NRG ONCOLOGY
NRG-BR002
(ClinicalTrials.gov NCT02364557)

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

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 organization: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Group, and SWOG

Coordinating Center:
NRG Oncology
Four Penn Center
1600 JFK Blvd, Suite 1020

Study Team (21-SEP-2022)

Co-Principal Investigator/Radiation Oncology	**Co-Principal Investigator/Radiation Oncology**
Steven Chmura, MD, PhD University of Chicago 5840 S. Maryland Ave, MC9006 Chicago, Il 60637 773-702-0817/Fax:773-834-7233 schmura@radonc.uchicago.edu	Julia R. White, MD Ohio State University Comprehensive Cancer Center 300 W. 10th Avenue, Suite 094D Columbus, OH 43212 614-688-7373/Fax: 614-688-7356 julia.white@osumc.edu
Radiation Oncology Co-Chair/ALLIANCE Joseph K. Salama, MD Duke University Medical Center Box 3085 Durham, NC 27710 919-668-7338/Fax: 919-668-7345 joseph.salama@duke.edu	Medical Physics Co-Chair Hania Al-Hallaq, PhD University of Chicago 5758 S. Maryland Ave., MC9006 Chicago, IL 60637 773-702-3309/Fax:773-834-7233 hal-hallaq@radonc.uchicago.edu
Medical Oncology Co-Chair Virginia F. Borges, MD, MMSc University of Colorado Anschutz Medical Center 19801 E 17th Avenue, RC1S 8112 Aurora, CO 80045 303-949-9964/Fax:720-848-1774 virginia.borges@ucdenver.edu	Medical Physics Co-Chair Martha Matuszak, PhD University of Michigan 1500 E. Medical Center Dr. Ann Arbor, MI 734-232-6195/Fax:734-936-7859 marthamm@med.umich.edu

NRG ONCOLOGY

NRG-BR002

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

Study Team Continued

Translational Research Co-Chair
Wendy A. Woodward, MD, PhD
M.D. Anderson Cancer Center
1515 Holcombe Blvd, Box 1202
Houston, TX 77005
713-563-8481/Fax: 713-563-6940
wwoodward@mdanderson.org

Surgical Oncology Co-Chair/ALLIANCE
Nora Jaskowiak, MD
University of Chicago
5841 S. Maryland Ave. MC 4052
University of Chicago Medical Center
Chicago, IL 60637
773-834-7032/Fax: 773-834-4022
njaskowi@surgery.bsd.uchicago.edu

Lead Statistician
Kathryn Winter, MS
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-574-3198
winterk@nrgoncology.org

Translational Research Statistician
Hanna Bandos, PhD
Department of Biostatistics, GSPH
University of Pittsburgh
NRG Oncology
201 North Craig St., Suite 350
Pittsburgh, PA 15213
412-383-2554/Fax: 412-383-1387
bandosh@nrgoncology.org

Quality Assurance Co-Chair
Michael T. Milano, MD, PhD
University of Rochester
601 Elmwood Ave. Box 647
Rochester, NY 14642
585-273-4096/Fax: 585-275-1531
michael_milano@urmc.rochester.edu

Protocol Administrator
Kathryn Okrent
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-717-0856
okrentk@nrgoncology.org

Data Managers
Debora Washington, RN, MSN
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-574-3206
washingtond@nrgoncology.org

Wendy Bergantz, RN
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-574-3230
bergantzw@nrgoncology.org

RT Technical Details
Susan McNulty, BS, RT (R) (T),CMD
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-940-8907
smcnulty@acr.org

The following NCTN Group Study Champion has been added to this trial:

SWOG	Reshma Jagsi, MD University of Michigan Health System 1500 E. Medical Center Drive Ann Arbor, MI 48109 734-936-4300 rjagsi@med.umich.edu

NRG ONCOLOGY

NRG-BR002

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

Participating Sites
☒ U.S.
☒ Canada
☒ Approved International Member Sites

Document History

	Version Date	Broadcast Date
Amendment 7	**September 21, 2022**	**N/A**
Amendment 6	August 12, 2021	N/A
Amendment 5	July 11, 2018	N/A
Amendment 4	June 14, 2018	N/A
Amendment 3	July 12, 2017	August 28, 2017
Amendment 2	9/16/16	10/10/16
Amendment 1	1/12/16	2/22/16
Activation	12/05/2014	12/24/2014

NRG ONCOLOGY

NRG-BR002

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

CONTACT INFORMATION (21-SEP-2022)

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at http://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU member's website (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 log in with a CTEP-IAM username and password.

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 Regulatory Support System (RSS).

For patient eligibility or treatment-related questions: Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line

For TRIAD access and installation support:
TRIAD-Support@acr.org

Triadhelp.acr.org

TRIAD Software Installation:
https://triadinstall.acr.org/triadclient/

TABLE OF CONTENTS

SCHEMA 8

1. OBJECTIVES 9
- 1.1 Primary Objectives 9
- 1.2 Secondary Objectives 9
- 1.3 Exploratory Objectives 9
- 1.4 Translational Research Objectives 9

2.BACKGROUND 10
- 2.1 NRG-BR002 Rationale and Trial Design 13
- 2.2 Translational Research 15

3.PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA 17
- 3.1 Patient Selection Guidelines 17
- 3.2 Eligibility Criteria 17
- 3.3 Ineligibility Criteria 18

4.REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP 20
- 4.1 Response/Failure Definitions 22
- 4.2 Disease Progression and Subsequent Treatment 23

5. TREATMENT PLAN/REGIMEN DESCRIPTION 24
- 5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy 24
- 5.2 Radiation Therapy (This section applies to Arm 2 only) 25
- 5.3 Surgery (Arm 2) 63
- 5.4 General Concomitant Medication and Supportive Care Guidelines 64
- 5.5 Duration of Therapy 65

6. TREATMENT MODIFICATIONS/MANAGEMENT 66

7.ADVERSE EVENTS REPORTING REQUIREMENTS 66
- 7.1 Protocol Agents 66
- 7.2 Adverse Events and Serious Adverse Events 66
- 7.3 Expedited Reporting of Adverse Events 66
- 7.4 Routine Reporting Requirements for Adverse Events 70

