) with CT-based conformal radiation methods, three-dimensional conformal radiation therapy (3DCRT), or intensity modulated radiation therapy (IMRT) makes this feasible.

2.7 Standardization of IMRT and 3DCRT for regional nodal XRT and dose volume analysis

It is known that the addition of regional nodal XRT with chestwall post-mastectomy or regional nodal XRT with breast XRT post-breast conserving surgery is associated with higher rates of toxicity. The NCIC MA.20 study demonstrated that women who received comprehensive regional nodal XRT + breast XRT compared to those who had breast XRT alone had higher rates of acute and delayed toxicity including radiation dermatitis, pneumonitis, dyspnea and lymphedema.[17] The toxicities reported in this study and all prior post-mastectomy radiation clinical trials evaluating regional nodal XRT reflect clinically directed or two-dimensional radiation planning for dose delivery. CT-based conformal radiation methods such as 3DCRT or IMRT allow DVA to be performed. Dose volume analyses quantitatively examine the dose delivery/distribution to the intended target and unintended normal tissue volumes. This provides a reliable means for comparing radiation treatments, and specifically, a method for quantifying

volume dose parameters for normal tissue and target volumes on radiation treatment plans that could avoid toxicity or predict efficacy.

Dose volume analyses in association with known toxicity outcomes are crucial components to more fully develop mathematical models that can predict normal tissue damage from radiation. The normal tissue complication probability (NTCP) can be calculated from the non-uniform dose distribution through an organ of interest in an integrative fashion.[21] As an example, previous studies have shown an increase in the number of nonfatal cardiac events associated with left-sided irradiation for breast cancer patients.[22–24] Ideally, at the time of the radiation plan evaluation, knowledge of the critical DVA parameters predictive of cardiac events based on NTCP could diminish its development. These models require DVA to quantify the partial organ irradiation. Modeling radiation induced heart disease is relatively limited in the literature due in large part to the lack of long-term results from 3D-based XRT in breast cancer.[21] The banking of radiation CT datasets and DVA in this trial will provide a means for developing NTCP for late radiation toxicities for regional nodal XRT post-mastectomy and breast conserving surgery that can impact all clinical practice.

One of the most important issues concerning IMRT and 3DCRT for breast cancer is the accurate definition of target and normal tissue volumes. Conventional radiation techniques for breast cancer used in all past clinical trials have been based predominantly on clinical palpation of breast tissue and bony anatomy. In contrast to standard techniques, IMRT and 3DCRT require a volume-based target to create conformal dose distributions. Since there may be a significant variation among physicians regarding the definitions of breast tissue target and regional nodal volumes, efforts to define accurately the location of boundaries of the breast tissue and lymph nodes are needed. A consensus committee within the RTOG has developed guidelines for the definition of clinical target volumes and normal structures on CT for radiation treatment planning. This atlas will be adopted for the definitions used in radiation treatment planning for this study.[25,26]

3.0 STUDY AIMS AND ENDPOINTS

3.1 Primary aim and endpoint

Aim: To evaluate whether the addition of chestwall + regional nodal XRT after mastectomy or breast + regional nodal XRT after breast conserving surgery will significantly reduce the rate of events for invasive breast cancer recurrence-free interval (IBC-RFI) in patients who present with histologically positive axillary nodes but convert to histologically negative axillary nodes following neoadjuvant chemotherapy.

Endpoint: IBC-RFI, defined as time from randomization until invasive local, regional, or distant recurrence, or death from breast cancer.

3.2 Secondary aims and endpoints

3.2.1 *Overall survival (OS)*

Aim: To evaluate whether the addition of chestwall + regional nodal XRT after mastectomy or breast + regional nodal XRT after breast conserving surgery will significantly prolong OS in patients who present with histologically positive axillary nodes but convert to histologically negative axillary nodes following neoadjuvant chemotherapy.

Endpoint: OS, defined as time from randomization to death from any cause.

3.2.2 *Loco-regional recurrence-free interval (LRRFI)*

Aim: To evaluate whether the addition of chestwall + regional nodal XRT after mastectomy or breast + regional nodal XRT after breast conserving surgery will significantly reduce the rates of events for LRRFI in patients who present with histologically positive axillary nodes but convert to histologically negative axillary nodes following neoadjuvant chemotherapy.

Endpoint: LRRFI, defined as the time from randomization to the recurrence of the primary breast cancer within the breast or in the lymph nodes in the ipsilateral axilla, infraclavicular fossa, or ipsilateral internal mammary chain without evidence of distant disease, or death due to breast cancer.

3.2.3 *Distant recurrence-free interval (DRFI)*

Aim: To evaluate whether the addition of chestwall + regional nodal XRT after mastectomy or breast + regional nodal XRT after breast conserving surgery will significantly reduce the rate of events for DRFI in patients who present with histologically positive axillary nodes but convert to histologically negative axillary nodes following neoadjuvant chemotherapy.

Endpoint: DRFI, defined as the time from randomization to the development of tumor in all areas beyond local or regional limits, or death due to breast cancer.

3.2.4 ***Disease-free survival-ductal carcinoma in situ (DFS-DCIS)***

Aim: To compare the rates of DFS-DCIS by treatment arm.

Endpoint: DFS-DCIS, defined as time from randomization to local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (invasive or DCIS), regional recurrence, distant recurrence, contralateral breast cancer (invasive or DCIS), second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colorectal carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer.

3.2.5 ***Second primary invasive cancer***

Aim: To compare the rates of second primary invasive cancer by treatment arm.

Endpoint: Second primary invasive cancer, defined as the time from randomization to the development of a second primary invasive cancer of any site excluding squamous and basal cell carcinoma of the skin.

3.2.6 ***Quality of life***

Aim: To compare the effect of adding XRT on the cosmetic outcomes in mastectomy patients who have had reconstruction.

Aim: To compare the effect of adding XRT on quality of life including arm problems, lymphedema, pain, and fatigue.

3.2.7 ***Toxicity***

Aim: To evaluate the toxicity associated with each of the radiation therapy regimens.

Endpoint: Frequencies of adverse events categorized using the NCI Common Terminology for Adverse Events Version 4.0 (CTCAE v4.0).

3.2.8 ***Treatment adequacy***

Aim: To determine whether CT-based conformal methods (IMRT and 3DCRT) for chestwall + regional nodal XRT post mastectomy and regional nodal XRT with breast XRT following breast conserving surgery are feasible in a multi-institutional setting and whether dose-volume analyses can be established to assess treatment adequacy and to develop normal tissue complication probabilities (NTCP) for the likelihood of toxicity.

3.2.9 ***Effect of XRT***

Aim: To compare the effect of XRT in patients receiving mastectomy and in patients receiving lumpectomy.

3.2.10 ***Molecular predictors of recurrence***

Aim: To examine the role of proliferation measures as a prognosticator for patients with residual disease after neoadjuvant chemotherapy.

Aim: To develop predictors of the degree of reduction in LRR.

4.0 RADIATION ONCOLOGY FACILITY CREDENTIALING AND QUALITY ASSURANCE

4.1 Pre-registration requirements for 3DCRT/IMRT treatment approach

In order to utilize either 3DCRT or IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the IROC Houston QA Center Web site. Visit http://irochouston.mdanderson.org and select "Credentialing".

This study will require each institution to submit a minimum of 1 case for credentialing (Arm 2/Groups 2A). If the institution is interested in treating patients using 3DCRT and IMRT, then two Arm 2/Group 2A Benchmark cases will need to be submitted, one planned using IMRT and the other 3DCRT. If the institution is interested in treating patients using 3DCRT only, then only 1 Arm 2/Group 2A Benchmark case will need to be submitted. When an institution has been credentialed for one technique only, and in the course of the trial, decides to add the other technique, the institution must do one more Benchmark case using the other technique. This Benchmark case **must** be submitted for Arm 2/Group 2A. Approval of this case will allow the institution to be credentialed in the new technique.

The Benchmark case is a treatment planning exercise. The Benchmark cases apply for both the 3DCRT and IMRT treatment modalities. CT scans for each case will be made available for downloading from the IROC Houston Web site http://irochouston.mdanderson.org, and the institution is expected to use this dataset to demonstrate their ability to generate an acceptable dose distribution. For Arm 2/Group 2A, the CT datasets will include contours of the breast and the supraclavicular, axillary, and internal mammary nodes. The planning results will be submitted electronically via TRIAD. For more information: ***http://www.rtog.org/CoreLab/TRIAD.aspx***. The results of this planning exercise will be examined and approved by IROC Houston before the first patient can be enrolled from a particular institution. Upon successful completion and approval of the Benchmark case, the NRG Oncology SDMC will notify the institution that they have completed this requirement.

4.2 Facility questionnaire and data submission

4.2.1 *Facility questionnaire*

The institution or investigator must complete the IROC Houston electronic Facility Questionnaire (FQ). The FQ should be updated with the most recent information about the institution. To access this FQ for review prior to enrolling any cases, contact IROC Houston via e-mail at irochouston@mdanderson.org to receive the FQ link.

4.2.2 *Data submission*

In order to submit the benchmark credentialing case and all digital data for registered patients, the institution site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user ID and password) used for the CTSU Members' Web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam. Information for establishing an account for digital data submission can be found at http://www.rtog.org/CoreLab/TRIAD.aspx. Upon review and successful completion of

all requirements, the NRG Oncology SDMC will notify the institution that they are eligible to enroll patients on the B-51/1304 study.

The quality assurance (QA) program will cover the delivery of both 3DCRT and IMRT. Each case will be submitted digitally via TRIAD where it will be processed and made available for review by study chairs or designees, and the IROC Houston or IROC Philadelphia RT Dosimetry Group.

Digital RT Data Submission to RTOG Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application, and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with CTEP and have a valid and active CTEP IAM account. Please see above for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG Oncology users should contact their site Lead RA to be added to the site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG Web site Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

4.3 Quality assurance for standard whole breast irradiation with boost (Arm 1/Group 1A)

During the review process, if the planned treatment modality for a patient is changed from the modality indicated at the time of randomization, the Data Manager at the NRG Oncology SDMC must be promptly notified of the change to allow the Review System to be updated. This is particularly important for Pre-Treatment Review cases because they determine which type of review is assigned to subsequent cases.

4.3.1 *Post-Treatment Reviews*

All Arm 1/Group 1A cases enrolled on the trial will be reviewed. The treatment plan must be submitted via TRIAD within 21 days of treatment initiation. These cases will be reviewed within the next 21 days with feedback given to the submitting radiation oncology facility. Institutions that receive 3 or greater "Deviation Unacceptable" on quality assurance review on any arm will be notified regarding their data quality.

4.4 Quality assurance for regional nodal irradiation + breast XRT or chestwall XRT (Arm 2/Groups 2A and 2B)

During the review process, if the planned treatment modality for a patient is changed from the modality indicated at the time of randomization, the Data Manager at the NRG Oncology SDMC must be promptly notified of the change to allow the Review System to be updated.

4.4.1 *Post-Treatment Reviews*

All Arm 2/Groups 2A and 2B cases enrolled on the trial will be reviewed and feedback given back to the institution on the radiation quality. The treatment plan must be submitted via TRIAD within 21 days of treatment initiation. These cases will be reviewed within the next 21 days with feedback given to the submitting radiation oncology facility. Institutions that receive 3 or greater "Deviation Unacceptable" on quality assurance review on any arm will be notified regarding their data quality.

5.0 PATIENT ELIGIBILITY AND INELIGIBILITY

5.1 Patient selection guidelines

Although the guidelines in Section 5.1 are not inclusion/exclusion criteria, investigators should consider each of these factors when selecting patients for the trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

- Patients should have a life expectancy of at least 10 years, excluding their diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)
- Women of reproductive potential must agree to use an effective non-hormonal method of contraception during radiation therapy.
- ***Submission of tumor samples is required for all patients*** (see Section 7.1). Therefore, the local pathology department policy regarding release of tumor samples must be considered in the screening process. Patients whose tumor samples are located in a pathology department that by policy will not submit any samples for research purposes should not be approached for participation in the B-51/1304 trial.

5.2 Conditions for patient eligibility

A patient cannot be considered eligible for this study unless all of the following conditions are met.

5.2.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

5.2.2 The patient must be female.

5.2.3 The patient must be ≥ 18 years old.

5.2.4 The patient must have an ECOG performance status of 0 or 1 (see Appendix A).

5.2.5 Patient must have clinically T_{1-3}, N_1 breast cancer at the time of diagnosis (before neoadjuvant therapy). Clinical axillary nodal involvement can be assessed by palpation, ultrasound, CT scan, MRI, PET scan, or PET/CT scan.

5.2.6 Patient must have had pathologic confirmation of ***axillary nodal involvement*** at presentation (before neoadjuvant therapy) based on either a positive FNA (demonstrating malignant cells) or positive core needle biopsy (demonstrating invasive adenocarcinoma). The FNA or core needle biopsy can be performed either by palpation or by image guidance. ***Documentation of axillary nodal positivity by sentinel node biopsy (before neoadjuvant therapy) is not permitted.***

5.2.7 Patients must have had ER analysis performed on the primary breast tumor before neoadjuvant therapy according to current ASCO/CAP Guideline Recommendations for hormone receptor testing. If negative for ER, assessment of PgR must also be performed according to current ASCO/CAP Guideline Recommendations for hormone receptor testing (http://www.asco.org).

5.2.8 Patients must have had HER2 testing performed on the primary breast tumor before neoadjuvant chemotherapy according to the current ASCO/CAP Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer (http://www.asco.org). Patients who have a primary tumor that is either HER2-positive or HER2-negative are eligible.

5.2.9 Patient must have completed a minimum of 8 weeks of standard ***neoadjuvant*** chemotherapy consisting of an anthracycline and/or taxane-based regimen.

5.2.10 For patients who receive ***adjuvant*** chemotherapy after surgery, a maximum of 12 weeks of intended chemotherapy may be administered but must be completed before randomization. (If treatment delays occur, chemotherapy must be completed within 14 weeks.) The dose and schedule of the adjuvant chemotherapy are at the investigator's discretion. ***Note: It is preferred that all intended chemotherapy be administered in the neoadjuvant setting.***

5.2.11 Patients with HER2-positive tumors must have received neoadjuvant anti-HER2 therapy (either with all or with a portion of the neoadjuvant chemotherapy regimen), unless medically contraindicated.

5.2.12 At the time of definitive surgery, all removed axillary nodes must be histologically free from cancer. Acceptable procedures for assessment of axillary nodal status at the time of surgery include:

- axillary node dissection;
- sentinel node biopsy alone provided that at least 2 sentinel lymph nodes are removed. Removal of at least 3 sentinel lymph nodes and use of dual tracer for lymphatic mapping are strongly recommended; or
- sentinel node biopsy followed by axillary node dissection.

Note: Patients are eligible whether there is residual invasive carcinoma in the surgical breast specimen or whether there is evidence of pathologic complete response.

*Patients who are found to be pathologically node-positive at the time of surgery, **based on sentinel node biopsy alone**, are candidates for A011202, a study developed by the Alliance in Oncology, an NCI Cooperative Group. If A011202 is open at the investigator's institution, patients should be approached about participating in the A011202 study.*

5.2.13 Patients with pathologic staging of $ypN0_{(i+)}$ or $ypN0_{(mol+)}$ are eligible.

5.2.14 Patient who have undergone either a total mastectomy or a lumpectomy are eligible. (Patients who have had a nipple-sparing mastectomy are eligible.)

5.2.15 For patients who undergo lumpectomy, the margins of the resected specimen or re-excision must be histologically free of invasive tumor and DCIS as determined by the local pathologist. Additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. (Patients with margins positive for LCIS are eligible without additional resection.)

5.2.16 For patients who undergo mastectomy, the margins must be histologically free of residual (microscopic or gross) tumor.

5.2.17 The interval between the last surgery for breast cancer (including re-excision of margins) and randomization must be no more than 70 days. Also, ***if adjuvant chemotherapy was administered***, the interval between the last chemotherapy treatment and randomization must be no more than 70 days.

5.2.18 The patient must have recovered from surgery with the incision completely healed and no signs of infection.

5.2.19 If adjuvant chemotherapy was administered, chemotherapy-related toxicity that may interfere with delivery of radiation therapy should have resolved.

5.3 **Conditions for patient ineligibility**

Patients with one or more of the following conditions are NOT eligible for this study.

5.3.1 Definitive clinical or radiologic evidence of metastatic disease.

5.3.2 T4 tumors including inflammatory breast cancer.

5.3.3 Documentation of axillary nodal positivity before neoadjuvant therapy by sentinel node biopsy alone.

5.3.4 N_2 or N_3 disease detected clinically or by imaging.

5.3.5 Patients with histologically positive axillary nodes post neoadjuvant therapy.

5.3.6 Patients with microscopic positive margins after definitive surgery.

5.3.7 Synchronous or previous contralateral invasive breast cancer or DCIS. (Patients with synchronous and/or previous contralateral LCIS are eligible.)

5.3.8 Any prior history, not including the index cancer, of ipsilateral invasive breast cancer or ipsilateral DCIS treated with radiation therapy. (Patients with synchronous or previous ipsilateral LCIS are eligible.)

5.3.9 History of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomization.

5.3.10 Any radiation therapy for the currently diagnosed breast cancer prior to randomization.

5.3.11 Any continued use of sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy. Patients are eligible if these medications are discontinued prior to randomization (see Section 5.1).

5.3.12 Prior breast or thoracic RT for any condition.

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

5.3.14 Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)***

5.3.15 Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.

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

6.0 REQUIREMENTS FOR ENTRY, TREATMENT, AND FOLLOW-UP

Tests, exams, and other assessments required prior to randomization are listed on Table 2. Requirements following randomization are outlined on Table.