8.REGISTRATION AND STUDY ENTRY PROCEDURES 70
- 8.1 CTEP Registration Procedures and Access Requirements for OPEN, Medidata Rave, and TRIAD ..... **Error! Bookmark not defined.**
- 8.2 Site Registration Requirements 71
- 8.3 RT-Specific Pre-Registration Requirements 74
- 8.4 Patient Enrollment 77

9.DRUG INFORMATION 78

10.PATHOLOGY/BIOSPECIMEN 78

11.SPECIAL STUDIES 85

12.MODALITY REVIEWS 85
12.1 Radiation Therapy Quality Assurance Reviews 85
12.2 Surgical Quality Assurance Reviews 86

13.DATA AND RECORDS 86
13.1 Data Management/Collection 86
13.2 Summary of Data Submission 87
13.3 Data Quality Portal 87
13.4 Global Reporting Monitoring 88

14.STATISTICAL CONSIDERATIONS 88
14.1 Study Design 88
14.2 Study Endpoints 88
14.3 Primary Objectives Study Design 88
14.4 Study Monitoring of Primary Objectives 93
14.5 Accrual Considerations 95
14.6 Secondary or Exploratory Elements 95
14.7 Gender/Ethnicity/Race Distribution 97

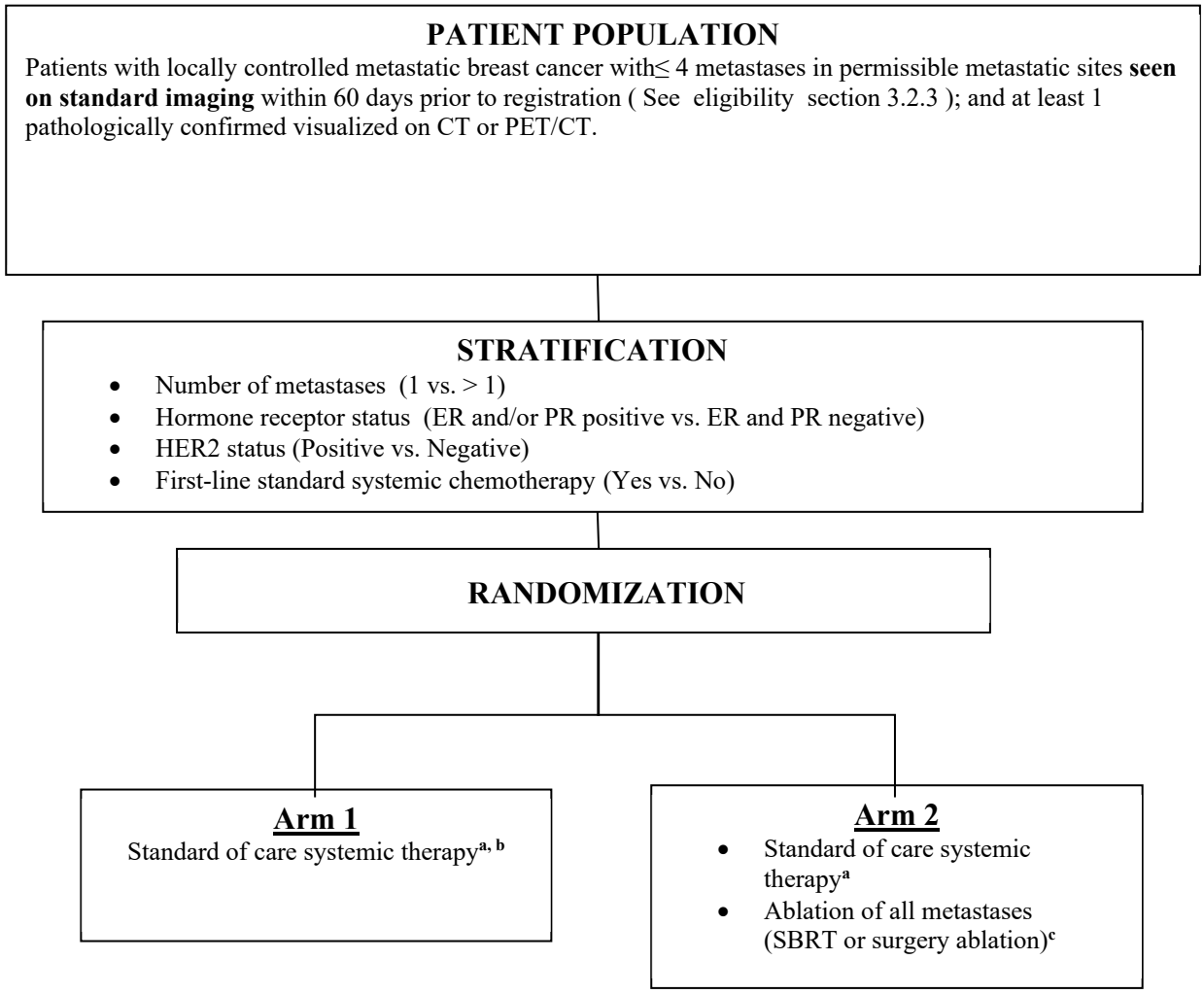
REFERENCES 98

NRG ONCOLOGY

NRG-BR002

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

SCHEMA (14-JUN-2018)



[a] Standard of care systemic therapy for metastatic disease will be given as appropriate for the patient's disease subtype (ER+, HER2 +, TNBC) at the discretion of the treating physician.

[b] Metastatic sites present at registration that require palliation in **Arm 1** can be addressed by standard palliative therapy (i.e., radiotherapy), surgery, or interventions such as vertebroplasty, RFA, etc.) (see Section 5.0).

[c] The selection of either surgery or radiation for ablation of a given metastasis in **Arm 2** is at the discretion of the treating physician. See Sections 5.2 and 5.3.

1. OBJECTIVES

1.1 Primary Objectives

Phase II-R

To determine whether ablation (through SBRT and/or surgical resection of all known metastases) in oligometastatic breast cancer patients provides a sufficient signal for improved progression-free survival (PFS) to warrant full accrual to the Phase III portion of the trial

Phase III

To determine whether ablation (through SBRT and/or surgical resection of all known metastases) in oligometastatic breast cancer patients significantly improves overall survival (OS)

1.2 Secondary Objectives (14-JUN-2018)

- To evaluate treated metastasis control according to tumor receptor status (ER, PR, HER-2), use of chemotherapy, surgery vs. ablative therapy, and number of metastases
- To evaluate whether the addition of ablative metastasis directed therapy significantly reduces the number of distant recurrences (new metastases) in patients who progress according to tumor receptor status (ER, PR, HER-2); use of chemotherapy, and number of metastases.
- To evaluate adverse events in patients who receive ablative metastasis-directed therapy to all known metastases in addition to standard medical therapy compared with those treated with standard medical therapy alone.