Table 2. Tests, exams, and other requirements prior to randomization

Required Assessments	Prior to Randomization	
Determination of local pathology department's policy regarding submission of tumor samples (Section 5.1)	X	
Consent form signed by the patient	X	
Determination of hormone receptor status (before neoadjuvant therapy was given [Section 5.2.7])	X	
HER2 analysis (before neoadjuvant therapy was given [Section 5.2.8])	X	
Menopausal status	X**a**	
History & physical exam	X**b**	Within 4 weeks
Assessment of performance status (Appendix A)	X	
Height & weight	X	
CBC/differential/platelet count	X**c**	
Pregnancy test	X**d**	Within 2 weeks
Bilateral breast imaging	X**e**	Within 12 months
CT of chest/abdomen/pelvis ***and*** bone scan or PET/CT scan	X**f**	
BAHO (QOL/PROs) questionnaire	X**g**	Within 2 weeks
Tumor blocks (from primary breast tumor and from definitive surgery) requested from local pathology department (See Section 7.1)	X**h**	

a Menopausal status at the time of breast cancer diagnosis.
b Complete H&P by physician or other healthcare professional.
c Required for all patients. Note: For patients who receive adjuvant chemotherapy, testing must be done at least 3 weeks from the last dose of chemotherapy.
d *For women of childbearing potential:* Pregnancy testing should be performed according to institutional standards.
e MRI is permitted as a substitute for mammogram ***before entry*** (ultrasound is not). Imaging may be unilateral for patients who have had mastectomy with or without reconstruction.
f There must be no definitive radiologic evidence of metastatic disease on imaging performed between time of breast cancer diagnosis until randomization. Imaging studies for patients with stage II breast cancer should be performed as clinically indicated at the investigator's discretion.
g For patients who agree to participate in the QOL study, the BAHO questionnaire must be administered after the informed consent is signed but before randomization (see Section 8.4). The BAHO questionnaire must be submitted to the NRG Oncology SDMC within 30 days following randomization.
h ***Before study entry,*** the blocks must be requested and the pathology department must agree to release the required tumor materials as outlined in Section 7.1. ***(Submit required tumor materials within 90 days following randomization.)***

Table 3. Tests, exams, and other requirements during therapy and follow-up for Arm 1 and Arm 2

Required assessments[a]	**After randomization**	**End of RT (see footnote b)**	**6 months from randomization**	**12 months from randomization**	**18 and 24 months from randomization**	**Years 3 through 10 from randomization (every 12 months)**
History & physical exam[c]		X	X	X	X	X
Breast assessment/exam		X	X	X	X	X
Adverse event assessment		X[d]				
Bilateral mammogram				X[e]	X (24 months only)	X
BAHO (QOL/PROs) questionnaire		X[f]	X	X	X (24 months only)	
Tumor block submission	X[g]					

a H&P, scans, and other testing may be performed more frequently at the discretion of the investigator.

b ***Patients in Arm 1/Group 1B will have exams and assessments at 3 months after randomization.*** Patients in Arm 1/Group 1A and Arm 2/Groups 2A and 2B will have exams and assessments at the end of RT.

c Updated H&P with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.

d An adverse event assessment at end of RT and a final adverse event assessment 30 days after the last dose of radiation therapy must be done for patients in Group Arm 1/Group 1A and Arm 2/Groups 2A and 2B and at 3 months after randomization for patients in Arm 1/Group 1B; assessment may be based on office notes from other physician visits or telephone contact with the patient.

e ***Mammogram*** is required; unilateral for patients who have had mastectomy with or without reconstruction. First mammogram will be 1 year from the most recent mammogram (or MRI) performed prior to randomization and then every 12 months. (Mammograms may be performed more frequently at the discretion of the investigator.)

f Questionnaire administered at the end of RT for patients in Arm 1/Group 1A and Arm 2/Groups 2A and 2B and at 3 months after randomization for patients in Arm 1/Group 1B.

g Blocks from the diagnostic core biopsy and residual tumor (if gross residual disease **>** 0.5 cm) are ***required*** within 90 days (see Section 7.1).

NOTE: *Tests, exams, and assessments,* ***are not required*** *following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months through 24 months and then every 12 months from Year 3 through Year 10. (See Section 11.0 for adverse event reporting requirements.)*

7.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

7.1 Overview of requirements

Tumor sample submissions are a protocol requirement and, therefore, mandatory for participation in the study (see Table 4 for specific requirements). ***By signing the B-51/1304 consent form, the patient has agreed to tumor sample submissions.***

Table 4. Summary of B-51/1304 tumor sample submission requirements

Specimen requirements	After randomization
Paraffin block from the primary breast tumor *(A study requirement for all patients)*	Yes* (within 90 days)
Representative paraffin block of residual tumor > 0.5 cm *(A study requirement, if applicable)*	Yes* (within 90 days)
Diagnostic H&E slides	No

* If the pathology department refuses to provide a block for research purposes but will provide alternative tissue specimens, refer to the B-51/1304 Pathology and Correlative Science Instructions for alternative sample submission instructions.

NOTE: Refer to the Members' Area of the NSABP Web site or the CTSU Member Web site for the B-51/1304 Pathology and Correlative Science Instructions.

7.2 Use of specimens

The tumor samples collected in this study will be used for studies specified in the B-51/1304 protocol and for studies to be conducted in the future related to the purposes of the B-51/1304 study and not currently described in the protocol document.

Specific aims include testing the role of proliferation measures as a prognosticator for patients with residual disease after neoadjuvant therapy and to develop predictors of the degree of reduction in LRR. ***The procured specimens, including DNA samples derived from them, 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.*** Results of the correlative science studies will not be reported to the patient or her physician and will not have any bearing on her treatment.

7.3 Specimen submission and identification procedures

Refer to the B-51/1304 Pathology Instructions in the Members' Area of the NSABP Web site or the CTSU Member Web site for details regarding submission of specimens.

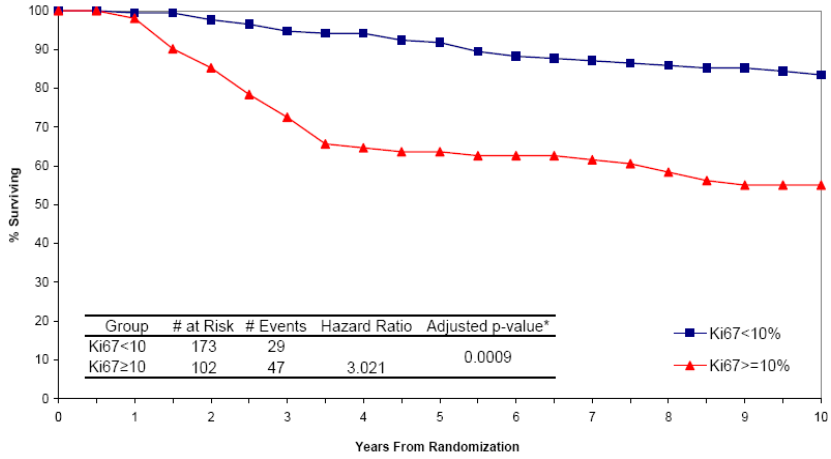
Submitted blocks are initially shipped to and logged into the database at the NRG Oncology SDMC. These samples are then stripped of patient identifiers except B-51/1304 Patient ID numbers and forwarded to the NSABP Division of Pathology where they are assigned a code number for further processing and study.

7.4 Hypotheses

- To examine the role of proliferation measures as a prognosticator for patients with residual disease after neoadjuvant chemotherapy.
- To develop predictors of the degree of reduction in LRR.

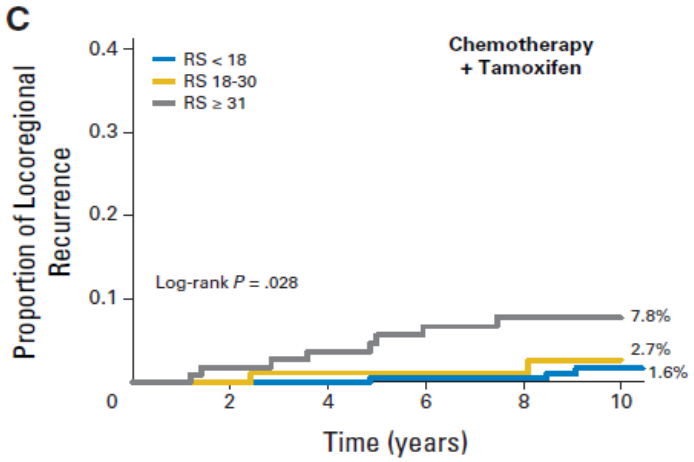
In B-27, ER expression by immunohistochemistry was as good a prognostic factor as the gene expression profile discovered through microarray analysis. Patients with residual disease had favorable prognosis if their pretreatment ER status was positive. However, with ER-positive tumors, Ki67 could identify high-risk patients independent of nodal status (Figure 6). Therefore, we can use pretreatment ER status by IHC, post-treatment Ki67 by IHC, and post-treatment nodal status to identify very high-risk patients among those with residual tumors after neoadjuvant chemotherapy. While we have not examined the B-27 data according to site of failure due to small sample size, we could hypothesize based on our experience with Recurrence Score that Ki67 may predict both loco-regional as well as distant recurrences.[27]

Figure 6. Survival of patients with residual disease after neoadjuvant chemotherapy according to Ki67 status



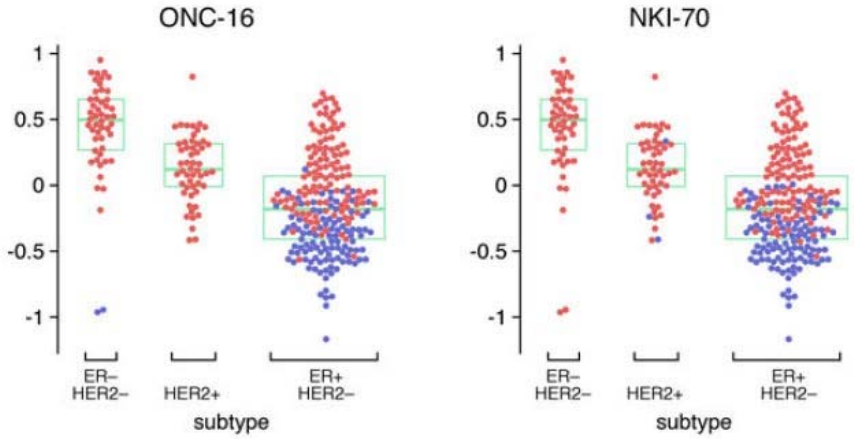
In B-14 and B-20, Recurrence Score was a significant predictor of loco-regional recurrences (Figure 7).[28] About one half of these patients received lumpectomy and radiotherapy.

Figure 7. LRR of patients from NSABP trial B-20 based on Recurrence Score



Meta-analyses of gene expression data by Wirapati et al. demonstrated that the main driver of Recurrence Score or other prognostic algorithms is the proliferation activity of tumor cells (Figure 8).[29] Therefore, it could be hypothesized that Ki67 will be strongly predictive of LRR after neoadjuvant chemotherapy.

Figure 8. Gene expression algorithms and proliferation activity



In Figure 8, the Y-axis represents proliferation score, and the red color represents cases with high risk classification by the algorithm. These data show that each algorithm identifies high-risk tumors among ER-positive/HER2-negative subsets based on their high proliferation activity.

Therefore, this trial will provide a good basis to test the prognostic role of Ki67 or other gene expression profiles assessed with residual tumor tissue. Furthermore, we will be able to test whether Ki67 or proliferation (or other) genes will be predictive of the degree of reduction in LRR.

We have significant experience using the NanoString platform to interrogate gene expression levels in formalin-fixed, paraffin-embedded samples.[30] We will use a custom-designed gene set of 800 genes that encompass all published prognostic genes, as well as genes associated with the apoptosis pathway. We have also developed a robust next-generation-sequencing-based digital gene expression method that can be readily applied to the residual tumor tissue collected from this study for a discovery approach. A separate protocol (to include analytical and statistical methodology) will be developed for use of the samples collected for the B-51/1304 study for marker assays (including exploratory high-throughput assays such as Nanostring) and submitted and approved in accordance with the National Clinical Trials Network.

8.0 BEHAVIORAL AND HEALTH OUTCOMES CORRELATIVE SCIENCE STUDY

8.1 Overview

Women who receive neoadjuvant therapy for breast cancer usually have more advanced disease and are hoping to obtain a clinical response that will permit breast conserving treatment. In addition to the biological benefits of a tumor and nodal response, conversion of positive pre-operative axillary nodal disease to a pathologically negative axilla may spare these women the need for combined modality therapy (i.e., surgery and radiation). The latter, while ensuring that any microscopic residual axillary disease is controlled, may lead to more extensive short and long-term morbidity, including reduced arm function, lymphedema, pain, greater fatigue (from addition of radiation if not necessary post-mastectomy), poorer cosmetic outcomes from breast reconstruction, greater time off from work, increased health care costs, and greater personal disruption from cancer treatment, which is extended over a longer period of time. Since the benefits of post-neoadjuvant radiation therapy are unknown at this time, the opportunity to study this question in a randomized trial provides an excellent opportunity for examining the impact of radiation therapy on symptoms and domains of quality of life that are very important to women. Integrating these health outcomes from the parent trial findings is essential. What are the human costs of additional radiation treatments in all women, as we will not know who is truly at risk for a local or regional recurrence? The goal of this correlative study is to answer this question. To accomplish this, we will collect patient-reported outcomes (PROs) prior to randomization to radiation or not, in both mastectomy and lumpectomy patients, and obtain follow-up data collection at 3, 6, 12, and 24 months after randomization. We will pay special attention to the impact of this treatment on women who have received immediate breast reconstruction as part of their mastectomy, as the cosmetic results of the reconstructive surgery may be affected by the addition of post-mastectomy chestwall irradiation (see Section 2.6). The 3-month/post-radiation therapy assessment is assumed to be the time of maximum impact in terms of inconvenience (for mastectomy patients who would not have received radiation) and the breast impact for those women who received reconstruction, specifically related to cosmetic issues and discomfort. Since a main focus of the BAHO study is the consequences of chestwall radiation on the mastectomy population who have received reconstruction, the 3-month/post-treatment evaluation comparing those with radiation to those who have no radiation, may be an essential data point and could be predictive of future cosmetic outcome assessed later in the follow-up.

NRG Oncology has extensive experience with the inclusion of quality of life (QOL) studies within its trials. Particularly relevant to this study concept is our past and ongoing work examining QOL outcomes in the local regional treatment of breast cancer. Specifically, in the NSABP B-32 trial that examined outcomes comparing sentinel node biopsy alone to sentinel node biopsy and axillary dissection, we were able to track PROs related to arm function, breast/chestwall and arm edema, pain, and QOL in over 700 women longitudinally for 36 months.[31] Our questionnaires were sensitive enough to detect significant differences between the two axillary treatment strategies, especially in the first 6 months. In addition, longitudinally, patients in the axillary dissection group were more likely to experience ipsilateral arm and breast symptoms, restricted work and social activity, and impaired QOL (all Ps ≤ 0.002).[31] Of note, our PRO data lined up extremely well with actual measures of arm range of motion and edema.[32] In addition, that evaluation demonstrated that women who had radiation afterwards had substantially increased odds of restricted shoulder motion (odds ratio 2.48) and lymphedema (odds ratio 3.47).[32] Thus, the addition of radiation therapy after axillary surgery will put women at substantially greater risk of these morbidities.

A more recent active NRG Oncology trial is NSABP B-39/RTOG 0413, which is examining breast cosmesis and function, comparing accelerated partial breast irradiation and standard whole breast therapy. We have excellent measures of cosmesis, arm function symptoms related to breast radiation, fatigue, pain, and disruption in everyday activities that have been completed by over 1000 women enrolled in the QOL study, followed for 36 months. The major validated scale being used in that trial is Stanton's Breast Cancer Treatment Outcome Scale (BCTOS), that was specifically designed to evaluate the cosmetic outcomes of breast conserving treatment with radiation.[33,34] Preliminary examination of the baseline results (pre-radiotherapy in B-39/0413 demonstrates excellent psychometric properties for the BCTOS. We expect that breast cosmetic concerns, as well as body image overall, will be relevant to all trial participants, but will be of most interest in answering the questions related to breast reconstruction in those women who have received mastectomy. The BCTOS scale approach will require minimal adaptation to be used in all patients, including mastectomy with or without reconstruction, for the B-51/1304 study.

In addition to using targeted PRO instruments for arm function, arm and breast edema, cosmesis, pain, and fatigue, we will track disruption in everyday function (work, childcare, disability time) related to the two strategies, along with overall QOL as measured by the MOS SF-36 and the EuroQol-5D (EQ-5D).[35–37] Fatigue will be measured with the Vitality scale from the MOS SF-36.[35]

8.2 Aims and hypotheses

8.2.1 *Primary aim*

To determine the effect of radiation therapy on cosmesis at 12 and 24 months after randomization among mastectomy patients who have had reconstructive surgery.

8.2.2 *Secondary aims*

- To compare the effect of adding XRT on the cosmetic outcomes in women who had a lumpectomy.
- To examine and compare the effect of XRT on the pattern of arm function, arm edema, pain, and breast/chestwall symptoms, as well as QOL, in women with mastectomy who are also receiving breast reconstruction.
- To explore the predictors of post-treatment arm problems and arm edema at 12 months, examining medical and demographic characteristics, as well as PROs at study entry.
- To explore the predictors of post-treatment fatigue at 12 months, examining medical and demographic characteristics, as well as PROs at study entry.
- To compare the effect of adding XRT on cosmetic outcomes evaluated at 24 months after randomization.

8.2.3 *Primary hypothesis*

Among mastectomy patients who have had reconstructive surgery, cosmetic results evaluated at 12 and 24 months after randomization will be worse for women assigned to radiation therapy compared to those assigned to the no radiation therapy group. (BCTOS scale will be used.)

8.2.4 *Secondary hypotheses*

- All patients assigned to radiation therapy will have greater problems with arm function, arm edema, breast/chestwall symptoms, pain, and restricted work and social activity at 12 months after randomization compared to those women without radiation. (NSABP B-32 scales will be used.)
- All patients assigned to radiation therapy will have greater post-treatment fatigue at 12 months after randomization compared to those women without radiation, as measured by the SF-36 Vitality scale.
- There will be no difference in overall QOL as measured by the SF-36 PCS and MCS scales (Physical and Mental Component Scales) at 12 and 24 months after randomization comparing those with breast conserving surgery who received radiation vs. those who did not.
- Mastectomy patients who do not receive radiation therapy will have a more rapid recovery at 12 months in SF-36 physical functioning and SF-36 vitality compared to those who receive radiation therapy.

8.3 **Administration of B-51/1304 patient-completed questionnaires**

8.3.1 *Time points for administration*

The B-51/1304 QOL questionnaire (Form QOL) will be administered at the following time points:

- Prior to randomization (after surgery/adjuvant chemotherapy): After the B-51/1304 consent form has been signed.
- Following randomization at:
  - 3 months for Arm 1/Group 1B or at the end of RT for Arm 1/Group 1A and Arm 2/Groups 2A and 2B
  - 6 months
  - 12 months
  - 24 months

8.3.2 *Administration instructions*

After the baseline, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of Form QOL may also be delayed. Form QOL should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are 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.

Patients who experience invasive breast cancer recurrence or invasive second primary cancer will not be expected to continue completing Form QOL. **Note:** Patients in Arm 1/Group 1A and Arm 2/Groups 2A and 2B who never initiate B-51/1304 study therapy or discontinue the study therapy for other reasons will be expected to continue completing Form QOL per protocol schedule.

If a patient declines to complete a scheduled Form QOL form or if the questionnaire is not completed for any other reason (and cannot be completed by phone or mail), a Missing Data Form for Quality of Life Questionnaire (Form QMD) should be submitted

online by the institution to the NRG Oncology SDMC. Completed questionnaires must be faxed to the NRG Oncology SDMC (see Information Resources).

8.4 BAHO patient population

PROs and QOL will be evaluated in 736 patients who read English, French, or Spanish consecutively enrolled on the B-51/1304 study, and who have completed the baseline questionnaire. If a patient chooses to not complete the baseline BAHO questionnaire or if completion of the baseline questionnaire is missed, the patient will not be included in the BAHO patient sample but will still be eligible for B-51/1304.

9.0 TREATMENT REGIMEN

- Radiation therapy must begin within 12 weeks of the last breast cancer surgery or the last dose of adjuvant chemotherapy.
- It is preferred that all intended chemotherapy be administered in the neoadjuvant setting. However, if adjuvant chemotherapy is administered, a maximum of 12 weeks of intended chemotherapy may be given. (If treatment delays occur, chemotherapy must be completed within 14 weeks.) Chemotherapy must be completed before randomization. The dose and schedule of adjuvant chemotherapy are at the investigator's discretion.

9.1 Arm 1/Group 1A

Patients who had a lumpectomy and are randomized to Arm 1/Group 1A will receive standard whole breast XRT as outlined in Section 10.0 and any additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

9.2 Arm 1/Group 1B

Patients who had a mastectomy and are randomized to Arm 1/Group 1B will not receive XRT but will receive any additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

9.3 Arm 2/Group 2A

Patients who had a lumpectomy and are randomized to Arm 2/Group 2A will receive comprehensive XRT, which is XRT to the breast plus regional nodal areas as outlined in Section 10.0 and any additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

9.4 Arm 2/Group 2B

Patients who had a mastectomy and are randomized to Arm 2/Group 2B will receive comprehensive XRT, which is XRT to the chestwall plus regional nodal areas as outlined in Section 10.0, in addition to any additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and anti-HER2 therapy for patients with breast cancer that is HER2-positive).