1.3 Exploratory Objectives (14-JUN-2018)

- To explore the most appropriate and clinically relevant technological parameters to ensure quality and effectiveness throughout the radiation therapy processes, including imaging, simulation, target and critical structure definition, treatment planning, image guidance, and delivery.

1.4 Translational Research Objectives (14-JUN-2018)

1.4.1 Primary Objective

To determine whether < 5 CTCs (per 7.5ml of blood) is an independent prognostic (outcome) marker for improved PFS and OS in oligometastatic breast cancer

1.4.2 Secondary Objectives

- To determine whether < 5 CTCs (per 7.5ml of blood) is an independent predictive (response to therapy) marker for improved PFS and OS in oligometastatic breast cancer
- To determine whether eliminating CTCs (0/7.5ml of blood in patients with at least 2 CTCs at registration) is both a prognostic and predictive marker for improved PFS and OS.
- To evaluate the prognostic and predictive properties of CTC count as a continuous measure of PFS and OS
- To store material for retrospective analysis of ctDNA.

- To store material for retrospective analysis of circulating microRNA.

2. BACKGROUND

Several clinically-based hypotheses have attempted to explain the metastatic spread of breast cancer. Halsted (1907) argued for an orderly spread from primary tumor to regional lymph nodes to metastases. Rubin and Green were the first to suggest, in 1968, (Rubin Solitary Metastases 1968) the notion of "solitary metastases" and that such metastatic tumors could be treated with curative intent. A systemic hypothesis articulated most clearly by Fisher (1980) suggested that widespread dissemination of disease occurred before clinical detection. Based on the observation that not all breast cancer may be widely metastatic at initial presentation, Hellman advanced our understanding of the natural history of metastasis by proposing a spectrum hypothesis of metastasis. Within this model, some breast cancers remain locoregionally confined, others metastatic at presentation, and some progress from locoregional confinement to metastatic (Hellman, 1994). Soon thereafter, Hellman and Weichselbaum described the clinically relevant oligometastatic state in patients with limited number of metastases and where long-term disease control may be achievable with metastasis-directed therapy (Hellman 1995).

The current standard of care (SOC) for metastatic breast cancer (MBC) patients is to deliver palliative chemotherapy, biologic and/or hormonal therapy when appropriate, with radiation and/or surgery reserved for the management of symptomatic or non-responsive metastases. In this paradigm, a very small number of MBC patients are alive long-term. A population-based analysis by Greenberg et al. (1996) reported the outcomes of over 1,500 women with MBC treated at M.D. Anderson Cancer Center with doxorubicin and alkylating agent-based chemotherapy; 1.6% remained free of relapse at 15 years. These data, coupled with the accepted curative role that adjuvant chemotherapy plays in the non-metastatic setting suggests that systemic therapies are helpful in addressing micrometastatic spread of breast cancer. However, single or poly-agent chemotherapy is unlikely to be curative in patients with gross (image detected) metastases.

For selected patients with limited metastatic disease, metastasis-directed therapy, either surgical resection or ablative radiotherapy (in addition to standard systemic therapies) to lung (Simpson 1997, Rusthoven 2009, Fumagalli 2012) liver (Fong 1997, Rusthoven 2009, Dewas 2012, Vlastos 2004, Fumagalli 2012), CNS (Wronski 1995, Kocher 2011, Maclean 2013), adrenal (Tanvetyanon 2008, Torok 2011), and multiple organs (Salama 2012, Milano 2012) has been shown to result in long-term disease control numerically superior to that seen when systemic therapy is administered alone. Specifically in breast cancer patients, ablative metastasis-directed therapies have been shown to result in promising PFS and OS (Abbott 2012, Fridel 2002, Staren 1992, Pockaj 2010, McDonald 1994, Milano 2009). While these reported series have been primarily retrospective, taken together they identify long-term survival from metastasis-directed therapy in patients with limited breast cancer metastases. The benefits these patients derive may come from delaying progression in known metastases, as well as preventing known metastases from seeding new metastases. Furthermore, ablative radiation may have an abscopal effect, improving outcomes by inhibiting progression of micrometastatic foci (Demaria 2004, Formenti 2008, Stamell 2012).

We hypothesize that ablative metastasis-directed therapy with either Stereotactic Body

Radiotherapy (SBRT) or surgery in combination with standard systemic therapy may meaningfully impact the natural history of some oligometastatic breast cancers. Indeed, Tree and colleagues observed in a 2013 review that a large number of non-randomized studies have found a 2-5 year progression-free survival rate approaching 20%, signaling a tremendous improvement with the application of SBRT to oligometastatic disease (Tree 2013).

In order to provide improved prognostic information for patients with oligo MBC and potentially to predict those patients likely to respond favorably to aggressive chemotherapy or biologic agents, new biomarkers have been developed. One of the most promising techniques relies on detecting the presence of circulating tumor cells (CTCs) in patients with MBC. Data suggest these circulating tumor cells may be close in origin to the tumor stem cells responsible for metastatic disease. Using the FDA-approved and commercially available CellSearch™ assay, ≥ 5 CTCs (per 7.5ml of blood) prior to first or second line chemotherapy predicts progression-free survival (PFS) and overall survival (OS) (Cristofanilli 2004). The prognostic value of CTCs in response to chemotherapy appears superior to other widely used prognostic tools such as metastases location or type of chemotherapy employed.

A recently completed Phase III trial (SWOG S0500) altered treatment selection of chemotherapy based on ≥ 5 CTCs (per 7.5ml of blood) detected and levels in the blood. These recently reported results showed those with high levels of CTCs that decreased with therapy did better than those with high levels of CTCs that persisted after therapy. Unfortunately, changing therapy did not improve outcomes for patients with high CTCs, potentially because the standard next line therapies available do not often have significant clinical benefit for this cohort. It is important to note that the current trial represents a very different population than the SWOG 0500 study. Herein the patients have oligometastatic disease as opposed to unselected metastatic disease. Further, those who progress on standard therapy will not be eligible representing a selection for good prognosis oligometastatic disease in this trial.