9.5 Breast surgery

- Surgery should be performed within 42 days after completion of neoadjuvant chemotherapy.
- Breast reconstructive surgery is permitted.

9.6 Adjuvant endocrine therapy

- Patients with ER-positive and/or PgR-positive tumors should receive a minimum of 5 years of endocrine therapy.

- Endocrine therapy may be initiated before, during, or after completion of XRT at the discretion of the investigator.
- LHRH agonist/antagonists (e.g., Lupron□ and Zoladex□) or ovarian ablation by surgery or RT are permitted for premenopausal patients.
- Adjuvant endocrine therapy should be administered according to the current ASCO guidelines (http://www.asco.org). However, selection of endocrine therapy will be at the investigator's discretion. The dose and schedule of endocrine therapy should be consistent with the drug package insert.

9.7 Anti-HER2 therapy

Anti-HER2 therapy is required for patients whose tumors are HER2-positive. It can be given either with all or with a portion of the neoadjuvant chemotherapy regimen with the remaining doses administered postoperatively at the investigator's discretion. Use of anti-HER2 therapy during radiotherapy is permitted.

9.8 Non-protocol therapy

Partial breast irradiation techniques ***are prohibited***.

9.9 Participation in other clinical trials

Contact the Clinical Coordinating Department (see Information Resources) to confirm that participation in another clinical trial (including supportive therapy trials) by a B-51/1304 patient is permitted.

10.0 RADIATION THERAPY

Note: Radiation therapy must begin within 12 weeks of the last breast cancer surgery or the last dose of adjuvant chemotherapy.

Note: The reader is referred to Section 4.0 to ensure that pre-registration requirements have been met before the institution is eligible to accrue patients.

Note: The reader is referred to the schema in Section 1.0 and to Sections 9.0 to 9.4 to help clarify the details of the radiation treatment.

10.1 Radiation therapy for Arm 1

10.1.1 *Post-lumpectomy (Arm 1/Group 1A)*

Post-lumpectomy patients are to receive whole breast irradiation only. Treatment will be delivered to the Breast Planning Target Volume (PTV) only with a boost to the Lumpectomy Cavity PTV. (In Arm 1/Group 1A, modification of the breast fields to specifically include the low axilla is not allowed.)

10.1.2 *Post-mastectomy (Arm 1/Group 1B)*

Patients who had a mastectomy and are randomized to Arm 1/Group 1B will not receive radiotherapy.

10.2 Radiation therapy for Arm 2

10.2.1 *Post-lumpectomy (Arm 2/Group 2A)*

Post-lumpectomy regional nodal irradiation and whole breast irradiation with boost are to be delivered to the following planning target volumes: undissected axilla, supraclavicular nodes, and internal mammary nodes in the first 3 intercostal spaces, and whole breast with a boost to the lumpectomy region.

10.2.2 *Post-mastectomy (Arm 2/Group 2B)*

Post-mastectomy radiation is to be delivered to the following planning target volumes: the chestwall, undissected axilla, supraclavicular nodes, and internal mammary nodes in the first 3 intercostal spaces. A boost to the scar region is to be delivered only when indicated (see Section 10.3.4.1 for details).

10.3 Dose specifications

10.3.1 *Post-lumpectomy whole breast irradiation with boost (Arm 1/Group 1A)*

10.3.1.1 *Breast:* 50 Gy in 25 fractions of 2 Gy

10.3.1.2 *Lumpectomy cavity:* Boost dose will be 12 or 14 Gy in 6 or 7 fractions of 2 Gy for cumulative total doses of 62 or 64 Gy

10.3.2 ***Post-mastectomy with no radiation therapy (Arm 1/Group 1B)***

Patients in Arm 1/Group 1B do not receive radiotherapy.

10.3.3 ***Post lumpectomy whole breast irradiation with boost + regional nodal irradiation (Arm 2/Group 2A)***

10.3.3.1 *Breast:* 50 Gy in 25 fractions of 2 Gy

10.3.3.2 *Lumpectomy cavity:* Boost dose will be 12 or 14 Gy in 6 or 7 fractions of 2 Gy for cumulative total doses of 62 or 64 Gy

10.3.3.3 *Undissected axilla, supraclavicular nodes, and internal mammary nodes:* 50 Gy in 25 fractions of 2 Gy

10.3.4 ***Post-mastectomy irradiation + regional nodal irradiation (Arm 2/Group 2B)***

10.3.4.1 *Chestwall: 50 Gy in 25 fractions of 2 Gy*

Chestwall boost - Permissible ONLY in cases with close (≤ 2 mm) surgical margins on the mastectomy specimen. Boost dose will be 12 or 14 Gy in 6 or 7 fractions of 2 Gy per investigator discretion for cumulative total doses of 62 or 64 Gy

10.3.4.2 *Undissected axilla, supraclavicular nodes, and internal mammary nodes:* 50 Gy in 25 fractions of 2 Gy

10.4 **Technical factors**

10.4.1 Allowed treatment modalities are 3D-CRT and IMRT. Electron beams can be used.

10.4.2 The guidelines for IMRT in this trial will conform to the policies set by the NCI (http://atc.wustl.edu/home/NCI/NCI_IMRT_Guidelines.html).

10.4.3 Each of the target volumes and normal structures listed below must be delineated on each slice from the 3D planning CT in which that structure exists.

10.4.4 Megavoltage photon beams with energies ≥ 4 MV are required.

10.4.5 Megavoltage electron beams are required.

10.4.6 Proton beams are not allowed.

10.5 **Localization, simulation, and immobilization**

10.5.1 Simulation and treatment may be performed with the patient in the supine or prone position post-lumpectomy for Arm 1/Group 1A and supine for Arm 2/Groups 2A and 2B.

10.5.2 Patients should be optimally positioned with alpha cradle casts, vac fix, breast boards, wing boards and/or other methods of immobilization at the discretion of the treating physician.

10.5.3 Methods to minimize the cardiac exposure to RT like heart block, gating, or breathhold are allowed at the discretion of the treating physician.

10.5.4 For post-lumpectomy large-breasted patients, including those with a large inframammary skin fold, devices to improve positioning of the breast and prone positioning are permissible.

10.5.5 A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV), planning target volumes (PTV), and Organs at Risk (OAR).

10.5.6 The CT required for generation of a virtual plan with 3DCRT or IMRT must be post-final surgery, either lumpectomy or mastectomy.

10.5.7 For post-lumpectomy (Arm 1/Group 1A and Arm 2/Group 2A) - Radio-opaque markers are to be placed on the patient skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the lumpectomy incision, 2) the outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock, and 3) the superior border of the breast tissue at 12 o'clock based on palpation. Note that on Arm 2/Group 2A this superior marker of the clinical extent of breast tissue can be at a different location than the match line between the breast and regional nodal irradiation fields.

10.5.8 For post-mastectomy (Arm 2/Group 2B) - Radio-opaque markers are to be placed on the patient skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the mastectomy scar, and 2) the clinical outline at least from 2 o'clock to 10 o'clock representing the physician's clinical assessment of the "at risk" chestwall which can include postoperative changes and where the ipsilateral breast previously was located. (Note: The position of the contralateral breast, if present, can be helpful.)

10.5.9 For patients that have an expander in place post-mastectomy for reconstruction, the amount of expansion during radiation is per the investigator's discretion. The position of the expander, ranging from collapsed to fully expanded, that is present at the time of acquisition of the CT scan for treatment planning must remain stable until the completion of radiotherapy.

10.5.10 The CT should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.5 cm should be employed.

10.5.11 External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

10.6 **Target and normal tissue volume definitions/treatment planning (See Appendix B for additional information)**

The definitions for the CTV, PTV, and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer http://www.rtog.org/corelab/contouringatlases/breastcanceratlas.aspx and the 1993 International Commission on Radiation Units and Measurements (ICRU) Report #50:

Prescribing, Recording And Reporting Photon Beam Therapy. Using these consensus definitions for a guideline, target volume contours may vary some to fit the individual, specific case according to the treating physician's judgment.

See Appendix B for Contouring Guidelines for Arm 1/Group 1A and Arm 2/Groups 2A and 2B.

The Target Volume **names** must be used exactly as they are in Table 5 when submitted via TRIAD. Resubmission will be required if they do not match exactly. The underscores are essential and the names are case sensitive.

Tables 5A and 5B. NSABP B-51/RTOG 1304 Structure Name List

*Note: All structures marked with the word **REQUIRED** in Tables 5A and 5B must be submitted for review with the exception of structures that do not apply for a particular case (see Section 10.10 for more detail).*

Table 5A. Structures list (Right Breast)

Target Volumes	Arm/Group	Dose Level/Gy	Description
Lumpectomy_R	Arm 1/1A & Arm 2/2A	62 or 64	The excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips **REQUIRED**
CTV_Lump_R	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy CTV **REQUIRED**
PTV_Lump_R	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy PTV **REQUIRED**
PTV_Lump_EVA_R	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy GTV Eval **REQUIRED**
CTV_WB_R	Arm 1/1A & Arm 2/2A	50	Breast CTV **REQUIRED**
PTV_WB_R	Arm 1/1A & Arm 2/2A	50	Breast PTV **REQUIRED**
PTV_WB_EVA_R	Arm 1/1A & Arm 2/2A	50	Breast PTV Eval **REQUIRED**
Scar_R	Arm 2/2B	62 or 64	Mastectomy Scar (only if applicable)
CTV_Scar_R	Arm 2/2B	62 or 64	Mastectomy Scar CTV (only if applicable)
PTV_Scar_R	Arm 2/2B	62 or 64	Mastectomy Scar PTV (only if applicable)
PTV_Scar_EVA_R	Arm 2/2B	62 or 64	Mastectomy Scar PTV Eval (only if applicable)
CTV_CW_R	Arm 2/2B	50	Chestwall CTV (only if applicable)
PTV_CW_R	Arm 2/2B	50	Chestwall PTV (only if applicable)
PTV_CW_EVA_R	Arm 2/2B	50 (or 62 or 64 if a boost is used)	Chestwall PTV Eval (62-64 is only for applicable cases)
CTVn_SCL_R	Arm 2/2A & 2B	50	Supraclavicular CTV (only if applicable)
PTVn_SCL_R	Arm 2/2A & 2B	50	Supraclavicular PTV (only if applicable)
CTVn_Ax_R	Arm 2/2A & 2B	50	Axillary CTV (only if applicable)
PTVn_Ax_R	Arm 2/2A & 2B	50	Axillary PTV (only if applicable)
CTVn_IMN_R	Arm 2/2A & 2B	50	Internal mammary nodal CTV (only if applicable)
PTVn_IMN_R	Arm 2/2A & 2B	50	Internal mammary nodal PTV (only if applicable)

Table 5A. Structures list (Right Breast) *(continued)*

Normal Tissue	Arm/Group	Dose Level/Gy	Description
LUNG_R	All		Ipsilateral lung **REQUIRED**
LUNG_L	All		Contralateral lung **REQUIRED**
Heart	All		Heart **REQUIRED**
Thyroid	All		Thyroid **REQUIRED**
BREAST_L	All		Contralateral Breast **REQUIRED**
External	All		External **REQUIRED**

Table 5B. Structures list (Left Breast)

Target Volumes	Arm/Group	Dose Level/Gy	Description
Lumpectomy_L	Arm 1/1A & Arm 2/2A	62 or 64	The excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips **REQUIRED**
CTV_Lump_L	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy CTV **REQUIRED**
PTV_Lump_L	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy PTV **REQUIRED**
PTV_Lump_EVA_L	Arm 1/1A & Arm 2/2A	62 or 64	Lumpectomy GTV Eval **REQUIRED**
CTV_WB_L	Arm 1/1A & Arm 2/2A	50	Breast CTV **REQUIRED**
PTV_WB_L	Arm 1/1A & Arm 2/2A	50	Breast PTV **REQUIRED**
PTV_WB_EVA_L	Arm 1/1A & Arm 2/2A	50	Breast PTV Eval **REQUIRED**
Scar_L	Arm 2/2B	62 or 64	Mastectomy Scar (only if applicable)
CTV_Scar_L	Arm 2/2B	62 or 64	Mastectomy Scar CTV (only if applicable)
PTV_Scar_L	Arm 2/2B	62 or 64	Mastectomy Scar PTV (only if applicable)
PTV_Scar_EVA_L	Arm 2/2B	62 or 64	Mastectomy Scar PTV Eval (only if applicable)
CTV_CW_L	Arm 2/2B	50	Chestwall CTV (only if applicable)
PTV_CW_L	Arm 2/2B	50	Chestwall PTV (only if applicable)
PTV_CW_EVA_L	Arm 2/2B	50 (or 62 or 64 if a boost is used)	Chestwall PTV Eval (62 or 64 is only for applicable cases)

CTVn_SCL_L	Arm 2/2A & 2B	50	Supraclavicular CTV (only if applicable)
PTVn_SCL_L	Arm 2/2A & 2B	50	Supraclavicular PTV (only if applicable)
CTVn_Ax_L	Arm 2/2A & 2B	50	Axillary CTV (only if applicable)
PTVn_Ax_L	Arm 2/2A & 2B	50	Axillary PTV (only if applicable)
CTVn_IMN_L	Arm 2/2A & 2B	50	Internal mammary nodal CTV (only if applicable)
PTVn_IMN_L	Arm 2/2A & 2B	50	Internal mammary nodal PTV (only if applicable)
Normal Tissue	Arm/Group	Dose Level/Gy	Description
LUNG_R	All		Contralateral lung **REQUIRED**
LUNG_L	All		Ipsilateral lung **REQUIRED**
Heart	All		Heart **REQUIRED**
Thyroid	All		Thyroid **REQUIRED**
BREAST_R	All		Contralateral Breast **REQUIRED**
External	All		External **REQUIRED**

See Section 10.6.1 for more detailed information.

10.6.1 ***Normal structures (Organs at Risk – OAR):***

10.6.1.1 *Ipsilateral lung:* This may be contoured with auto-segmentation with manual verification.

10.6.1.2 *Contralateral lung:* This may be contoured with auto-segmentation with manual verification.

10.6.1.3 *Heart:* This is to be contoured on all cases-not just the left-sided. The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

10.6.1.4 *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.

10.6.1.5 *Contralateral breast*

The contralateral breast can be at risk for exposure to excess inadvertent dosing, particularly in cases of very medially located lumpectomy sites in Arm 1/Group 1A and the inclusion of the IMN PTV for Arm 2/Groups 2A and 2B. Therefore dose to the contralateral breast will be constrained in the treatment planning.

Includes the apparent CT glandular breast tissue visualized by CT and consensus definitions regarding "breast" of anatomical borders from the RTOG Breast Atlas. In general the borders are:

Posterior border: At the anterior surface of the pectoralis, serratous anterior muscles excluding chestwall, ribs, boney thorax, and lung/heart

Medial border: The sternal-costal junction

Lateral border: Varies based on the size of the breast but typically is at the mid-axillary line and excludes the ipsilateral lattisimus dorsi muscle

Cephald border: First or second rib medially

Caudal:border: Inframammary fold or inferior extent of the breast on CT

Anterior border: Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface

10.6.2 ***Breast target volumes post-lumpectomy (Arm 1/Group 1A and Arm 2/Group 2A)***

Lumpectomy volumes:

10.6.2.1 *Lumpectomy Gross Target Volume (GTV)*: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended).

10.6.2.2 *Lumpectomy Clinical Target Volume (CTV)*: Lumpectomy GTV + 1 cm 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient's pathology.

10.6.2.3 *Lumpectomy Planning Target Volume (PTV)*: Lumpectomy CTV + 7 mm 3D expansion (excludes heart).

10.6.2.4 *Lumpectomy PTV Eval*: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval which is edited. This Lumpectomy 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 the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chestwall, pectoralis muscles, and lung) when pertinent. The lumpectomy PTV should not cross midline. This Lumpectomy PTV Eval is the structure used for DVH analysis. This Lumpectomy PTV Eval should not be used for beam aperture generation.

Breast volumes:

10.6.2.5 *Breast CTV:* Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see Section 10.5), the apparent CT glandular and fatty breast tissue visualized by CT, consensus definitions of anatomical borders from the RTOG Breast Cancer Atlas, and should include the Lumpectomy CTV (Section 10.6.2.2). The Breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chestwall, boney thorax, and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the Breast CTV unless clinically warranted by the patient's pathology. RTOG anatomy consensus guidelines are available at: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

10.6.2.6 *Breast PTV:* Breast CTV + 7 mm 3D expansion (excludes heart and does not cross midline).

10.6.2.7 *Breast PTV Eval:* The Breast PTV Eval is intended to exclude the portion of the Breast PTV that extends outside the patient or into the boney thorax and lungs. The Breast PTV is copied to a Breast PTV Eval which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient 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 posteriorly is limited to no deeper than the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis.

10.6.3 ***Chestwall target volumes post-mastectomy (Arm 2/Group 2B)***

10.6.3.1 *Mastectomy Scar:* Around the mastectomy scar is a common location for chestwall recurrences post-mastectomy. To help reproducibility in the design and evaluation of post-mastectomy radiotherapy treatment plans, an initial clinical target volume for the mastectomy scar will be created. The Mastectomy Scar will first be contoured by delineating the radiopaque wire placed over the scar at CT simulation as a surrogate of the scar and including any visible postoperative changes on CT in the subcutaneous tissue deep to the wire per the investigator's discretion.

10.6.3.2 *Mastectomy Scar CTV:* Mastectomy Scar and associated surgical change + 1 cm 3D expansion. Limit the CTV expansion posteriorly at anterior surface of the ribs and anterolaterally at skin and should not cross midline.

*(**NOTE:** Occasionally, the Mastectomy Scar location will lead to a CTV that does cross midline. The investigator will have to assess clinically whether adequate radiation can be delivered if the Mastectomy Scar CTV is truncated at midline. If it is felt that the Mastectomy Scar CTV must cross midline – this case may have significant challenges in meeting Compliance Criteria for this protocol and might not be suitable for enrollment.)*

10.6.3.3 *Mastectomy Scar PTV:* Mastectomy Scar CTV + 7 mm 3D expansion (excludes heart).

10.6.3.4 *Mastectomy Scar PTV Eval:* Since a substantial part of the Mastectomy Scar PTV often extends outside the patient – a Mastectomy Scar PTV Eval is

created. This Mastectomy Scar PTV Eval is limited to exclude the part that extends outside the ipsilateral body/chestwall and the first 2-3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to exclude lung and heart. The Mastectomy Scar PTV Eval should not cross midline and should be contained within the borders of the Chestwall PTV Eval. This is the structure used for DVH constraints, analysis, and compliance.

*(**NOTE:** Occasionally, the Mastectomy Scar location will lead to a CTV and PTV Eval that does cross midline. The investigator will have to assess clinically whether adequate radiation can be delivered if the Mastectomy Scar CTV and PTV Eval is truncated at midline. If it is felt that the Mastectomy Scar CTV and PTV Eval must cross midline – this case may have significant challenges in meeting Compliance Criteria for this protocol and might not be suitable for enrollment.)*

10.6.3.5 *Chestwall CTV:* Includes the Mastectomy Scar CTV, and takes into account the radiopaque markers placed at CT identifying clinical extent of chestwall, surgical changes visualized by CT, and consensus definitions of anatomical borders of chestwall from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

The Chestwall CTV is limited by the skin anteriorly and should not extend deeper than the ribs so that it excludes the lung and heart. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum medially and the axilla deep to anterior surface of the pectoralis major muscle laterally. In general, the chestwall CTV should not cross midline.

Expanders, implants, or autologous tissue present for reconstruction will be included in the Chestwall CTV. The degree of expander expansion present is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation.

10.6.3.6 *Chestwall PTV:* Chestwall CTV + 7 mm 3D expansion (excludes heart and does not cross midline).

10.6.3.7 *Chestwall PTV Eval:* As a part of the Chestwall PTV often extends outside the patient, the Chestwall PTV is then copied to a Chestwall PTV Eval which is edited. This Chestwall PTV Eval is limited anteriorly to exclude the part outside the patient and the first 2-3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. In general, the Chestwall CTV should not cross midline. This Chestwall PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

*(**NOTE:** Occasionally the Mastectomy Scar location will lead to a Chestwall CTV and PTV Eval that does cross midline. The investigator will have to assess clinically whether adequate radiation can be delivered if the Chestwall CTV and PTV Eval is truncated at midline. If it is felt that the Chestwall CTV*

and PTV Eval must cross midline – this case may have significant challenges in meeting Compliance Criteria for this protocol and might not be suitable for enrollment.)

10.6.4 ***Regional nodal target volumes (Arm 2/Groups 2A and 2B)***

10.6.4.1 *Supraclavicular CTV:* Based on consensus definitions from RTOG Breast Cancer Atlas. Superior extent typically is below the level of the cricoid; medially excludes thyroid, trachea, and esophagus. The lateral border extends to the lateral edge of the sternocleidomastoid muscle superiorly and the clavicle at its more inferior extent, and the inferior border extends to the caudal aspect of the clavicular head.

10.6.4.2 *Supraclavicular PTV*: Supraclavicular CTV + 5 mm margin in all directions. The following structures should be excluded from the Supraclavicular PTV to minimize excess dose to normal tissues: ipsilateral thyroid, trachea, esophagus, ipsilateral lung, and skin minus 5 mm. This means that some or all of the medial border of the Supraclavicular CTV and PTV will be similar. The Supraclavicular PTV should exclude the vertebral body and skin plus 5 mm.

10.6.4.3 *Axillary CTV:* The extent of axilla to be targeted for regional nodal irradiation will depend on the extent of axillary surgery performed. The axillary CTV consists of the portion of the axilla that remains "undissected." When an axillary node dissection has been done, the inferior border of the axillary CTV will be the most cephalic extent of the dissection. Review of the operative report, postoperative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the Axillary CTV. Axillary dissection typically removes level 1–2 axillary nodes, so that the Axillary CTV in these cases is expected to include level 3 primarily and some of level 2 of the axilla. When a sentinel node biopsy alone is done without completion axillary dissection, the axillary CTV will then include all 3 levels of the axilla as all three levels are "undissected." The consensus definitions for anatomical borders of the axillary levels are from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

10.6.4.4 *Axillary PTV:* Axillary CTV + 5 mm. The ipsilateral lung should be excluded from the Axillary PTV. This means that some or all of the medial border of the Axillary PTV can be similar to the Axillary CTV.

10.6.4.5 *Internal mammary node (IMN) CTV:* Includes the internal mammary/thoracic vessels in the first three intercostal spaces.

10.6.4.6 *Internal mammary node (IMN) PTV:* The IMN CTV + 5 mm medially, laterally, superiorly, and inferiorly. The IMN PTV is limited medially to not extend into the sternum. In order to minimize excess normal tissue irradiation, no additional expansion of the IMN CTV into the lung or heart should be done for the IMN PTV. The deep edge for the IMN PTV will be similar to the IMN CTV. No anterior expansion of the CTV into the chestwall or breast volumes will be done.

10.6.5 ***Treatment planning (See Appendix B for additional information)***

CT-based planning with tissue inhomogeneity correction is required.

10.6.5.1 *IMRT or 3D-CRT are permitted*

The following definitions and conditions are applied concerning IMRT in this protocol:

1. The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints.
2. The plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose-volume constraints are met and at least 3 apertures for each beam direction are used.
3. If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam as defined in Section 10.6.5.1 (1) should deliver > 50% of the total number of monitor units for the beam orientation.
4. If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, a 3D composite dose distribution and DVHs should be generated.
5. All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and-shoot, VMAT, tomotherapy) are allowed and classified as IMRT as long as target and critical structure dose-volume constraints are met.
6. IMRT planning and delivery systems using physical beam-intensity compensators designed by an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.
7. A patient-specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

All plans that do not fit into the above definitions and conditions are classified as 3DCRT plans. Specifically:

- The plans generated using forward-planning methods or segmental techniques such as "field-in-field" to meet dose-volume constraints are considered as 3DCRT plans. These forward-planned or segmental treatment techniques are those intended to mainly improve the uniformity of the dose distribution but not to produce steep dose gradients to protect critical structures (e.g., heart or lung).
- The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms

10.6.5.2 *Whole breast plus boost radiation therapy (Arm 1/Group 1A and Arm 2/Group 2A)*

Whole breast plus boost irradiation alone is used in Arm 1/Group 1A and with regional nodal irradiation in Arm 2/Group 2A. The Breast PTV is used to generate the beam apertures with an additional margin to take into account penumbra. Fields should include all of the Breast PTV and boost PTV. The aperture margin generally needed beyond the PTV is 5 mm. The goals of treatment planning are to encompass the breast PTV and minimize inclusion of the heart and lung and other normal tissue organs.

Field arrangements for 3DCRT and IMRT irradiation of the Breast PTV are at the discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the Breast PTV and normal tissues outlined in Section 10.10 under Compliance Criteria. Treatment planning can include the use of respiratory motion control such as gating or deep inspiration breast hold (DIBH), as necessary.

The lumpectomy boost may be given by either electron beam or photon beams using either 3DCRT or IMRT. A composite dose distribution and DVHs that include whole breast irradiation using either IMRT or 3DCRT and lumpectomy cavity boost using electron beams, IMRT or 3DCRT must be completed and provided for review. Simultaneous integrated boost using IMRT is not allowed. Brachytherapy boost is not allowed.

Boost radiation must be planned from the initial CT for radiation planning. Changes in patient positioning for the boost are discouraged. If re-planning is done due to a change in lumpectomy cavity volume, or other patient issue, another CT plan should be submitted to demonstrate that compliance criteria are still met by the re-plan. If electron boost is used, there must be adequate dosimetric coverage of the Lumpectomy PTV Eval.

10.6.5.3 *Chestwall with or without reconstruction radiation therapy (Arm 2/Group 2B)*

The goals of treatment planning are to encompass the Chestwall PTV (and regional node targets) and minimize inclusion of the heart and lung and other normal tissues. Field arrangements for 3DCRT and IMRT are at the discretion of the treating physician. Multiple beam arrangements that use photons alone of various or mixed energies or in combination with electrons are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the Chestwall PTV and normal tissues outlined in Section 10.10 under Compliance Criteria. Treatment planning can include the use of respiratory motion control such as gating or deep inspiration breast hold (DIBH), as necessary.

In those cases where an expander is in place for purposes of breast reconstruction, there can be a metal port that will need to be taken into account in the radiation treatment planning. Every attempt should be made to acquire the correct density of the expander port so correct modeling can be accomplished. Beam arrangements are to be designed in these cases so that the

dose to the chestwall PTV eval is considered "Per Protocol" or "Variation Acceptable" on DVH analysis (see Section 10.10).

In general, there will be no boost for the chestwall post-mastectomy. For cases with close surgical margins on the mastectomy specimen (e.g., ≤ 2 mm), the treating physician can elect to deliver a chestwall boost (see Section 10.3.4.1). For ARM 2 cases, boost radiation must be planned from the initial CT for radiation planning. A composite dose distribution and DVHs that include chestwall irradiation using either IMRT or 3DCRT and chestwall boost using electron beams, IMRT or 3DCRT must be completed and provided for review to evaluate for adherence to Compliance Criteria (see Section 10.10). Simultaneous integrated boost using IMRT is not allowed. Brachytherapy boost is not allowed. Changes in patient positioning for the boost are not allowed. If electron boost is used, the dose will be 12 or 14 Gy in 6 or 7 fractions of 2 Gy and, there must be adequate dosimetric coverage of the Mastectomy Scar PTV Eval on the plan composite dose volume analysis. The Recommended Criteria for Chestwall boost are:

- ***Per Protocol:*** At least 95% of the Mastectomy Scar PTV Eval will receive 58.9 or 60.8 Gy which is 95% of the cumulative boost prescribed dose of 62 or 64 Gy for the additional 6 or 7 fractions

  Variation Acceptable: At least 90% of the Mastectomy Scar PTV Eval will receive 55.8 or 57.6 Gy which is 90% of the cumulative boost prescribed dose of 62 or 64 Gy

10.6.5.4 *Regional nodal radiation therapy (Arm 1/Group 1A and Arm 2/Group 2B)*

The goals of treatment planning are to encompass the supraclavicular, axillary and internal mammary node targets along with the Breast PTV eval in Arm 1/Group 1A and the Chestwall PTV eval in Arm 2/Group 2B, respectively, and minimize inclusion of the heart and lung. Field arrangements for 3D conformal and IMRT are at the discretion of the treating physician. When planning with IMRT, it is recommended to create an additional structure that includes the SCL-PTV and the Axilla-PTV for optimization. In some, but not all cases, it can be helpful to combine the chestwall PTV and IMN PTV into one PTV. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal composite plan that meets the dose-volume Compliance Criteria in Section 10.10 on the supraclavicular, axillary, and internal mammary node PTVs with either the Breast PTV (Arm 2/Group 2A) or the Chestwall PTV (Arm 2/Group 2B), respectively, and normal tissues outlined below. In particular, for inclusion of the internal mammary nodes with either the chestwall or breast, there are multiple known field arrangement methods, (e.g., partially wide tangents, combined photon and electron fields, "Danish Technique," IMRT, etc.). These or any other treatment approach is permissible as long as the plan evaluation demonstrates that the goals for dose coverage of the supraclavicular, axillary, internal mammary node targets, Breast PTV (Arm 2/Group 2A) or the Chestwall PTV (Arm 2/Group 2B), respectively, and the normal tissue meet Compliance Criteria (see Section 10.10).

10.7 Required dose-volume histogram (DVH) analysis

The composite treatment plan for the whole breast with boost in Arm 1/Group 1A, whole breast with boost and regional nodal irradiation in Arm 2/Group 2A, and chestwall and regional nodal irradiation (with boost when used) in Arm 2/Group 2B must be done prior to the start of irradiation. Every plan will undergo a Quality Assurance Review as outlined in Section 4.3 and Section 4.4 and must meet the REQUIRED dose-volume constraints listed in Section 10.10 under Compliance Criteria and in Table 6A. There are **Recommended** dose-volume constraints listed in Section 10.10 and in Table 6B as a guide for treatment planning. The **Recommended** constraints will not be part of scoring for assessment of the plans data quality on post-treatment review.

All **maximum doses** should be defined in one dose calculation voxel, e.g., 3 mm x 3 mm x 3 mm or 0.03 cm^3.

The institution will be notified when 3 plans whose DVH analysis does not meet the Compliance Criteria defined in Section 10.10 and are labeled "Deviation Unacceptable" on Quality Assurance review occur. If 3 plans are labeled "Deviation Unacceptable" on a Post-Treatment Review, the institution will notified of problems with radiation quality.

10.8 Skin bolus

Skin bolus is not allowed on the intact breast in Arm 1/Group 1A or Arm 2/Group 2A. The use of skin bolus for post-mastectomy irradiation in Arm 2/Group 2B is per the treating physician's discretion. If using bolus, the skin dose should follow the same constraints as the Chestwall PTV Eval.

10.9 Treatment verification

10.9.1 *Before first treatment*

Portal films or images of each 3DCRT beam and an orthogonal pair for all patients must be obtained and approved by a physician prior to initiation of treatment. For IMRT, orthogonal films or 3D images (e.g., conebeam CT [CBCT], MV CT, kV CT) are required to document verification of isocenter.

10.9.2 *Subsequent images or films*

At the minimum, orthogonal pair films or treatment images must be obtained prior to fraction number 5 and every 5 fractions subsequently. The imaging modality, frequency, and process should be performed based on the institutional guidelines. Orthogonal pair images or 3D images may be obtained before every fraction depending on the clinical situation and the complexity of the radiotherapy plan.

10.9.3 *Documentation requirements*

Please refer to Information Resources for data submission.

10.10 **Compliance Criteria**

The composite treatment plan for the whole breast with boost in Arm 1/Group 1A, whole breast with boost and regional nodal irradiation in Arm 2/Group 2A, and chestwall and regional nodal irradiation in Arm 2/Group 2B will be reviewed for adherence to the following Compliance Criteria. In Arm 2/Group 2B, a chestwall boost is indicated only when there are close surgical margins, and in this case, the submitted composite plan should include the chestwall with boost and regional nodal irradiation.

There are **REQUIRED** Compliance Criteria for each target and normal tissue that will be used for scoring the radiation quality of the composite treatment plan. There are also **Recommended** dose guidelines listed below to assist with treatment planning. These will be not used for scoring the radiation quality but will be collected for later evaluation of the submitted dose distribution. In order to perform this later analysis of the dose distribution, all applicable contours listed in Tables 5A and 5B must be submitted regardless of being marked as **REQUIRED**.

All treatment plans will be submitted for Quality Assurance Review per Protocol Section 4.3 and Section 4.4. DVHs for the target volumes and designated normal structures will be compared to determine protocol compliance according to the following rules based on the parameters below:

10.10.1 *Per Protocol*: All specified DVH requirements identified as *Per Protocol* have been met.

10.10.2 *Variation Acceptable*: Specified DVH requirements within the *Variation Acceptable* have been met.

10.10.3 *Deviation Unacceptable*: Specified DVH requirements for *Variation Acceptable* are **not** met.

10.10.4 **TARGETS**

See Tables 6A and 6B for the following compliance criteria for each arm presented in a table format.

Chestwall or Breast PTV Eval:

REQUIRED Compliance Criteria:

Per Protocol: At least 95% of the Chestwall or Breast PTV Eval will receive 47.5 Gy which is 95% of the chestwall or breast prescribed dose of 50 Gy

Variation Acceptable: At least 90% of the Chestwall or Breast PTV Eval will receive 45 Gy which is 90% of the whole breast prescribed dose of 50 Gy

RECOMMENDED Treatment Planning Guidelines:

Ideally, no more than 50% of the volume of Breast PTV Eval will receive 56 Gy which is 112% of the prescribed dose of 50 Gy when a boost is included in the composite plan DVH

Ideally, no more than 35% of the Breast/Chestwall PTV Eval will receive 100% of the ***boost*** prescribed dose of 62 or 64 Gy

Maximum point doses listed below are for a volume that is 0.03 cm^3:

- **Arm 1/Group 1A**
  Ideally, the maximum point dose is recommended to be ≤ 120% of the prescription chestwall or whole breast dose, i.e., no more than 60 Gy for a prescribed dose of 50 Gy. The maximum dose should be evaluated without boost fields.

- **Arm 2/Groups 2A and 2B**
  Ideally, the maximum point dose when photons only are used for a composite plan that includes the Chestwall or Breast PTV Eval and IMN PTV is no more than 120% of the prescription chestwall or whole breast dose, i.e., no more than 60 Gy for a prescribed dose of 50 Gy

  The maximum dose to the Chestwall PTV Eval or Breast PTV Eval should be evaluated without the contribution of the boost fields.

  Ideally the maximum point dose when electron and photons are mixed for a composite plan that includes the Chestwall or Breast PTV Eval and IMN PTV is no more than 130% of the prescription chestwall or whole breast dose, i.e., no more than 65 Gy for a prescribed dose of 50 Gy **OR** no more than 10 cm^3 of composite plan receives 130% of the prescription chestwall or whole breast dose, i.e., no more than 65 Gy for a prescribed dose of 50 Gy

Optional constraint: Conformity Index (CI) for Arm 1/Group 1A: defined as "the ratio of the volume covered by the 95% prescription isodose over the volume of Breast PTV Eval."
Ideally: $0.95 \leq CI \leq 2.0$ *up to* $0.85 \leq CI \leq 2.5$

Lumpectomy PTV Eval:

Arm 1/Group 1A and Arm 2/Group 2A

REQUIRED Compliance Criteria:

Per Protocol: At least 95% of the Lumpectomy PTV Eval will receive 58.9 or 60.8 Gy which is 95% of the cumulative boost prescribed dose of either 62 or 64 Gy

Variation Acceptable: At least 90% of the Lumpectomy PTV Eval will receive 55.8 or 57.6 Gy which is 90% of the cumulative boost prescribed dose of either 62 or 64 Gy

RECOMMENDED Treatment Planning Guidelines:

Ideally, no more than 10% of the Lumpectomy PTV Eval will receive 68.2 or 70.4 Gy which is 110% of the boost prescribed dose of 62 or 64 Gy, respectively.

Ideally, the **maximum point dose** (*volume that is 0.03 cm^3*) will be no more than 74.4 or 76.8 Gy or no more than 120% of the boost prescribed dose of 62 or 64 Gy, respectively.

Supraclavicular (SCL) PTV:

REQUIRED Compliance Criteria:

Per Protocol: At least 95% of the SCL PTV will receive 47.5 Gy which is 95% of the prescribed dose of 50 Gy

Variation Acceptable: At least 90% of the SCL PTV will receive 45 Gy which is 90% of the prescribed dose of 50 Gy

RECOMMENDED Treatment Planning Guidelines:

Ideally, the maximum point dose (*volume that is 0.03 cm*^{3}) will be no more than 57.5 Gy which is 115% of the SCL prescribed dose of 50 Gy

Axillary PTV:

REQUIRED Compliance Criteria:

Per Protocol: At least 95% of the Axillary PTV will receive 47.5 Gy which is 95% of the prescribed dose of 50 Gy

Variation Acceptable: At least 90% of the Axillary PTV will receive 45 Gy which is 90% of the prescribed dose of 50 Gy

RECOMMENDED Treatment Planning Guidelines:

Ideally, the **maximum point dose** (*volume that is 0.03 cm*^{3}) will be no more than 57.5 Gy which is 115% of the Axillary prescribed dose of 50 Gy

Internal mammary nodal (IMN) PTV:

REQUIRED Compliance Criteria:

Per Protocol: At least 95% of the IMN PTV will receive 45 Gy which is 90% of the prescribed dose of 50 Gy

Variation Acceptable: At least 90% of the IMN PTV will receive 40 Gy which is 80% of the prescribed dose of 50 Gy

RECOMMENDED Treatment Planning Guidelines:

Ideally, the **maximum point dose** will be no more than 57.5 Gy which is 115% of the IMN prescribed dose of 50 Gy

10.10.5 **ORGANS AT RISK (OAR)**

Ipsilateral lung:

- **Arm 1/Group 1A**

  REQUIRED Compliance Criteria:

  Per Protocol: No more than 15% of the ipsilateral lung should receive 20 Gy
  Variation Acceptable: No more than 20% of the ipsilateral lung should receive 20 Gy

- **Arm 2/Groups 2A and 2B**

  REQUIRED Compliance Criteria:

  Per Protocol: No more than 35% of the ipsilateral lung should receive 20 Gy
  Variation Acceptable: No more than 40% of the ipsilateral lung should receive 20 Gy

  RECOMMENDED Treatment Planning Guidelines:
  Ideally, no more than 65% of the ipsilateral lung should receive 10 Gy
  Ideally, no more than 75%% of the ipsilateral lung should receive 5 Gy

Contralateral lung (Both arms):

RECOMMENDED Treatment Planning Guidelines:

Ideally, no more than 15% of the contralateral lung should receive 5 Gy

Contralateral breast (Both arms):

REQUIRED Compliance Criteria:

Per Protocol: No more than 10% receives 3 Gy

Variation Acceptable: No more than 10% receives 5 Gy

Heart (Both arms):

REQUIRED Compliance Criteria:

Per Protocol: Mean heart dose should be ≤ 4 Gy

Variation Acceptable: Mean heart dose should be ≤ 5 Gy. Every attempt should be made to make the cardiac exposure to radiation as low as possible

Per Protocol: No more than 10% of the whole heart should receive greater than 25 Gy for left-sided breast cancers, and no more than 2% of the heart should receive more than 25 Gy for right-sided breast cancers

Variation Acceptable: No more than 10% of the whole heart should receive 30 Gy for left-sided breast cancers, and no more than 2% of the heart should receive no more than 30 Gy for right-sided breast cancers

Table 6A. **REQUIRED Compliance Criteria** Table for Volumes and Structures **REQUIRED** for Dose Scoring

Chestwall or Breast PTV Eval

	Compliance Criteria			**ARM 1/ Group 1A**	**ARM 2/ Group 2A**	**ARM 2/ Group 2B**
				Breast: 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost[a]** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
Target	Criteria	Volume	Dose			
Breast or Chestwall PTV Eval receiving whole-breast /chestwall dose	Per Protocol	At least 95% of the PTV Eval receives	At least 95% of 50 Gy	47.5 Gy	47.5 Gy	47.5 Gy
	Variation Acceptable	At least 90% of the PTV Eval receives	At least 90% of 50 Gy	45 Gy	45 Gy	45 Gy

Lumpectomy PTV Eval

	Compliance Criteria			**ARM 1/ Group 1A**	**ARM 2/ Group 2A**	**ARM 2/ Group 2B**
				Breast: 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **RNI Scl, Ax, IMN:** 50 Gy in 25 f. **MASTEC-TOMY**
Target	Criteria	Volume	Dose			
Lumpectomy PTV Eval receiving boost dose	Per Protocol	At least 95% of the lumpectomy PTV Eval receives	95% of cumulative boost dose 62 or 64 Gy	58.9 or 60.8 Gy	58.9 or 60.8 Gy	NA
	Variation Acceptable	At least 90% of the lumpectomy PTV Eval receives	90% of boost dose	55.8 or 57.6 Gy	55.8 or 57.6 Gy	NA

NA – Not applicable in this ARM/Group

Table 6A continued on next page.