The challenge for ablative therapy in MBC is to identify those patients for whom this approach might be at least beneficial and possibly curative. Pragmatically, it should be curative for patients in whom the visible disease to be treated is truly all of the disease, and where the ability of existing circulating disease to seed new sites is minimal, either because there are few circulating cells being shed, or because a high volume of cells are circulating but they lack the biology to seed. The former is easier to identify using CTCs. One might expect that in metastatic patients with few or no CTCs, ablative therapy may provide durable NED status, since new metastases are less likely to form because small volume circulating disease that is not seeding may be eradicated by systemic agents more readily than gross deposits of tumor. For those with high levels of CTCs, we hypothesize that eradication of CTCs by ablative therapy will indicate that the primary source of CTCs is the known and treatable metastases, and not occult metastases likely to re-seed after ablative therapy and prevent durable no evidence of disease (NED) status. Of course, failure to ablate the known disease would also fail to eradicate CTCs.

The proportion of MBC patients who present with 1-2 metastases is high. Prior first-line MBC trials were reviewed to determine an estimated frequency of patients who would fit the inclusion criteria for this clinical trial. Approximately 50% of the patients from these trials representing differing ER and HER2 status enrolled with ≤ 2 metastases. A current Phase I

trial is assessing the safety of ablating ≤ 4 metastases [NRG-BR001]. If this Phase I trial confirms the safety of ≤4 metastases as targetable for ablative therapy, then an amendment to the current protocol would increase the enrolling population to upwards of 75% of first-line MBC patients as potentially eligible. These studies demonstrate that first-line metastatic patients likely to enroll on clinical trials often present with oligometastatic disease and would qualify for enrollment in this clinical trial.

SBRT is being increasingly used as a technique to treat patients with limited MBC. A recent international survey of radiation oncologists (Lewis 2013) found that 61% of respondents were using SBRT to treat patients with limited metastatic disease. Furthermore, of those not currently offering this treatment, more than half were planning to start offering SBRT for limited metastases in the next 3 years. Therefore, at the time of activation of this study, >75% of practicing radiation oncologists will be offering this treatment to patients with limited metastatic disease. While there is increasing evidence that administration of SBRT for oligometastatic disease is measurably beneficial and its use is becoming more common, the initiation of randomized trials to ultimately prove clinical benefit will be increasingly difficult due to SBRT becoming the de facto standard of care (Tree 2013). Therefore, this proposed randomized clinical trial is profoundly important not only due to the anticipated treatment outcomes, but also because of the imperative to ensure safety and benefit before an unproven consensus of approach becomes more widely accepted.

Table 2-1. Frequency of patients enrolled on first-line metastatic breast cancer trials with limited number of metastatic sites who appear potentially eligible for ablative therapy.

Author/ Study	Phase	n	ER/PR + (%)	HER2+	≤ 2 met sites (%)	≤ 4 Met Sites (%)	Arms	PFS (Mo.)
Albain 2008		599	32	-	57	91	1. Gem + Paclitaxel 2. Paclitaxel	9.89 8.4
Bergh 2012		593	72	Pos.	52	-	1 Sunitinib+ Docetaxel 2. Docetaxel	8.6 8.3
Tawfik 2013	II	30	77	Neg.	50	-	1. Vinorelbine, capecitabine	8.6*
Hurvitz 2013	IIR	137	54	Pos	49.3	-	1. Trastuz + Docetaxel 2. T-DM1	9.2 14.2
Gianni 2013	III AVEREL	424	51	Pos	50	-	1. Docetaxel+ Trastuz 2. Docet + Tras + BEV	13.7 16.5
Sledge 2003	III E1193	739	45	-	49	-	1. Doxorubicin 2. Paclitaxel 3. Doxorubicin + Paclitaxel	6* 6.3* 8.2*

*Time To Failure

2.1 NRG-BR002 Rationale and Trial Design

We propose to evaluate an alternative treatment paradigm for this subset of oligometastatic MBC patients: elective ablation of all metastases after systemic therapy with a Phase II/III trial design.

The randomized Phase II portion will compare the standard of care, systemic therapy and palliative surgery/radiation therapy (non-SBRT) only to areas of pain or potential and significant clinical risk (Arm 1), with ablation of all visible metastases in addition to standard systemic therapy (Arm 2). If a PFS signal is observed, a Phase III trial would be warranted to determine whether OS at five years is significantly improved. As a secondary endpoint, we will evaluate whether 1) the absence or low number of CTCs (using the FDA approved Cellsearch™ assay at registration) may be predictive of those likely to obtain durable PFS, 2) eradication of CTCs from registration to follow-up sufficient to complete SBRT (4 weeks after SBRT) on Arm 2 and initiate SOC therapy on Arm 1 (3 months) is predictive of durable PFS, and 3) whether this successful eradication can be of prognostic value for PFS and OS. We predict those with few or no CTCs are ideal candidates for SBRT and will have longer PFS than those with ≥ 5 CTCs (per 7.5ml of blood), and that eradication of CTCs with SBRT will be possible and will identify

patients in whom CTCs originated from ablated metastases as opposed to those with CTCs from occult disease or CTCs from ablated metastases that seeded prior to ablation of metastases. Further, we hypothesize that PFS will be longer in those with zero or low levels of CTCs (< 5/7.5ml of blood) treated with ablative therapy than with supportive care, and that those with eradication of CTCs in either arm will have longer PFS than those with persistent CTCs at the follow-up collection. If the former were true, CTCs could be used to identify patients for ablative therapy and if the latter were true, change in CTCs could be used to identify those who should receive additional adjuvant therapies after ablative therapy.