Table 6A. **REQUIRED** Compliance Criteria Table for Volumes and Structures **REQUIRED** for Dose Scoring *(continued)*

Regional nodes

Target	Compliance Criteria			**ARM 1/ Group 1A**	**ARM 2/ Group 2A**	**ARM 2/ Group 2B**
				Breast: 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
	Criteria	Volume	Dose			
Supraclavicu-lar (SCL) PTV receiving Nodal dose	Per Protocol	At least 95% of the SCL PTV receives	95% of 50 Gy	NA	47.5 Gy	47.5 Gy
	Variation Acceptable	At least 90% of the SCL PTV	90% of 50 Gy	NA	45 Gy	45 Gy
Axillary (Ax) PTV receiving Nodal Dose	Per Protocol	At least 95% of the Ax PTV receives	95% of 50 Gy	NA	47.5 Gy	47.5 Gy
	Variation Acceptable	At least 90% of the Ax PTV	90% of 50 Gy	NA	45 Gy	45 Gy
IMN PTV receiving Nodal Dose	Per Protocol	At least 95% of the IMN PTV receives	90% of 50 Gy	NA	45 Gy	45 Gy
	Variation Acceptable	At least 90% of the IMN PTV	80% of 50 Gy	NA	40 Gy	40 Gy

NA – Not applicable in this ARM/Group

Table 6A continued on next page.

Table 6A. **REQUIRED** Compliance Criteria Table for Volumes and Structures **REQUIRED** for Dose Scoring *(continued)*

Normal Tissue Constraints

OAR	Compliance Criteria		ARM 1/ Group 1A	ARM 2/ Group 2A	ARM 2/ Group 2B
			Breast: 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost[a]** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
Description	Criteria	Volume			
Heart dose* constraint	Per Protocol	No more than 10% of the heart for left-sided cancer 2% of the heart for right-sided receives	≤ 25 Gy	≤ 25 Gy	≤ 25 Gy
	Variation Acceptable	No more than 10% of the heart for left-sided cancer 2% of the heart for right-sided receives	≤ 30 Gy	≤ 30 Gy	≤ 30 Gy
Heart dose* constraint	Per Protocol	Mean dose is	≤ 4 Gy	≤ 4 Gy	≤ 4 Gy
	Variation Acceptable	Mean dose is	≤ 5 Gy	≤ 5 Gy	≤ 5 Gy
Ipsilateral lung dose	Per Protocol	% of the ipsilateral lung that can receive 20 Gy	≤ 15%	≤ 35%	≤ 35%
	Variation Acceptable	% of the ipsilateral lung that can receive 20 Gy	≤ 20%	≤ 40%	≤ 40%
Contralateral Breast	Per Protocol	No more than 10% receives	3 Gy	3 Gy	3 Gy
	Variation Acceptable	No more than 10% receives	5 Gy	5 Gy	5 Gy

Footnote:

***** The mean dose, percent dose, and volume irradiated to heart should be **as low as possible**.

a. **Arm 2/Group 2B:** No boost to be delivered post-mastectomy except in the case of close invasive cancer margins post-mastectomy. If boost is delivered – it should comply with the constraints outlined in Section 10.6.5.3.

Table 6B. Compliance Criteria Table for **RECOMMENDED Guidelines** for Treatment Planning (will not be scored)

Chestwall or Breast PTV Eval

	Treatment Planning Guidelines			ARM 1/ Group 1A	ARM 2/ Group 2A	ARM 2/ Group 2B
Target	Guideline	Volume	Dose	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost[a]** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
Breast/ Chestwall PTV Eval receiving boost dose	Ideally	No more than 35% of the breast/ chestwall PTV Eval receives	100% of boost dose	62 or 64 Gy	62 or 64 Gy	– (see footnote a)
Breast PTV Eval receiving above the whole breast dose	Ideally	No more than 50% of the volume of breast/ chestwall PTV Eval receives	112% of 50 Gy	56 Gy	56 Gy	– (see footnote a)
Breast/ Chestwall PTV Eval **MAXIMUM DOSE[b]**	Ideally	Point dose[b]	120% of 50 Gy	60 Gy	All photons: 60 Gy	60 Gy
Breast/ Chestwall PTV Eval maximum dose (Photon electron mix)	Ideally	Point dose[b] **OR**	Electron: 130% **OR**	–	≤ 65 Gy	≤ 65 Gy
		10 cm^3 of composite plan	130% of 50 Gy	–	65 Gy	65 Gy
Conformity Index (Ratio of irradiated volume covered by 47.5 Gy/ volume of Breast PTV Eval)	Ideally		0.95 ≤ CI ≤ 2.0 to 0.85 ≤ CI ≤ 2.5		-	-

Table 6B continued on next page.

Table 6B. Compliance Criteria Table for **RECOMMENDED Guidelines** for Treatment Planning (will not be scored) *(continued)*

Lumpectomy PTV Eval

	Treatment Planning Guidelines			ARM 1/ Group 1A	ARM 2/ Group 2A	ARM 2/ Group 2B
Target	Guideline	Volume	Dose	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
Lumpectomy PTV Eval receiving boost dose	Ideally	No more than 10% of the lumpec-tomy PTV Eval receives	110% of boost dose	68.2 or 70.4 Gy depending on boost dose	68.2 or 70.4 Gy depending on boost dose	NA
Lumpectomy PTV Eval **MAXIMUM DOSE[b]**	Ideally		120% of boost dose	74.4 or 76.8 Gy depending on boost dose	74.4 or 76.8 Gy depending on boost dose	NA

NA – Not applicable in this ARM/Group

Regional Nodes

	Treatment Planning Guidelines			ARM 1/ Group 1A	ARM 2/ Group 2A	ARM 2/ Group 2B
Target	Guideline	Volume	Dose	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost[a]** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
Supraclavi-cular (SCL) PTV Maximum Point Dose[b]	Ideally	Point dose[b]	115% of 50 Gy	-	57.5 Gy	57.5 Gy
Axillary (Ax) PTV Maximum Point Dose[b]	Ideally	Point dose[b]	115% of 50 Gy	–	57.5 Gy	57.5 Gy
IMN PTV Maximum Point Dose[b]	Ideally	Point dose[b]	115% of 50 Gy	–	57.5 Gy	57.5 Gy

Table 6B. Compliance Criteria Table for **RECOMMENDED Guidelines** for Treatment Planning (will not be scored) *(continued)*

Organs at Risk

OAR	Treatment Planning Guidelines		ARM 1/ Group 1A	ARM 2/ Group 2A	ARM 2/ Group 2B
			Breast: 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **No RNI**	**Breast:** 50 Gy in 25 f. with a sequential 12 or 14 Gy boost to total of 62 or 64 Gy **RNI Scl, Ax, IMN:** 50 Gy in 25 f.	**Chestwall:** 50 Gy in 25 f. **No Boost[a]** **RNI Scl, Ax, IMN:** 50 Gy in 25 f.
	Guideline	Volume			
Ipsilateral Lung	Ideally	No more than 65% receives	NA	10 Gy	10 Gy
Ipsilateral Lung	Ideally	No more than 75 % receives	NA	5 Gy	5 Gy
Contralateral Lung	Ideally	No more than 15% receives	5 Gy	5 Gy	5 Gy

NA – Not applicable in this ARM/Group

Footnotes:

a. **Arm 2/Group 2B:** No boost to be delivered post-mastectomy except in the case of close invasive cancer margins post-mastectomy. If boost is delivered – it should comply with the constraints outlined in Section 10.6.5.3.

b. **Point dose:** All maximum doses should be defined in one dose calculation voxel; e.g., 3 mm x 3 mm x 3 mm or 0.03 cm^3.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Adverse event characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

11.2 Adverse events and serious adverse events

11.2.1 *Definition of an adverse event*

An AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product/intervention, whether or not considered related to the medicinal (investigational) product/intervention (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH] E2A, E6).

11.2.2 *Definition of a serious adverse event*

Any adverse event (experience) occurring during any part of protocol treatment and 30 days after that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

11.2.3 *Radiation therapy adverse events*

- Short Term

  Fatigue is an anticipated systemic reaction to radiation treatment. Skin erythema, desquamation, breast edema, breast tenderness, and myositis are potential local reactions.

- Long Term

  Long term effects possibly include radiation pneumonitis, rib fractures, and for left-sided lesions there could be cardiac complications.

11.3 Expedited reporting of adverse events

NRG Oncology follows procedures for centralized reporting of adverse events. Centralized reporting requires that adverse events be reported to NRG Oncology. The NRG Oncology forwards reports to the appropriate regulatory agencies. Expedited reporting for B-51/1304 utilizes the CTEP Adverse Event Reporting System (CTEP-AERS).

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. Events involving radiation therapy-only must be reported via the CTEP-AERS radiation therapy-only pathway.

NRG Oncology is identified in CTEP-AERS as the Lead Group for protocols that require CTEP-AERS reporting. Expedited AE reporting for this study must be submitted to the NRG Oncology Lead Group using CTEP-AERS, accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NRG oncology by telephone at 412-624-2666. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

11.3.1 *Expedited reporting methods*

- **CTEP-AERS-24 Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted to the NRG Oncology Lead Group **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 3 Calendar Day Report (see Table 7).
- **CTEP-AERS 5 Calendar Day Report** requires that a complete report is electronically submitted to NRG Oncology Lead Group **within 5 calendar days** of learning of the AE.
- **Supporting documentation** is required for all expedited (CTEP-AERS) reports. Include the protocol number, patient's ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology SDMC (412-622-2113).

11.3.2 *Expedited reporting requirements – CTEP-AERS-24 and CTEP-AERS*

Expedited reporting requirements begin with the administration of the first radiation therapy dose. Expedited reporting requirements for all patients are provided in Table 7.

11.3.3 *Other recipients of adverse event reports*

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

Table 7. Expedited reporting requirements for adverse events that occur within 30 days of the last dose of radiation therapy[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the radiation therapy (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		5 Calendar Days	24-Hour, 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		5 Calendar Days	

Expedited AE reporting timelines are defined as**:**

- "24-Hour, 3 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "5 Calendar Days" – A complete expedited report on the AE must be submitted within 5 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of protocol treatment and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report with 3 calendar days for:

- All Grade 4 and Grade 5 AEs

Effective Date: May 5, 2011

11.3.4 *Reporting a secondary malignancy*

A ***secondary malignancy*** is a cancer caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur on NCI-sponsored trials either during or following treatment must be reported via CTEP-AERS within 5 days of learning of the secondary malignancy. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Supporting documentation, including pathology and cytogenetics reports which confirm the secondary malignancy, must be faxed to the NRG Oncology SDMC expedited fax at 412-622-2113. Each page of supporting documentation must include the NCI protocol number, the CTEP-AERS ticket number, and the protocol-specific Patient ID number provided during trial registration.

11.3.5 *Expedited reporting of pregnancy, fetal death, and death neonatal occurring during radiation therapy*

Any pregnancy or fetal death occurring while the patient is receiving radiation therapy must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

Upon learning of a pregnancy, fetal death, or death neonatal that occurs during radiation therapy the investigator is required to:

- Call the Clinical Coordinating Department (see Information Resources). ***Patients must immediately discontinue receiving radiation therapy.***
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6):
  - Create and submit an CTEP-AERS report;
  - Complete the Pregnancy Information Form (located in the NSABP Members' Area in Protocol B-51 "Forms and Supporting Documents") and on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm; and
  - Fax the completed Pregnancy Information Form with all available supporting documentation to the NRG Oncology SDMC's expedited fax number at 412-622-2113.
- For questions concerning AE reporting, contact the AE Reporting Nurse (see Information Resources).
- For clinical questions concerning study therapy, contact the Clinical Coordinating Department (see Information Resources).

11.4 Routine reporting of adverse events

11.4.1 *Reporting routine adverse events through Medidata Rave*

- Reporting of adverse events is done through Medidata Rave (see Section 14.3).
- **All ≥ grade 2 adverse events not reported via CTEP-AERS** that occurred during study therapy or during the 30 days following the last dose of XRT must be reported on one of the B-51/1304 Adverse Event forms (the Listed Adverse Event form or the Other Adverse Event form) through Medidata Rave, regardless of whether these adverse events are expected or unexpected (**even if no AEs were experienced** by the patient).
- Reporting of AEs is **not required** following a documented invasive breast cancer recurrence or diagnosis of a second primary malignancy, if treated with systemic anticancer therapy.
- Supporting documentation for each AE reported on either of the B-51/1304 Adverse Event forms through Medidata Rave must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation.

11.4.2 *Schedule for reporting routine adverse events*

Adverse event forms are to be submitted through Medidata Rave, **even if no AEs were experienced by the patient**, according to the following schedule:

- Submit at the end of XRT for Arm 1/Group 1A and Arm 2/Groups 2A and 2B or at 3 months after randomization for Group 1B.
- Submit 30 days ***after*** the end of XRT (not required for Arm 1/Group 1B patients).

11.5 Reporting breast cancer recurrence and second primary cancer

Report breast cancer recurrence and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the B-51/1304 Follow-up folder in Medidata Rave. Fax supporting documentation that confirms the breast cancer recurrence or second primary cancer diagnosis with the transmittal form (provided at the time of enrollment) to 412-622-2111.

12.0 DOCUMENTATION OF BREAST CANCER RECURRENCE AND SECOND MALIGNANCIES

12.1 General instructions

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. Suspicious findings do not provide adequate documentation of a breast cancer recurrence, and should not be an indication to alter protocol therapy.
- Tumor marker evaluations alone do not document breast cancer recurrence.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

12.2 Local recurrence

Note: If the first local recurrence is non-invasive breast cancer, the first invasive breast cancer must also be reported.

Recurrent local tumor is defined as evidence of invasive breast cancer or DCIS in the ipsilateral breast or invasive breast cancer in the skin of the ipsilateral breast. Patients who develop clinical evidence of local recurrence in the ipsilateral breast must have a biopsy confirmation of recurrence. However, if a patient also meets criteria for regional or distant metastatic disease, results of clinical exams alone will be sufficient to document local recurrences.

12.2.1 *Ipsilateral breast tumor recurrence (IBTR)*

An IBTR event is defined as recurrent invasive breast cancer or DCIS in the ipsilateral breast parenchyma or invasive breast cancer in the skin of the breast occurring after lumpectomy.

Acceptable documentation includes core, incisional or excisional biopsy. Cytology alone will not be adequate to establish IBTR.

12.2.2 *Other local recurrence*

Defined as recurrence in the skin of the chestwall (exclusive of the breast) or chestwall.

Acceptable documentation includes core, incisional or excisional biopsy, as well as cytology.

12.3 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, following surgery. Recurrence must be confirmed by biopsy or cytology. However, if a patient meets criteria for distant metastatic disease, results of clinical exams alone will be sufficient to document regional recurrences.

12.4 Distant recurrence

Defined as evidence of tumor in all areas, with the exception of those described in Sections 12.2 and 12.3. Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

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

Acceptable documentation includes positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease.

12.4.2 *Bone marrow*

Acceptable documentation includes positive cytology, aspirate, biopsy, or MRI scan.

12.4.3 *Lung*

Acceptable documentation includes: (i) positive cytology, aspirate, or 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, needle aspiration, PET-CT scan, or PET scan should be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

12.4.4 *Skeletal*

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

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

12.4.5 *Liver*

Acceptable documentation includes: (i) abdominal CT scan, liver scan, ultrasound, MRI, PET-CT scan, or PET scan 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.

12.4.6 *Central nervous system*

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

12.5 **Contralateral breast cancer**

Contralateral breast cancer is defined as evidence of invasive breast cancer or DCIS in the contralateral breast or chestwall. The diagnosis of a contralateral breast cancer must be confirmed by core, incisional, or excisional biopsy. Cytology alone will not be adequate to document a contralateral breast cancer.

12.6 **Second primary cancer**

Second primary cancer is defined as any ***invasive*** non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

12.7 **Documentation requested following death**

- Autopsy reports should be secured whenever possible and should be submitted to NRG Oncology SDMC.
- A copy of the death certificate should be forwarded to NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

13.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

13.1 CTEP investigator registration procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

13.2 CTEP associate registration procedures/CTEP-IAM account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

13.3 CTSU registration procedures

This study is supported by the NCI CTSU.

13.3.1 *IRB approval*

Each 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 be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials

at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

13.3.2 ***Downloading site registration documents***

Site registration forms may be downloaded from the NSABP B-51 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the NRG link to expand, then select trial protocol NSABP B-51
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided

13.3.3 ***Requirements for B-51/1304 site registration***

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form

  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. If this form has been previously submitted to CTSU, it does not need to be submitted unless updates have occurred at the RT facility.

13.3.4 ***Submitting regulatory documents***

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent, if applicable, to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

13.3.5 *Checking your site's registration status*

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

13.4 Patient consent form

Before the patient is enrolled, the consent form, including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

13.5 Required submission of tumor samples

As part of the B-51/1304 consent form, all patients have agreed to allow the submission of tumor blocks (see Section 7.1).

13.6 Patient enrollment

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

13.7 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the NRG Oncology or CTSU Web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration, including the Patient ID number for the study, and treatment information. Please print this

confirmation for your records. Additionally, a transmittal form to be used when faxing the signed consent form to the NRG Oncology SDMC will be provided. If it is necessary to reprint the randomization confirmation or the transmittal form, they can be reprinted through Coordinator Online via the ***View a Patient Entry Report*** under Patient Entry.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU Web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.8 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 other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study therapy or other treatments for breast cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws from the study (see Section 13.10).

13.9 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 study therapy is stopped but she still allows the investigator to submit information, study data and other materials should be submitted according to the study schedule.

13.10 Patient-initiated withdrawal from the study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology SDMC), the investigator must provide NRG Oncology SDMC with written documentation of the patient’s decision to fully withdraw from the study.

14.0 REQUIRED DATA COLLECTION

14.1 Data collection

B-51/1304 data collection will include the following elements:

- Patient characteristics
- Characteristics of the breast cancer
- AJCC TNM stage
- Radiation therapy administered
- Other treatment including endocrine therapy and anti-HER2 therapy
- Adverse events as described in Section 11.0
- Breast cancer events (local, regional, and distant)
- Second primary cancer events
- Survival
- QOL/PROs for QOL patients as described in Section 8.0

14.2 Instructions for completion of B-51/1304 forms and materials

- Data form worksheets and specimen transmittal forms, as well as instructions for completion and submission of data and materials, are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu or on the CTSU Member Web site, https://www.ctsu.org. Contact the Support Desk at support@nrgoncology.org for an account to access the NSABP Web site.
- Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the Table of Required Forms and Materials document available in the Members' Area of the NSABP Web site or on the CTSU Member Web site.

14.3 Instructions for submission of B-51/1304 data, forms, and materials

B-51/1304 will use the Medidata Rave clinical data management system for remote data capture of all data. Query generation and resolution for B-51/1304 are part of the Rave program. All queries will be issued and responded to electronically within Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members'

website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Exceptions to submission of data through Medidata Rave are the BAHO questionnaire and required source documents which should be faxed to NRG Oncology SDMC according to the instructions on the form worksheet. When submission of supporting documentation to NRG Oncology SDMC is required, fax to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation. Do not include a cover sheet for faxed data.

14.4 Data reporting to CTEP

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0 (CDUS Abbreviated). Cumulative CDUS data will be submitted quarterly by NRG Oncology SDMC to CTEP by electronic means.

14.5 Dosimetry digital data submission

14.5.1 *Preliminary dosimetry information (DD)*

- Digital Data Submission – The Treatment Plan is submitted via TRIAD exported from the treatment planning machine by the Physicist. Access TRIAD using your active CTEP-IAM user ID and password. See Section 4.2.2 for more details.

- Digital data submission includes the following:
  - CT data, critical normal structures, all GTV, CTV, and PTV contours
  - Digital beam geometry for initial and boost beam sets
  - Doses for initial and boost sets of concurrently treated beams
  - Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan

14.5.2 *Digital Data Submission Information (DDSI) form*

The DDSI form is submitted online. The form is located on the RTOG Web site at http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx.

15.0 STATISTICAL CONSIDERATIONS

15.1 Primary endpoint

The primary endpoint is invasive breast cancer recurrence-free interval (IBC-RFI).

15.2 Secondary endpoints

Secondary efficacy endpoints include overall survival (OS); loco-regional recurrence-free interval (LRRFI) (separately analyzed for mastectomy patients and for lumpectomy patients); distant recurrence-free interval (DRFI); disease-free survival-ductal carcinoma in situ (DFS-DCIS); second primary invasive cancer; effect of XRT in mastectomy and lumpectomy patients; and the frequency and severity of adverse events graded according to the CTCAE v4.0.

15.3 Stratification and randomization

Assignment of treatments to patients will be balanced with respect to type of breast surgery (mastectomy, lumpectomy), hormone receptor status (ER-positive and/or PgR-positive, ER- and PgR-negative), HER2 status (negative, positive), adjuvant chemotherapy (yes, no), and pCR in breast (yes, no) using a biased-coin minimization algorithm.[38]

15.4 Sample size calculation

15.4.1 *Estimates of annual hazard rates*

When focusing on the subset of B-18 and B-27 patients with clinically positive nodes who converted to pathologically node negative status following neoadjuvant therapy, the average annual hazard rate of events for invasive breast cancer recurrence-free interval was determined to be 0.0354. Reducing this value by 15% to account for the fact that these legacy trials tend to over-estimate the rates in today's population brings the estimate of the expected annual hazard rate to 0.0301. This rate equates to a 5-year cumulative rate of events for invasive breast cancer recurrence-free interval of about 14%. A 35% reduction in the average annual hazard rate to 0.0196 would reduce the 5-year cumulative rate to about 9.3% for an absolute risk reduction in the 5-year cumulative rate of 4.6%.

15.4.2 *Accrual rate and total sample size*

Using the hazard rate of 0.0301 and assuming a two-tailed test at an alpha level of 0.05, 1636 patients accrued over a 5 year period (about 28 patients per month) with 2 additional years of follow-up would provide a statistical power of 80% to test the hypothesis that treatment with XRT would reduce the annual hazard rate of events for invasive breast cancer recurrence-free interval by 35%.

To account for delays in getting the trial approved by local IRBs and initiated at each potential site of accrual, we assume linear ramp-up during the first year of accrual. A steady monthly accrual of 28 patients was assumed thereafter.

As with all protocols, accrual to this trial will be closely monitored on a monthly basis. If 9 months after activation of the protocol it appears that we are not going to reach target monthly accrual, the appropriate activities will be initiated to boost the accrual.

Unless the average monthly accrual in the sixth quarter or the accrual during the last month of the sixth quarter is above 20% of our projected monthly accrual, the trial will be stopped.

If the average monthly accrual in the eighth quarter is below 75% of our projected numbers, the appropriate activities will be initiated to increase the accrual.

15.5 Statistical analysis

The primary analysis will be based on the primary endpoint of IBC-RFI. Events for this outcome include any invasive local, regional, or distant recurrence, or death from breast cancer. Analysis will be based on the intent-to-treat principle, with all patients analyzed as randomized, regardless of eligibility or protocol compliance. The difference between treatment arms will be assessed by the stratified log rank test, controlling for all stratification factors.

Analysis of the secondary endpoints of overall survival, local-regional recurrence-free interval, distant recurrence-free interval, disease-free survival-ductal carcinoma in situ, second primary cancer, and the comparison of the effect of XRT in mastectomy and lumpectomy patients will be carried out in a fashion similar to that described above. All statistical tests for the secondary endpoints will be two-sided and will be carried out at the 0.05 Type I error level. As part of a secondary analysis of all time-to-event endpoints, Cox proportional hazards models will be used to estimate and to control for the effects of potential prognostic variables. Likelihood ratio tests will be used to assess the prognostic importance of each variable and treatment/covariate interactions will be investigated.

15.6 Interim analyses

Three formal interim analyses of the primary endpoint will be carried out when 43, 86, and 129 events are observed in the study, respectively. The fourth and final analysis will be carried out when 172 events are observed. Fleming-Harrington-O'Brien[39] alpha levels are the basis for superiority boundaries; however, the p-value for the definitive analysis is computed by alpha spending[40] to account for the presence of a futility boundary. The superiority and futility boundaries for the four analyses to be used to make formal recommendations to the NRG Oncology Data Monitoring Committee are shown in Table 8. In addition, if ten years after initiation of the protocol, the total number of events is still less than required to trigger the final analysis, the considerations will be given to stop the trial and report the results.

Table 8. Proposed interim monitoring boundaries

Interim and final analysis (k)	Approximate number of events in each comparison	Lower Boundary significance level (for futility)[a]	Upper Boundary significance level (for superiority)[a]
1	43	0.01	0.000835
2	86	0.20	0.000970
3	129	0.30	0.001165
Final analysis	172	N/A	0.024209

a One-sided p-values

15.7 Statistical considerations for BAHO

15.7.1 *BAHO sub-study analyses*

The primary aim is determine the effect of radiation therapy on cosmesis at 12 and 24 months after randomization among mastectomy patients who have had reconstructive surgery. For our primary hypothesis, the BCTOS cosmetic status for mastectomy patients who have had reconstructive surgery measured at 12 months and 24 months after randomization will be compared between the two treatment groups using analysis of covariance (ANCOVA) with adjustment for the corresponding baseline measurement. The comparison will be performed at the significance level of 0.05.

For the secondary analyses, the fatigue score, pain, arm-related morbidity, restricted work and social activity, mental component summary (MCS) and physical component summary (PCS) of the SF-36 measured at 12 months after randomization will be compared between the two treatment groups using ANCOVA with adjustment for the corresponding baseline measurement.

The variation of the MCS, PCS, fatigue score, arm-related morbidity scale score, BCTOS cosmetic status score, and other symptoms over time will be evaluated using longitudinal models with adjustment for the baseline evaluation. Presence of treatment-by-time interaction will be tested for each of these endpoints. If the interaction effect is significant, treatment differences will be tested at each time point using individual ANCOVAs.

Outcomes from the broader symptom checklist (including subscales and some individual items) evaluated at 12 months after randomization will be compared between the two treatment groups by dichotomizing it as absent or present and using a logistic model controlling for the presence of the item at baseline.

All secondary analyses will be performed at 0.05 alpha level.

15.7.2 *Statistical power for BAHO study*

A sample size of 196 mastectomy patients with reconstructive surgery would be sufficient to provide a statistical power of 80% to detect a difference of 0.31 points on BCTOS scale between treatment groups assuming a standard deviation of 0.7733 and controlling the α-level at 0.05. Since we expect half of all randomized patients entering the trial to receive mastectomy and 2/3 of the mastectomy patients to have received reconstruction, a sample size of 588 patients is required to answer this endpoint question. Adjusting upward to allow for 20% missing data at the 12 month time point we require 736 patients to be accrued into the quality of life sub-study to have sufficient numbers of patients who have had mastectomy and reconstruction.

Among 736 patients, we expect that 294 lumpectomy patients will be available for the assessment of the cosmetic outcome at the 12 month time point. This will be sufficient to provide a statistical power of more than 90% to detect a difference of 0.31 points on the BCTOS scale between two treatment groups under the assumptions specified above.

In addition, the total sample size of 736 will provide 86% power to detect a difference of 0.25 standard deviations at significance level of 0.05 for other endpoints.

15.7.3 *Missing BAHO data*

A certain amount of missing data is expected. The information from patients with missing data will be reviewed in order to determine whether data analytic procedures are likely to be biased. Patients with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, institution, and reason for non-adherence. When QOL data are missing at a particular time point, data from prior time points will be reviewed in order to investigate whether missing status was preceded by a significant change in QOL scores. In addition, we will investigate whether missing item status is related to other scores on the same questionnaire. If no missing data mechanism can be detected following this review, the data will be analyzed assuming the data are missing at random. If, on the other hand, 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. We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

15.8 **Issues relating to racial and ethnic differences**

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians.[41,42] This difference has been attributed to many factors, including more advanced disease at the time of diagnosis,[43] social and economic factors,[44] or specific tumor characteristics such as ER positivity.[45,46] Although outcomes tend to be less favorable for African-Americans, significant race-by-treatment interactions have not been previously reported suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.[47,48]

Potential for the enrollment of minority patients in this protocol is enhanced by the NRG Oncology's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NRG Oncology investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distributions of ethnicity and race for B-51/1304 are projected from the NSABP B-28 study. The ethnicity distribution of the NSABP B-28 population consisted of 3% Hispanic and 97% non-Hispanic. The racial distribution in the B-28 study was 86% white; 8% black, not of Hispanic origin; 4% Asian or Pacific Islander descent; and 2% American Indian or Alaskan Native. The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power 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-51/RTOG 1304

Ethnic Category	Total
Hispanic or Latino	49
Not Hispanic or Latino	1587
Ethnic Category: Total of all subjects	**1,636**
Racial Category	
American Indian or Alaskan Native	33
Asian	49
Black or African American	131
Native Hawaiian or other Pacific Islander	16
White	1407
Racial Category: Total of all subjects	**1,636**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, 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.

16.0 PUBLICATION INFORMATION

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

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APPENDIX A

ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v4.0 grading criteria are based on ADL:

- *Instrumental ADL* refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- *Self-care ADL* refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B

CONTOURING GUIDELINES

1.0 CONTOURING TARGETS AND ORGANS AT RISK (OAR)

Contouring accurately and consistently is essential for case evaluation and data comparison. The structures to be contoured vary by ARM to which the patient is randomized and her surgical treatment. Patients undergoing lumpectomy for breast conservation will be "Group A" within each treatment ARM and those undergoing mastectomy will be in "Group B."

See Section 10.6 for specific details.

2.0 CONTOURING LUMPECTOMY AND WHOLE BREAST TARGETS

The targets to be contoured for each arm and group are listed in the protocol under Section 10.6.2. The lumpectomy and whole breast targets will be contoured for patients randomized to Arm 1/Group1A that are to receive whole breast irradiation with boost, and Arm 2/Group 2A that receives whole breast irradiation with boost plus regional nodal irradiation.

2.1 Lumpectomy Target Volumes

2.1.1 Lumpectomy: See Figure 1. For this protocol, the term "lumpectomy" will represent the surgical cavity from the breast conserving surgery. Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended).

2.1.2 Lumpectomy Clinical Target Volume (CTV): See Figure 1. The Lumpectomy CTV consists of the contoured lumpectomy plus a 1 cm 3D expansion with the following 3 limitations: 1) limit the CTV posteriorly at anterior surface of the pectoralis major; 2) limit anterolaterally 5 mm from skin; and, 3) should not cross midline. In general, the pectoralis muscles and/or serratus anterior muscles are excluded from the Lumpectomy CTV unless clinically warranted by the patient's pathology.

2.1.3 Lumpectomy Planning Target Volume (PTV): See Figure 2. The Lumpectomy PTV is a 7 mm expansion on the Lumpectomy CTV and excludes the heart. This is the structure used for beam aperture generation.

2.1.4 Lumpectomy Planning Target Volume for Evaluation (PTV-eval): See Figure 3. This Lumpectomy PTV-eval is limited to exclude the portion of the PTV that extends outside the ipsilateral breast beyond skin or into the chestwall or thorax. The Lumpectomy PTV-eval consists of the Lumpectomy PTV excluding 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 the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chestwall, pectoralis muscles, and lung) when pertinent. This Lumpectomy PTV-eval is the structure used for DVH constraints and analysis.

Figure 1. Lumpectomy and Lumpectomy Clinical Target Volume (CTV)

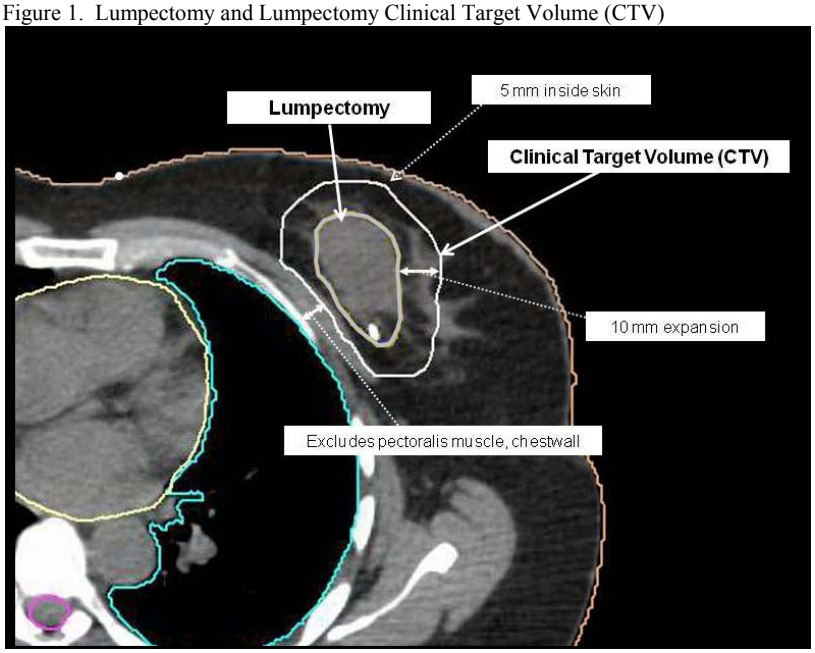


Figure 2. Lumpectomy Planning Target Volume (PTV)

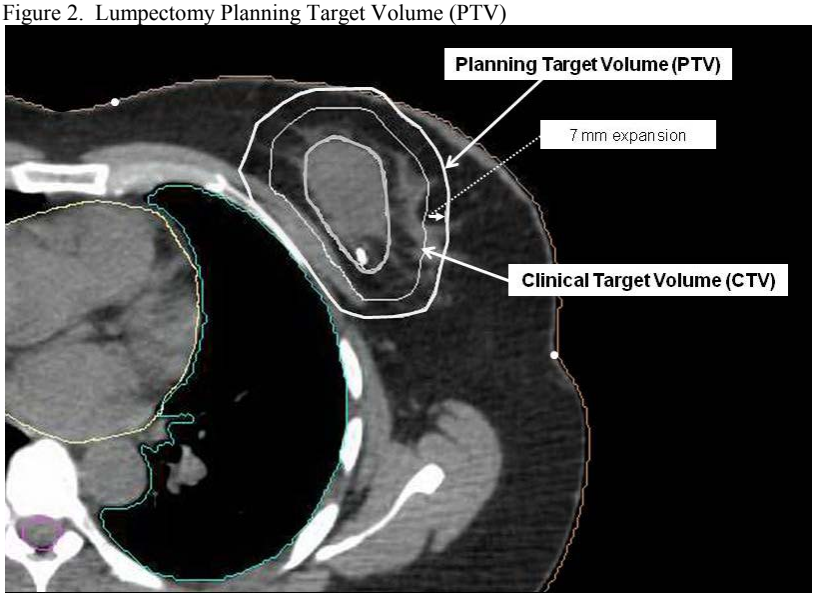
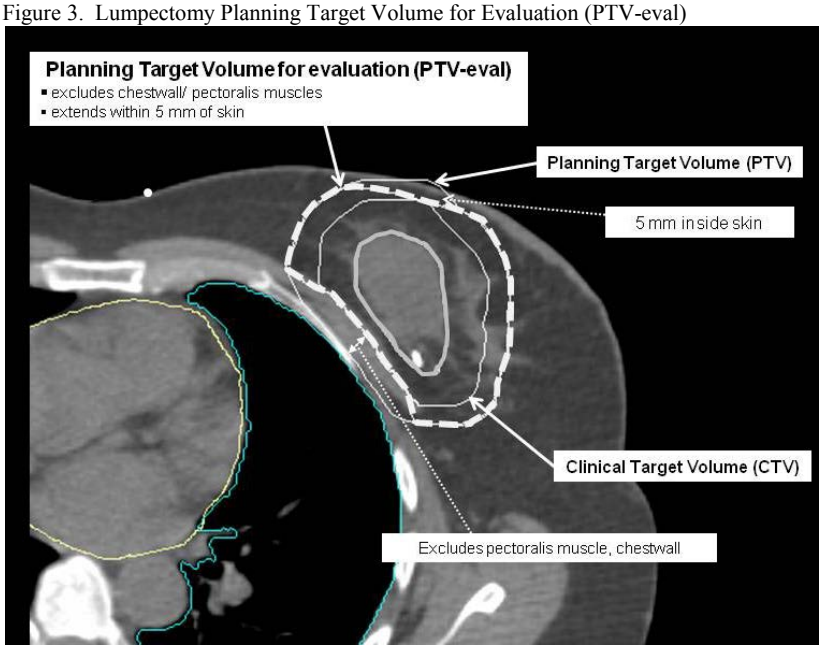


Figure 3. Lumpectomy Planning Target Volume for Evaluation (PTV-eval)



2.2 **Breast Target Volumes**

2.2.1 Breast Clinical Target Volume (CTV): See Figure 4. Consists of and takes into account the clinical borders placed at the time of CT simulation, the apparent glandular and fatty breast tissue visualized by CT, consensus definitions of anatomical borders from the RTOG Breast Cancer Atlas, and should include the Lumpectomy CTV. The Breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis muscles, serratus anterior muscle/chestwall, boney thorax, and lung. In general, the pectoralis and serratous anterior muscles/chestwall are excluded from the Breast CTV unless clinically warranted by the patient's pathology. RTOG anatomy consensus guidelines are available at http://www.rtog.org/pdf_document/BreastCancerAtlas.pdf.