This design would directly test the hypothesis that some metastases may be the source of new disease spread, as suggested by recent translational studies (Karnoub 2007,Valastyan 2009). For example, patients for whom there are minimal shed CTCs at the time of presentation or in cases where CTCs shed from ablative-treatable lesions lack the biology to seed new metastases effectively, ablative therapy may establish durable PFS. If low levels of CTCs at registration correlate with PFS after ablative therapy, this would be a meaningful adjunct to clinical findings in order to select patients for this approach. Further outcome can be compared between those on each arm with low levels of CTCs (< 5/7.5ml of blood) for hypothesis generation regarding the optimal therapy in this setting. If ablative therapy in the setting of eradication of CTCs correlates with PFS, this could be incorporated in future studies to determine the timing and utility of systemic chemotherapy most beneficial in these cases. These data would truly help shape practice in the metastatic setting, where limited metastatic disease is amenable to ablative therapy. The rate of eradication of high levels of CTCs (≥ 5/7.5ml of blood) can be compared in the ablative and SOC arms to generate hypotheses regarding the preferred approach in this setting as well.

This would be the first randomized trial to answer whether ablation through surgery or SBRT can alter the progression of MBC treated with standard systemic therapy. Furthermore, this would be the first National Clinical Trials Network randomized study to evaluate prospectively the multimodal use of ablative metastasis-directed therapy (either surgery and/or radiotherapy) integrated into the metastatic treatment. While ablative radiotherapy is currently being used either in small, single institution trials or off protocol, no data exist in a randomized setting to demonstrate its efficacy or justify the adoption. The results of this trial paired with ongoing and recently completed studies would significantly enhance our knowledge about the impact of these therapies. A seamless randomized Phase II/III design is critical to first observe a signal in PFS indicating the need for a Phase III investigation.
Whether through demonstrating either an improved PFS, OS, or through elucidating a better understanding of the biology of metastatic disease, this trial would alter clinical practice by determining which, if any, population of patients should be offered elective metastasis-directed ablative treatment.

Arm 1 (Standard of Care)
Patients randomized to standard of care therapy (Arm 1) will continue with their current planned systemic therapy as appropriate for their disease subtype (ER+, HER2 +, TNBC) at the discretion of the treating physician. National Comprehensive Cancer Center (NCCN) guidelines for metastatic breast cancer are recommended. Areas of symptomatic

metastatic disease or at risk of injury that require palliation can be addressed by standard palliative therapy (i.e., radiotherapy (non-SBRT), surgery, or interventions such as vertebroplasty, RFA, etc.) consistent with best medical practice. Radiotherapy in Arm 1 will be limited to known progressive lesions that are causing symptoms including hemorrhage, neurologic deficits, pain, obstruction of a hollow visceral organ, dyspnea, etc. Prophylactic treatment of asymptomatic metastasis, unless the risk of an impeding clinical event exists, is not allowed in Arm 1 and will represent a treatment violation.

Arm 2 (SBRT +/- Surgery)

Patients randomized to receive metastasis-directed therapy (Arm 2) will have ablative radiotherapy and/or surgical resection to distinct metastases visualized on standard imaging studies. Following completion of the radiotherapy and/or surgery, patients will then continue with additional systemic therapy as planned, at the discretion of the treating physician.

2.2 Translational Research (14-JUN-2018)

The translational endpoints of this trial will confirm the prognostic value of CTCs in this cohort and investigate the interaction with treatment and effect of change in CTCs in this oligometastatic population. Funding for this portion has been obtained through philanthropy as outlined in Section 10. We hypothesize baseline zero or low levels of CTCs (<5/7.5ml of blood) will be associated with longer PFS (OS) than a baseline of ≥ 5 CTCs (per 7.5ml of blood). Secondary analysis will examine the interaction of CTC number with treatment, and if eradication of CTCs (among patients starting with any number > 2/7.5ml of blood to eliminate false positive findings or sample variability) will be associated with longer PFS (OS). For further correlative studies, we will collect and store plasma at all CTC timepoints to later isolate the circulating tumor DNA (ctDNA), perform the same analyses, and compare directly to CTCs. Standard tumor banking will be performed as well.

We propose to collect CTCs for consenting patients at registration, 4 weeks from completion of ablative therapy in the ablative therapy study arm and 3 months from registration (to be delayed until after first cycle of chemotherapy if none received at 3 months) in the standard of care arm and at progression in both arms, if applicable, in order to address the above hypotheses (see Section 10).

As in Table 2-3, studies of CTC count in metastatic patients reveal CTCs in 40-60% of enrolled patients. In the prospective study by Cristofanilli et al. (2004), which enrolled patients with measurable disease starting a new therapy, 60% of patients had at least 2 CTCs per 7.5ml of blood (no healthy control had 2 CTCs), and 49% had 5 or more CTCs per 7.5ml of blood. These data are reflected in the recent SWOG 0500 study where 50% of patients had ≥ 5 CTCs per 7.5ml of blood. The number of cases with 5 or more CTCs per 7.5ml of blood was only influenced by whether they were selected for chemotherapy, with 30% of those receiving only hormonal or immunotherapy treatments having 5 or greater CTCs per 7.5ml of blood. Therefore, given the fact that some patients will be ineligible based on progression on chemotherapy, we conservatively expect 50% of patients to have > 2 CTCs per 7.5ml of blood and 25% to have 5 or greater CTCs per 7.5ml of blood. In addition, we seek to determine whether the conversion of patients with

two or more CTCs per 7.5ml of blood to negative following ablative therapy will be prognostic for improved PFS and OS. Based on prior published work in both non-metastatic (Table 2-2) and the first or second line metastatic population (Table 2-3), we expect that at least 25% of patients will have CTCs ≥ 5/7.5ml of blood. We estimate, based on neoadjuvant CTC conversion rates, that 25% of these patients will be CTC positive post-ablative therapy.