2.2.2 Breast Planning Target Volume (PTV): See Figure 4. Consists of the Breast CTV generated above plus a 7 mm 3D expansion (excluding heart and not to cross midline). This is the structure used for beam aperture generation.

2.2.3 Breast Planning Target Evaluation for evaluation (PTV-eval): See Figure 5. The Breast PTV-eval is intended to exclude the portion of the Breast PTV that extends outside the patient or into the boney thorax and lungs. This Breast PTV-eval consists of the breast PTV limited to exclude the part anteriorly outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and posteriorly is limited no deeper to the anterior surface of the ribs (excludes boney thorax, and lung). This Breast PTV-eval is the structure used for DVH constraints and analysis.

Figure 4. Breast Clinical Target Volumes (CTV) and Breast Planning Target Volumes (PTV)

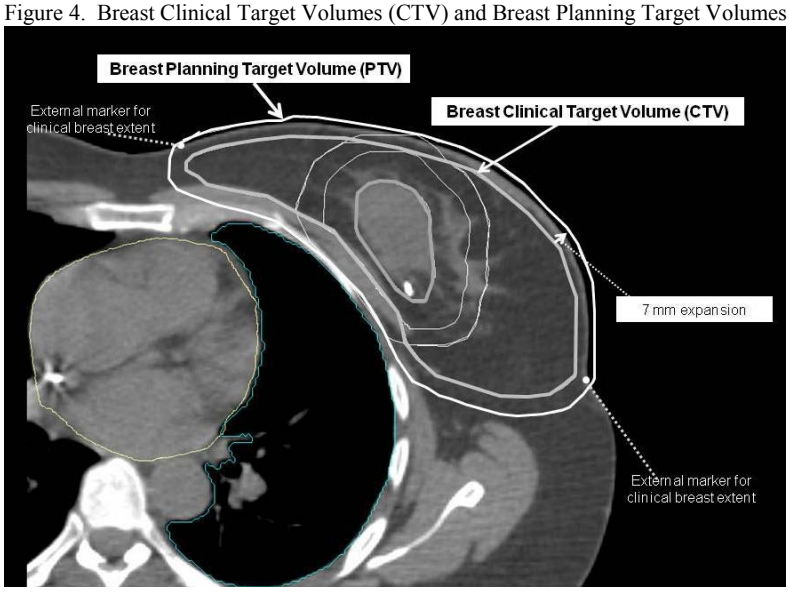
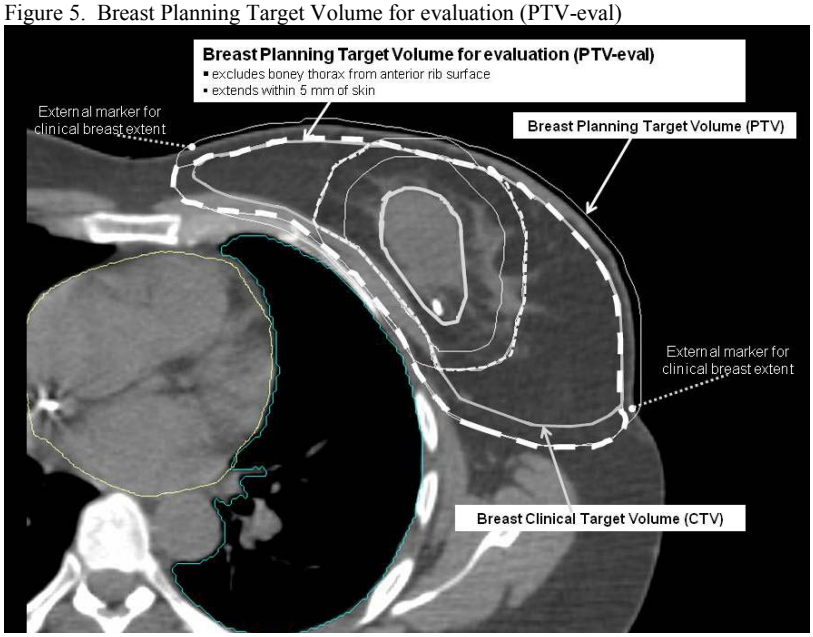


Figure 5. Breast Planning Target Volume for evaluation (PTV-eval)

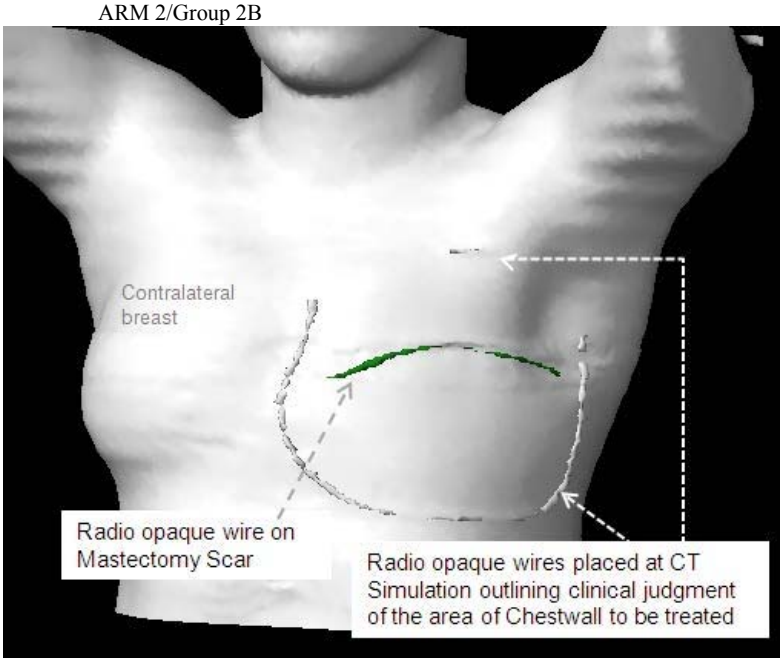


3.0 CONTOURING MASTECTOMY SCAR AND CHESTWALL TARGETS (Arm 2/Group 2B–Post-mastectomy chestwall and regional nodal irradiation)

3.1 CT simulation

Contouring the post-mastectomy chestwall targets on CT is aided by the physician placing radiopaque marker at the time of CT simulation for identification of: 1) the mastectomy scar; and 2) the area of the chestwall, in the physician's clinical judgment, at risk for recurrence and ideally to be included in the prescription dose. The medial, lateral, superior, inferior extent of this should be marked with radiopaque markers. This area should clinically include the mastectomy scar (see Figure 6).

Figure 6. Example of radiopaque wire placement at CT simulation for post-mastectomy radiotherapy on ARM 2/Group 2B

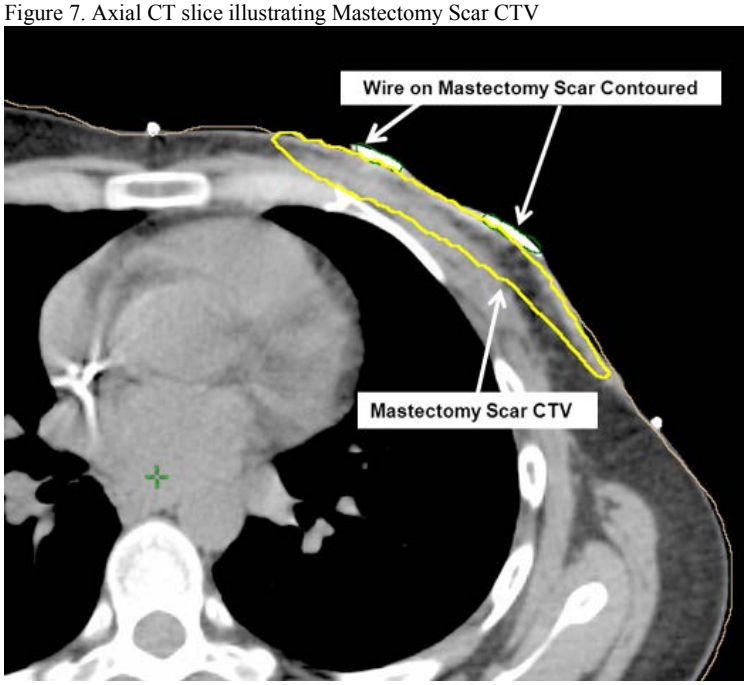


3.2 Mastectomy scar targets

3.2.1 Mastectomy Scar: The mastectomy scar and the surrounding immediate vicinity are a common location for chestwall recurrences post-mastectomy. To ensure this area of the chestwall is adequately covered by post-mastectomy radiotherapy, an initial clinical target volume for the mastectomy scar will be created. The Mastectomy Scar will first be contoured by delineating the radiopaque wire placed over the scar at CT simulation as a surrogate of the scar and including any additional visible postoperative changes on CT in the subcutaneous tissue deep to the wire per the investigator's discretion.

3.2.2 Mastectomy Scar CTV: See Figure 7. Mastectomy scar and associated surgical change + 1 cm 3D expansion. Limit the CTV expansion posteriorly at anterior surface of the ribs and anterolateral at skin and should not cross midline. The Mastectomy Scar CTV should be contained within the Chestwall CTV.

Figure 7. Axial CT slice illustrating Mastectomy Scar CTV



3.2.3 Mastectomy Scar PTV: See Figure 8. Mastectomy scar CTV + 7 mm 3D expansion (excludes heart).

3.2.4 Mastectomy Scar PTV-eval: See Figure 9. Since a substantial part of the Mastectomy Scar PTV often extends outside the patient – a Mastectomy Scar PTV-eval is created. This Mastectomy Scar PTV-eval is limited to exclude the part that extends outside the ipsilateral body/chestwall and the first 2-3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to exclude lung and heart). The Mastectomy Scar PTV-eval should not cross midline and should be contained within the borders of the Chestwall PTV-eval. This is the structure used for DVH constraints, analysis, and compliance.

Figure 8. Same axial CT slice illustrating Mastectomy Scar PTV

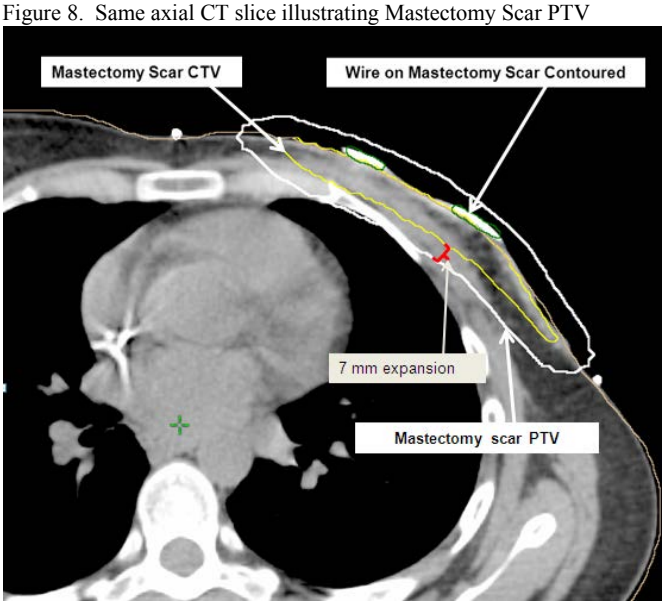
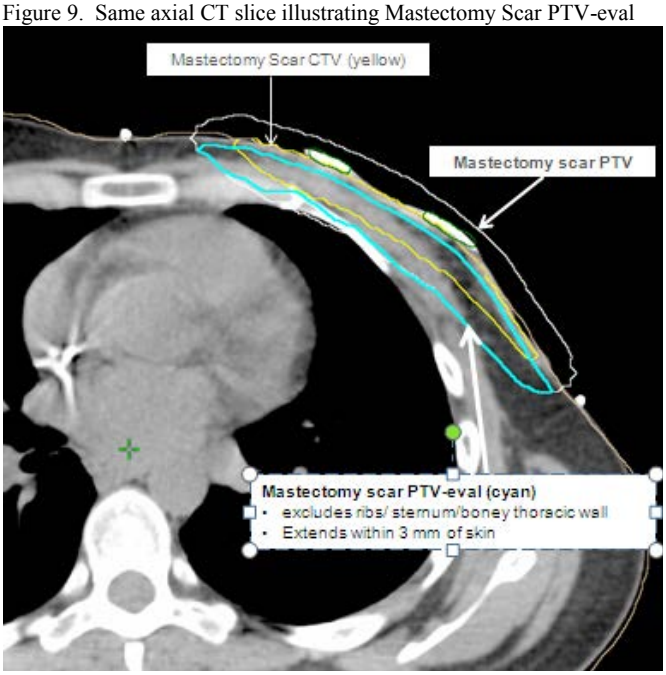


Figure 9. Same axial CT slice illustrating Mastectomy Scar PTV-eval



3.3 **Chestwall Targets** (See Figure 10, Figure 11, Figure 12, Figure 13, Figure 14, Figure 15)

3.3.1 Chestwall CTV: Includes the Mastectomy Scar CTV and takes into account the radiopaque markers placed at CT identifying clinical extent of chestwall, surgical changes visualized by CT, and consensus definitions of anatomical borders of chestwall from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

The Chestwall CTV is limited by the skin anteriorly and should not extend deeper than the ribs so that it excludes the lung and heart. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum and the axilla deep to anterior surface of the pectoralis major muscle laterally. In general, the Chestwall CTV should not cross midline.

Expanders, implants or autologous tissue present for reconstruction will be included in the Chestwall CTV. The degree of expander expansion present is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation

3.3.2 Chestwall PTV: Chestwall CTV + 7 mm 3D expansion (excludes heart and does not cross midline).

3.3.3 Chestwall PTV-eval: As a part of the Chestwall PTV often extends outside the patient, the Chestwall PTV is then copied to a Chestwall PTV-eval which is edited. This Chestwall PTV-eval is limited anteriorly to exclude the part that extends outside the body/patient and the first 2-3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis), medially excludes the sternum, and posteriorly is limited to no deeper than the ribs to exclude all intra thoracic structures; e.g., vessels, lung, and heart. This Chestwall PTV-eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

Figure 10. Axial CT Slice illustrating **Chestwall CTV** and **Chestwall PTV**; and the relation to the **Mastectomy Scar CTV** and **Mastectomy Scar PTV-eva**l

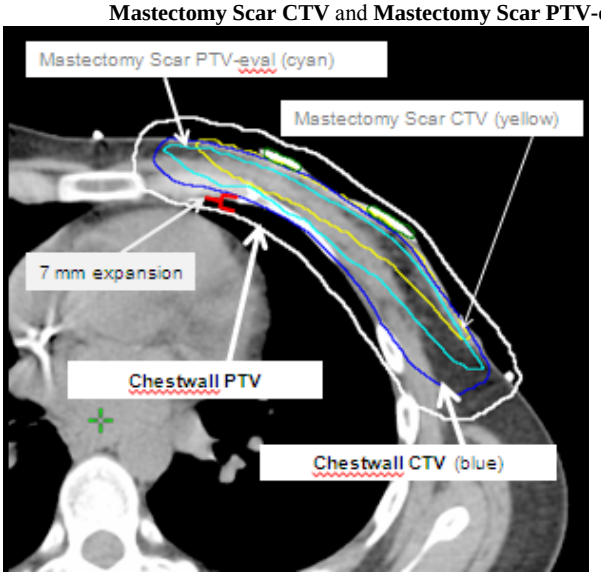


Figure 11. Same axial CT slice illustrating Chestwall PTV-eval

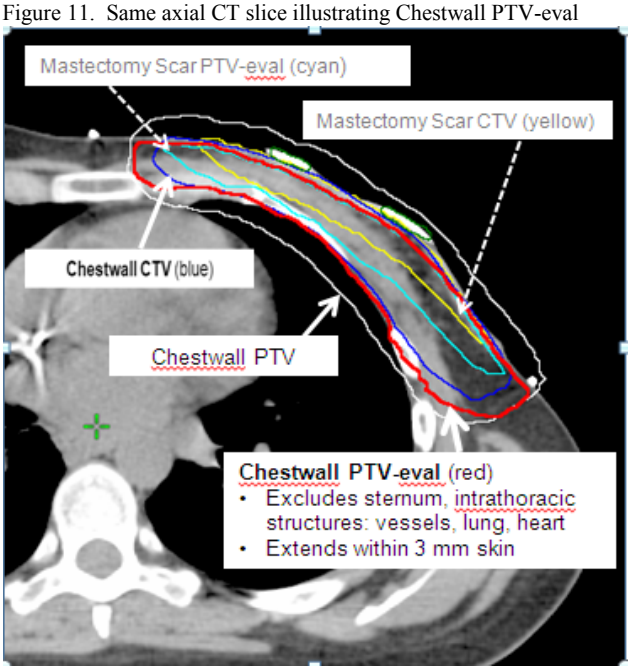


Figure 12 Different and more caudal axial CT slice illustrating **Chestwall CTV** (blue), **Chestwall PTV** (white), and **Chestwall PTV-eval** (white)

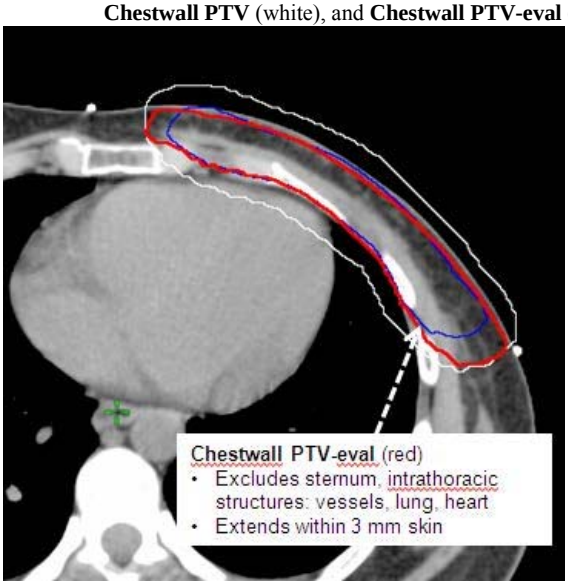


Figure 13. Sagittal CT slice illustrating **Mastectomy scar** and **Chestwall** targets