Table 2-2

Prognostic significance of CTCs* in non-metastatic Breast Cancer					
Author	Year	# Patients	CTC+ (%)	Follow-up (months)	Prognostic
Rack [19]	2010	2026	22%	35	DFS/ OS
Rack [20]	2010	1489	9%	32	DFS/ OS
Franken [23]	2012	404	19%	48	DFS/ OS
Pierga [28]	2008	118	23%	18	DFS c
Bidard [30]	2010	115	23%	36	DFS/ OS

* CellSearch™ Assay

Table 2-3

Prognostic Significance of CTCs* Metastatic Breast Cancer				
Author	Year	# Patients	CTC+ (%)	Prognostic
Giordano [67]	2012	517	40% a	PFS/ OS
Wallwiener [69]	2013	486	42%	PFS/ OS
Pierga [68]	2012	267	44% a	PFS/ OS
Giuliano [73]	2011	235	40% a	PFS/ OS
Cristofanilli [13]	2004	177	60%	PFS/ OS
Hayes [65]	2006	177	54%	PFS/ OS
Budd [74]	2006	138	43%	OS
Nakamura [75]	2010	107	37%	PFS
Nole [77]	2008	80	61%	PFS

* CellSearch™ Assay

In addition to CTCs, circulating tumor DNA (ctDNA) has recently been shown in several cancer types to also act as a prognostic marker of poor outcomes (Heitzer 2013; Alix-Panabieres 2012; Bidard 2014). In these small studies, the detection of ctDNA proved to be as good as or superior as a prognostic marker to CTCs. By storing plasma from the same time points as the CTC collection, we will batch analyze the ctDNA to determine their respective clinical significance. Details of this analysis will be determined at the time of batch analysis. The Kuhn Laboratory at the University of Southern California (USC) will oversee these analyses. This lab is widely recognized as the forefront of the state of the art and USC will shortly begin a new institute specifically dedicated to the multi-scale science approach co-locating Math/Modeling, Rare Cell Analysis, Medical Sciences and Engineering. As such from the same ctDNA tube, Dr. Kuhn and his collaborators will use high-content single cell

liquid biopsy (HD-SCA) analyses of all patients before and after treatment, and more importantly the mathematical model development to bring together clinical and experimental data. This provides the real opportunity to enhance the model with a specific modern data set, which in turn has the potential of giving us new insights into the spread of breast cancer to guide future treatment concepts. Markovian models have demonstrated the ability to recapitulate clinical observations in metastatic progression. The specific setting of oligometastatic disease in NRG-BR002 provides an ideal setting for data assimilation into the existing mathematical framework. This will involve correlation of the clinical response data from the patients on NRG-BR002 to the laboratory based translational science study.

See Section 10 for details.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted.

For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact IROC Philadelphia (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential who are sexually active should be willing and able to use medically acceptable forms of contraception during protocol treatment.

3.2 Eligibility Criteria (14-JUN-2018)

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

3.2.1 Pathologically confirmed metastatic breast cancer

3.2.2 Known estrogen, progesterone, and HER2 status of either primary tumor or metastasis; **Note: estrogen, progesterone and HER2 status of metastasis preferred for stratification**

3.2.3 Number of allowable metastases:

≤ 4 metastases **seen on standard imaging within 60 days prior to registration when all metastatic disease is located within the following sites:**

- peripheral lung
- osseous (bone)
- spine
- central lung
- abdominal–pelvic(lymph node/adrenal gland)
- liver
- mediastinal/cervical lymph node

3.2.4 All known disease amenable to metastasis-directed therapy with either SBRT or resection; **NOTE:** Symptomatic bone metastasis are allowed if ablative therapy can be delivered.

NOTE: Sites for possible surgical excision include lung, liver, adrenal gland, bone, small intestine, large intestine, ovary, and amenable nodal disease sites.
NOTE: Surgical stabilization is allowed for a metastasis if it is followed by conventionally fractionated external beam radiotherapy.

3.2.5 Maximum diameter of individual metastasis in any dimension ≤ 5 cm;

3.2.6 There are no restrictions on distance between the metastases.

3.2.7 Patients must be registered within 365 days of the ***initial*** metastatic breast cancer diagnosis. First-line standard systemic therapy (chemotherapy, anti-endocrine therapy, anti-HER2 or other standard targeted therapy) for metastatic breast cancer must be given or planned to be given. If given before study entry, it cannot have exceeded a duration of 12 months at the time of registration. (Note: Sequencing of ablative therapy (surgery or SBRT) relative to systemic therapy, for patients randomized to Arm 2, is at the discretion of the treating physician.)

- See Section 5.4.1 for washout required for experimental therapeutics;

3.2.8 The primary tumor site must be controlled prior to registration

- For those who present with s***ynchronous primary*** and oligometastatic disease:
  - Primary must be controlled prior to registration.
  - The definition of control is definitive surgery by excision or mastectomy (+/- radiotherapy) per institution preference
- For those who present with local recurrence and oligometastatic disease, local recurrence must be controlled prior to registration
  - The definition of control is definitive surgery by excision or mastectomy (+/- radiotherapy) per institution preference

3.2.9 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination within 60 days prior to registration;
- Clinical grade CT scans of the chest, abdomen, and pelvis with radionuclide bone scan OR whole body PET/CT within 60 days prior to study registration;

3.2.10 Age ≥ 18;

3.2.11 Zubrod Performance Status ≤ 2 within 60 days prior to registration;

3.2.12 CBC/differential obtained within 60 days prior to registration on study, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 500 cells/mm^3;
- Platelets ≥ 50,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable);

3.2.13 For females of child-bearing potential, negative serum or urine pregnancy test within 14 days prior to study registration;

3.2.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.2.15 Patient must be female

3.3 Ineligibility Criteria (14-JUN-2018)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Pathologic evidence of active primary disease or local/regional breast tumor recurrence at the time of registration;

3.3.2 Co-existing or prior invasive malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years; previous RT dose, date, fraction size, must be reported

3.3.3 Metastases with indistinct borders making targeting not feasible;
NOTE: A potential issue with bone metastases is that they often are not discrete. Since many patients on this protocol will have bone metastases, this will be an important issue. Theoretically, Houndsfield units might provide an appropriate measure; however, a sclerotic lesion against dense cortical bone will not have a sharp demarcation based on HU. Therefore, we acknowledge that such determinations will pose a challenge and thus the physician's judgment will be required;

3.3.4 Prior palliative radiation treatment for metastatic disease to be treated on the protocol (including radiopharmaceuticals);

3.3.5 Metastases located within 3 cm of the previously irradiated structures:
- Spinal cord previously irradiated to > 40 Gy (delivered in ≤ 3 Gy/fraction)
- Brachial plexus previously irradiated to > 50 Gy (delivered in ≤ 3 Gy/fraction)
- Small intestine, large intestine, or stomach previously irradiated to > 45 Gy (delivered in ≤ 3 Gy/fraction)
- Brainstem previously irradiated to > 50 Gy (delivered in ≤ 3 Gy/fraction)
- Whole lung previously irradiated with prior V20Gy > 30% (delivered in ≤ 3 Gy/fraction)
- Primary tumor irradiated with SBRT
- Metastasis irradiated with SBRT

3.3.6 Brain metastases;

3.3.7 Exudative, bloody, or cytological proven malignant effusions;

3.3.8 Severe, active co-morbidity defined as follows:
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;

3.3.9 Pregnancy. Lactating females must cease expression of milk prior to signing consent to be eligible.

3.3.10 HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS (14-JUN-2018)

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
Initial diagnosis of metastatic breast cancer	≤ 365 days	
History/physical examination	≤ 60 days	
CT Scans of the chest/abdomen/ pelvis with radionuclide bone scan OR whole body PET/CT	≤ 60days	
Performance Status	≤ 60 days	
CBC w/ diff & ANC, platelets	≤ 60 days	
ALT, AST		If SBRT will be delivered to liver
Serum/urine pregnancy test (if applicable)	≤ 14 days	
MRI of the liver		Highly recommended prior to initiating SBRT or surgical resection to the liver (for radiation treatment planning)
MRI of the vertebral column		Highly recommended for all patients with suspected epidural tumor extension
Optional studies: CTC Blood Collection, Whole blood, Plasma (for biobanking and ctDNA), Serum, and Tissue		≤14 days

ASSESSMENTS DURING SBRT TREATMENT

Assessment	Time Points			
	Week 1 during SBRT	Week 2 during SBRT (if applicable)	Week 3 during SBRT (if applicable)	Last day of SBRT
Physical examination	X	X	X	X
Performance status	X	X	X	X
ALT, AST				If SBRT delivered to liver

Adverse event evaluation	X	X	X	X

ASSESSMENTS IN FOLLOW UP: Arm 1 (14-JUN-2018)

Assessment	**Timepoints**		
	3 mos after randomization and every 3 months to 24 months	**Yearly thereafter**	**At progression**
Physical examination	X	X	
Assessment by treating surgeon and/or Radiation Oncologist and/or other health care provider responsible for your protocol follow-up	X	X	
Performance status	X	X	
Adverse event evaluation	X	X	
Optional studies*: CTC Collection, Plasma (ctDNA)	X		X
Tissue (optional)			X
Imaging studies**	X	X	

*Note: CTC and ctDNA collections are only required at month 3 time point; to be delayed until after first cycle of chemotherapy if none received at 3 months

**Note: We strongly encourage the use of PET/CT to follow patients for disease progression in patients randomized to Arm 2 and who undergo SBRT.

ASSESSMENTS IN FOLLOW UP: Arm 2 (14-JUN-2018)

Assessments	Timepoints			
	25-35 d post ablation	**3 mos after random-ization and every 3 months to 24 months**	**Yearly thereafter**	**At progression**
Physical examination		X	X	
Assessment by treating surgeon and/or Radiation Oncologist and/or other health care provider responsible for your protocol follow-up		X	X	
Performance status		X	X	
ALT, AST		X (If SBRT delivered to the liver)	X (If SBRT delivered to the liver)	
Adverse event evaluation		X	X	
Optional studies: CTC Collection, Plasma (ctDNA)	X			X
Tissue (Optional)				X
Imaging studies**		X	X	

**Note: We strongly encourage the use of PET/CT to follow patients for disease progression in patients randomized to Arm 2 and who undergo SBRT.

4.1 Response/Failure definitions

It is strongly preferred that the same imaging method that was used to originally detect the metastases be used in follow-up assessments.

Arm 1 metastases or Arm 2 metastases treated with SBRT:
Response and progression for these metastases will be evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

- **Complete Response (CR)**: Disappearance of the target lesion.

- **Partial Response (PR):** At least a 30% decrease in the longest dimension (LD) of the target lesion, taking as reference the baseline LD.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for progression below, taking as reference the smallest LD since the treatment started.

- **Progression:** At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started. The measurable tumor with criteria meeting progression should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET (if performed), OR the measurable tumor should be biopsied confirming viable carcinoma. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation vs. treated metastasis progression.

- **Recurrence:** Reappearance of metastases following a CR in the SBRT treated area.

Arm 2 metastases treated with Surgery:

- Complete resection – total resection with negative margins
- Incomplete resection – gross or microscopic residual disease (i.e. positive margins)
- Progression: Evidence of tumor/soft tissue mass growth or new metastases in the region of prior surgery on imaging (strongly preferred that the same imaging method that was used to originally detect the metastases be used in follow-up assessments).

4.2 Disease Progression and Subsequent Treatment:

Patients who develop progression will be followed on protocol for subsequent disease and survival events. Patients who progress should receive best medical therapy as judged per their treating physician. These may include, but not limited to chemotherapy, hormonal therapy, biologic therapy, radiosurgery, cryotherapy, and radio-frequency ablation (RFA).

5. TREATMENT PLAN/REGIMEN DESCRIPTION (14-JUN-2018)

Patients randomized to standard of care therapy (Arm 1) will continue with their current planned systemic therapy as appropriate for their disease subtype (ER+,HER2 +, TNBC) at the discretion of the treating physician. Metastatic disease present at registration that requires palliation can be addressed by standard therapy (i.e., radiotherapy, surgery, or other interventions such as vertebroplasty, RFA, etc.) consistent with best medical practice. Radiotherapy in Arm 1 is permissible with palliative intent to known lesions present at registration that are causing symptoms not controlled by medical therapy (e.g. pain medications). Typical radiotherapy regimens for symptom control include 30 Gy in 10 fractions, 24 Gy in 6 fractions , 20 Gy in 5 fractions, 8 Gy in 1 fraction or other similar equivalent regimens. As there is not level 1 evidence of improved **symptom control** with SBRT compared to typical palliative radiotherapy regimens its use is strongly discouraged in the standard arm. Prophylactic treatment of metastasis present at registration that are asymptomatic, unless at risk for an impeding clinical event such as cord compression or pathologic fracture, is not allowed in Arm 1 and will represent a treatment violation.

Patients enrolled onto Arm 2 of this study will be treated with ablative therapy (surgery and/or SBRT) to all known metastases. Surgery or SBRT are acceptable treatments for an individual metastasis. In a given patient, metastases may be treated with surgery to all, radiation to all, or surgery to one and radiation to the other.

NOTE: The combination of surgery **and** SBRT to the same metastasis is **NOT** allowed. The selection of surgery or radiation is at the discretion of the treating physicians within the following recommendations: following the completion of ablative therapy (surgery and/or SBRT), systemic therapy may be continued at the discretion of the treating oncologist.

NOTE: The clinical scenario where a patient presents with oligometastatic disease with an osseous metastasis requiring surgical stabilization, or decompressive surgery, surgery followed by conventionally fractionated RT is allowed at the discretion of the treating physician. SBRT **will NOT** be delivered post-operatively to the operative bed. There must be one metastasis amenable to ablative therapy following surgical stabilization.
NOTE: For Arm 2 patients, sequencing of ablative therapy (surgery or SBRT) relative to systemic therapy is at the discretion of the treating physician. It is anticipated that most ablative therapy (surgery or SBRT) will be done after systemic therapy has started.

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

Standard of care systemic therapy should be administered at the discretion of the treating medical oncologist. It is recommended that the systemic therapy follow standard guidelines for use of chemotherapy, hormonal therapy, bone protective therapy, and biologic therapy as appropriate for the patient's metastatic breast cancer. Parameters for withholding systemic therapy around the ablative therapy of patient's randomized to Arm 2 are outlined in Section 5.4.

5.2 Radiation Therapy (This section applies to Arm 2 only) (14-JUN-2018)

NOTE: PRE-TREATMENT REVIEWS are required for the first patient for each of the listed disease site categories (see Section 5.2.1). Three (3) business days are required to complete a pretreatment review. See Section 12.1 for more details.
For patients receiving radiation SBRT must begin within 6 weeks of study entry

SBRT for all metastases should be completed within 3 weeks of the first dose of SBRT. It is recommended that metastases are treated on an every other day schedule. Not all metastases need to receive radiation therapy on the same day.

The goal of SBRT treatment is to deliver appropriate metastasis-directed radiotherapy while minimizing exposure of surrounding normal tissues. Many different ways of delivering SBRT exist, and all are acceptable as long as the treating institution has completed the necessary credentialing. Most commercially available photon-producing treatment units are allowed. As such, conventional linear accelerators and specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TrueBeam) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, or Tomotherapy) are allowed provided they meet the technical specifications of the protocol and are used in a fashion that passes the credentialing required by the protocol. Conventional linear accelerators without add-on IGRT must have some other IGRT capability like CT-on-rails in the treatment room.

IGRT is required for this study. Either 3DCRT or IMRT (including VMAT) are acceptable planning techniques. IMRT (including VMAT) can result in dosimetric inaccuracies in circumstances where tumor motion is not properly considered. Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique when the target or targets are in or near the thorax region.

5.2.1 Dose Fractionation

Patients will receive 1, 3, or 5 fractions of radiation. SBRT doses to be used are listed below in Tables 5-1 and 5-2. Doses were selected based on available evidence. Where evidence was minimal, expert consensus was used. Metastases should be assigned to one of the following seven metastatic locations to determine preferred dosing schedules:

1. Lung Peripheral
2. Lung Central
3. Mediastinal/Cervical Lymph Nodes
4. Liver
5. Spinal/Paraspinal
6. Osseous
7. Abdominal-pelvic (including abdomino-pelvic lymph nodes/adrenal glands)

Dosing schemes are in general divided between patients with osseous and non-osseous disease as shown in Tables 5-1 and 5-2. For each metastatic location, preferred dosing schemes are described together with the Variation Acceptable range used for plan scoring. Doses falling outside the range of Per Protocol and Variation Acceptable will be scored as Deviation Unacceptable.

NOTE: Utilizing the same dosing scheme is strongly suggested when a given OAR receives >5Gy (total for the radiation course) contribution from multiple treatment sites (see Section 5.2.6).

There should be a minimum of 40 hours between treatments to any single metastasis; however, a patient may receive radiation for different metastases on consecutive days

Table 5-1

	NON-OSSEOUS SITES (Lung Peripheral, Lung Central, Mediastinal/Cervical, Liver, Abdominal-pelvic)	
	Prescription Dose	
Number of Fractions	**Per Protocol**	**Variation Acceptable**
1 (Single fraction regimen will be limited to peripheral lung and single liver metastases)	30 Gy	28 - 30.3 Gy
3 (Preferred for lung-peripheral, liver, and abdominal-pelvic metastases)	45 Gy	42.5 – 45.5 Gy
5 (Preferred for central lung. Mediastinal/ cervical lymph nodes)	50 Gy	48 – 50.5 Gy

Note: Doses outside the range of Per Protocol and Variation Acceptable will be scored as Deviation Unacceptable.

Table 5-2

	OSSEOUS SITES (Spinal/Paraspinal, Other Osseous)	
	Prescription Dose	
Number of Fractions	**Per Protocol**	**Variation Acceptable**
1 (Single fraction regimen will be limited to spinal metastases)	20 Gy	14 – 20.2Gy
3 (Preferred for non-spinal metastases)	30 Gy	27 – 30.3 Gy
5 (Preferred for thoracic/cervical spine)	35 Gy	30 – 35.4 Gy

Note: Doses outside the range of Per Protocol and Variation Acceptable will be scored as Deviation Unacceptable.

The dose per fraction shown in Table 5-1 is to be prescribed to the prescription line covering 95% of the PTV (see Section 5.2.5). **NOTE**: Metastases in different anatomical locations may be treated to different doses and with different fractionation schedules in the same patient (e.g., spine metastasis treated to 30Gy in 1 fraction while a central lung metastasis is treated to 50Gy in 5 fractions). However, it is preferable to use the same dose to treat all metastases, when reasonable, to allow for more straightforward dose volume analysis of organs at risk (e.g., both spine and central lung metastases treated to 50Gy in 5 fractions).

5.2.2 Technical Factors

Physical Factors

Only photon (x-ray) beams with photon energies ≥ 6MV will be allowed. For metastases located within 3 cm of the lungs, photon energies of 6-10MV are required. Cobalt-60 and charged particle beams (including electrons, proton, and heavier ions) are not allowed.

For lung central and lung peripheral metastases, photon beam energies > 10 MV are allowed only for a limited number (