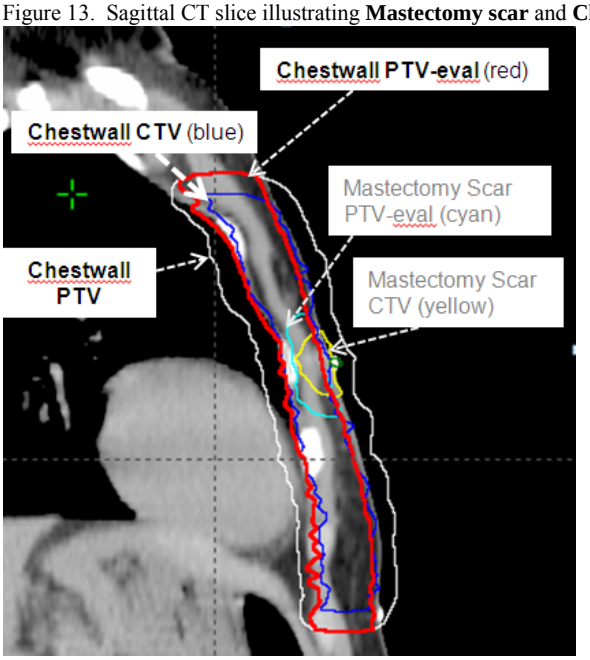


Figure 14. Coronal CT slice illustrating Mastectomy scar targets – **Mastectomy scar CTV** (yellow) and **Mastectomy Scar PTV-eval** (cyan), and Chestwall targets-**Chestwall CTV** (blue), Chestwall PTV (white), and **Chestwall PTV-eval** (red)

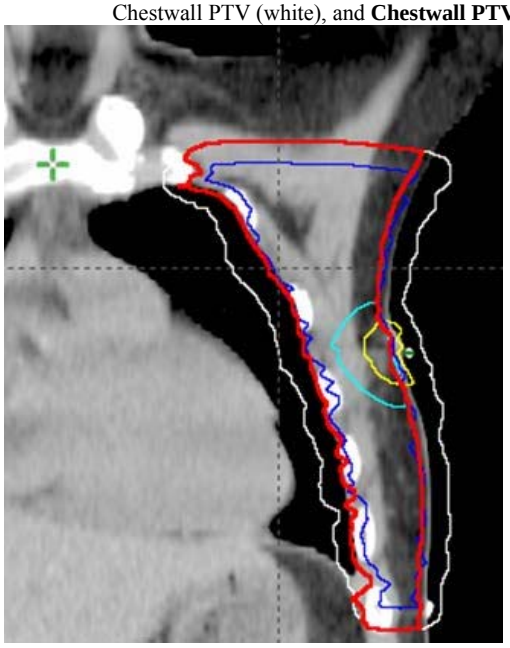
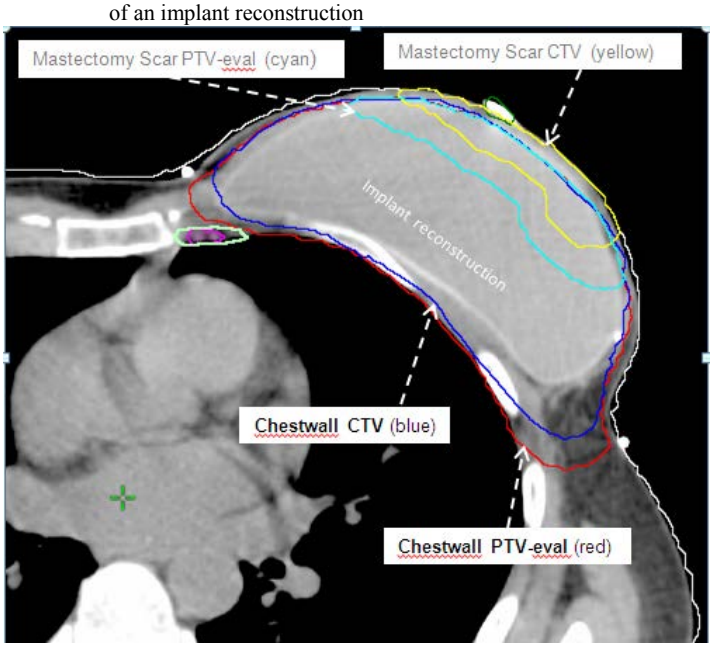


Figure 15. Axial CT slice illustrating **Mastectomy scar** targets and **Chestwall** targets in the presence of an implant reconstruction



4.0 CONTOURING REGIONAL NODAL TARGET VOLUMES: ARM 2/GROUPS 2A AND 2B

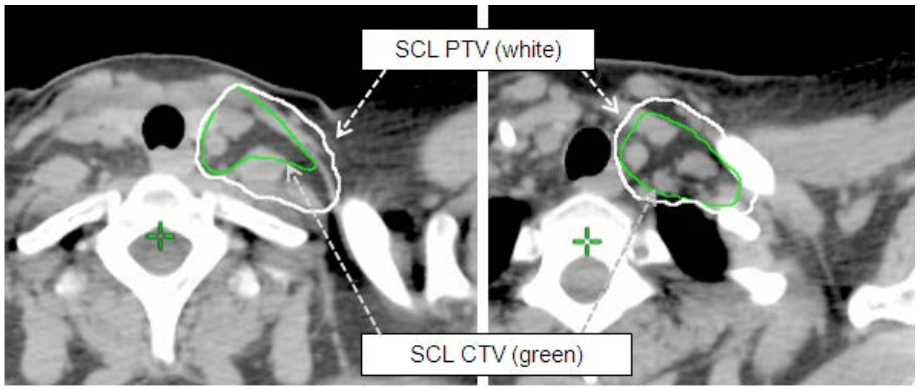
4.1 Regional node target volumes will be contoured for patients randomized to Arm 2/Group 2A or Group 2B

4.1.1 Supraclavicular CTV: See Figure 16A and Figure 16B. Consensus definitions based on the RTOG Breast Cancer Atlas. Superior extent typically is below the level of the cricoid; medially excludes thyroid, trachea, and esophagus; extends laterally to the edge of the sternocleidomastoid muscle superiorly and the clavicle at its more inferior extent, and the inferior border extends to the caudal aspect of the clavicle head.

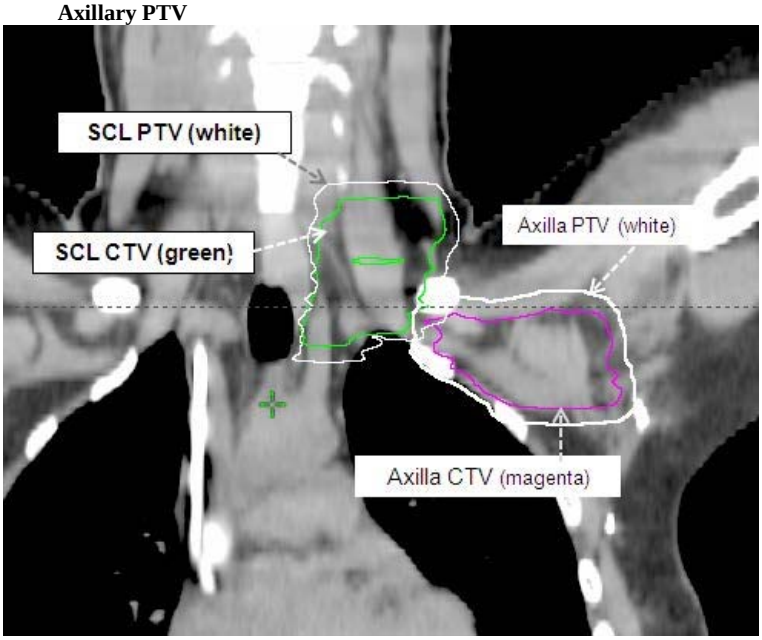
4.1.2 Supraclavicular PTV: See Figure 16A and Figure 16B. Supraclavicular CTV + 5 mm margin in all directions. The following structures should be excluded from the Supraclavicular PTV to minimize excess dose to normal tissues: ipsilateral thyroid, trachea, esophagus, ipsilateral lung, and skin minus 5 mm. This means that some or the entire medial border of the Supraclavicular CTV and PTV will be similar. The Supraclavicular PTV should exclude the vertebral body and skin plus 5 mm.

Figure 16A and Figure 16B. **Supraclavicular (SCL) CTV** and **SCL PTV**

16A. Non-contiguous Axial CT slices illustrating the **Supraclavicular (SCL) CTV** and **SCL PTV**. The **SCL PTV** is a 5 mm expansion on the **SCL CTV**. Note that the **SCL PTV** excludes thyroid, trachea, etc., medially and therefore some or all of it can have a similar medial extent as the SCL CTV.



16B. Coronal CT slice illustrating the SCL CTV and **SCL PTV** in relation to the **Axillary CTV** and **Axillary PTV**



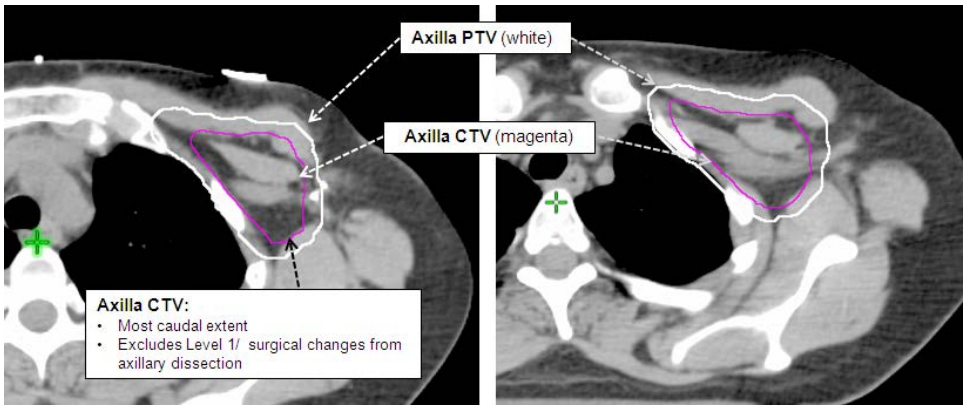
4.1.3 Axillary CTV: The extent of axilla to be targeted for regional nodal irradiation will depend on the extent of axillary surgery performed. The axillary CTV consists of the portion of the axilla that remains "undissected." When an axillary node dissection has been done, the inferior border of the axillary CTV will be the most cephalic extent of the dissection. Review of the operative report, postoperative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the axillary CTV. Axillary dissection typically removes level 1–2 axillary nodes, so that the axillary CTV in these cases is expected to include level 3 primarily and some of level 2 of the axilla. When a sentinel node biopsy alone is done without completion axillary dissection, the axillary CTV will then include all 3 levels of the axilla as all three levels are "undissected." The consensus definitions from the RTOG breast cancer for anatomical borders of the axillary levels are from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

4.1.4 Axillary PTV: See Figure 17A and Figure 17B and Figure 18A and Figure 18B. Axillary CTV + 5 mm. The ipsilateral lung should be excluded from the Axillary PTV. This means that some or all of the medial border of the Axillary PTV can be similar to the Axillary CTV.

Note: When planning with IMRT, it is recommended to create an additional structure that includes the SCL-PTV and the Axilla-PTV for optimization.

Figure 17A and Figure 17B. **Axillary CTV** and **Axillary PTV** after **AXILLARY DISSECTION**

17A. Non-contiguous Axial CT slices illustrating **Axillary CTV** and **Axillary PTV**. **Axillary PTV** is a 5 mm expansion on the **Axillary CTV**. Axillary PTV excludes the lung.



17B. Coronal CT slice illustrating **Axillary CTV and Axillary PTV** in setting of **AXILLARY DISSECTION**

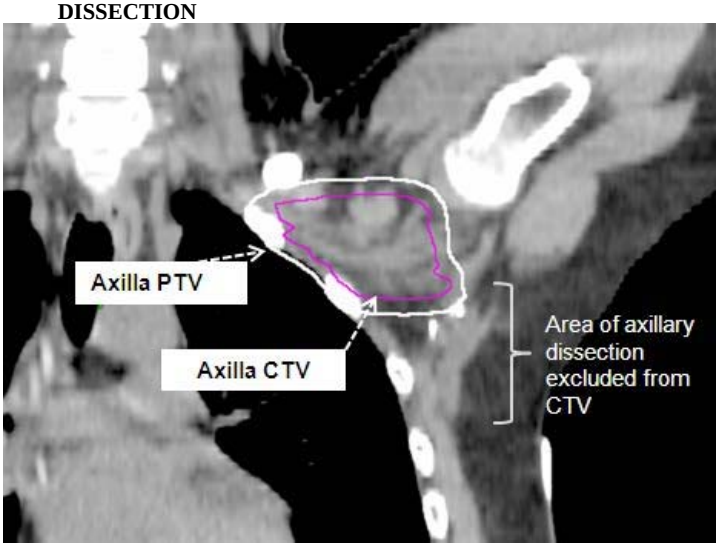
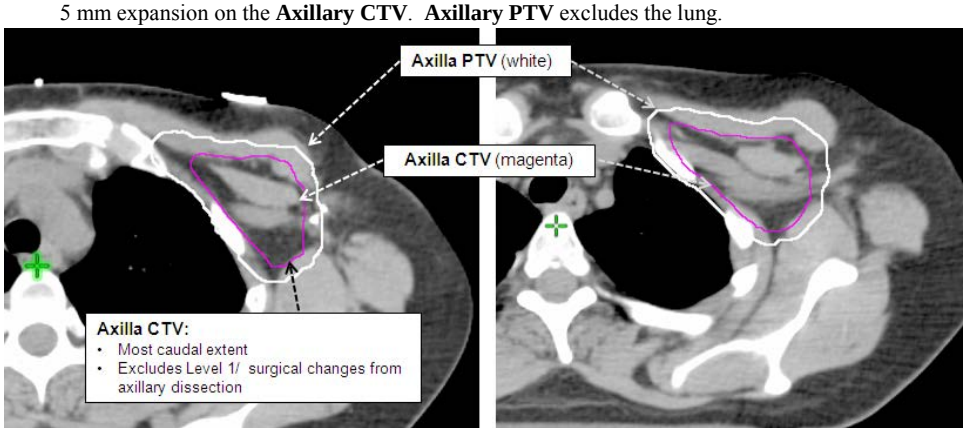
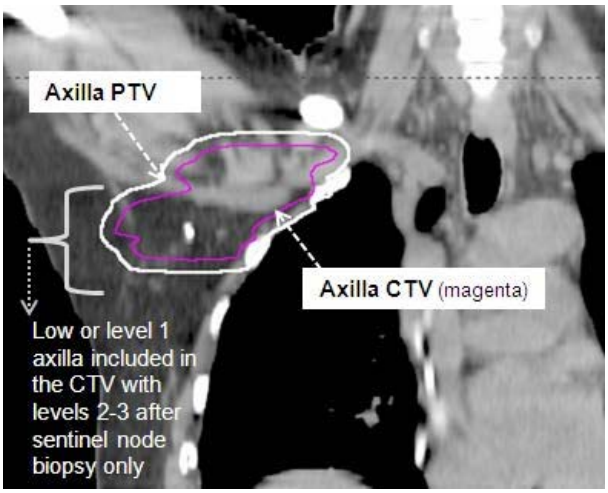


Figure 18A and Figure 18B. **Axillary CTV** and **Axillary PTV** after **AXILLARY DISSECTION**

18A. Non-contiguous Axial CT slices illustrating **Axillary CTV** and **Axillary PTV**. **Axillary PTV** is a 5 mm expansion on the **Axillary CTV**. **Axillary PTV** excludes the lung.



18B. Coronal CT slice illustrating **Axillary CTV** and **Axillary PTV** in setting of **SENTINTEL NODE BIOSY ONLY WITHOUT AXILLARY DISSECTION**

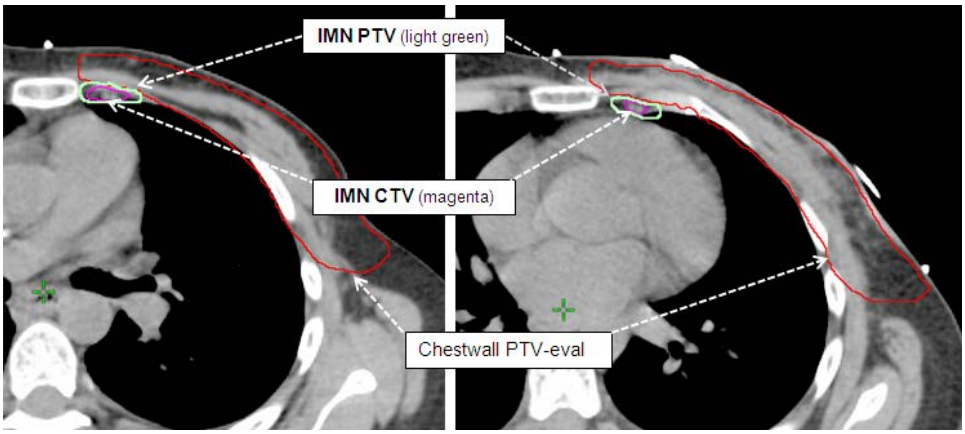


4.1.5 Internal mammary node (IMN) CTV: See Figure 19A and Figure 19B. Includes the internal mammary/thoracic vessels in the first three intercostal spaces.

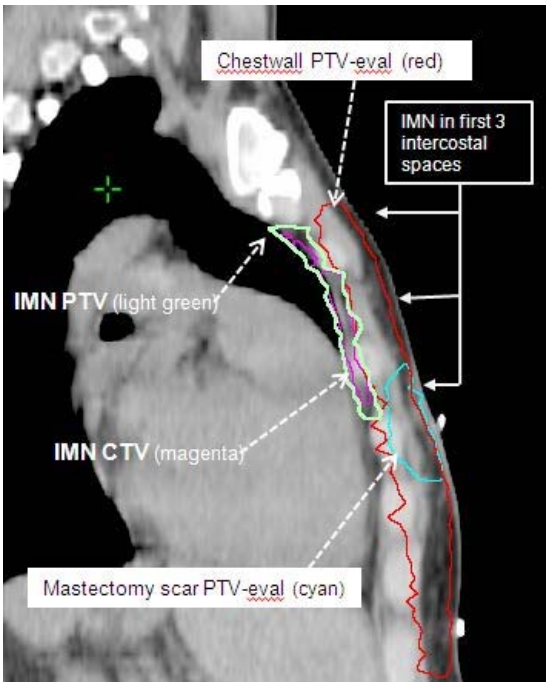
4.1.6 Internal mammary node (IMN) PTV: The IMN CTV + 5 mm expansion medially, laterally, superiorly, and inferiorly. The IMN PTV is limited medially to not extend into the sternum. In order to minimize excess normal tissue irradiation, no additional expansion into the lung should be done for the IMN PTV. The deep edge of the IMN PTV will be similar to the IMN CTV. No anterior expansion into the chestwall or breast volumes will be done.

Figure 19A and Figure 19B. **IMN CTV** and **IMN PTV**

19A. Non-contiguous Axial CT slices illustrating **IMN CTV** and **IMN PTV**. **IMN PTV** is a 5 mm medial and lateral expansion of the **IMN CTV**. **IMN PTV** excludes the lung, heart, sternum, chestwall and/or breast



19B. Sagittal CT slice illustrating **IMN CTV** and **IMN PTV** are limited to the first 3 intercostal spaces



5.0 **ORGANS AT RISK (OAR)**

The OAR to be contoured on all cases are the ipsilateral and contralateral lung, heart, thyroid, and contralateral breast.

5.1 Ipsilateral and contralateral lung: This may be contoured with auto-segmentation with manual verification.

5.2 Heart: **This is to be contoured on all cases - not just the left-sided ones**. The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, and great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

5.3 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.

5.4 Contralateral Breast: Includes contralateral breast as defined by clinical markers and apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Cancer Atlas. In general the borders are:

Posterior border: At the anterior surface of the pectoralis, serratus anterior muscles excluding chestwall, ribs, boney thorax, and lung/heart.

Medial border: The sternal-costal junction.

Lateral border: Varies based on the size of the breast but typically is at the mid-axillary line and excludes the ipsilateral lattisimus dorsi muscle.

Cephald border: Should be similar to that of the ipsilateral breast CTV.

Caudal border: Inframammary fold and should be similar to that of the ipsilateral breast CTV.

Anterior border: Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface.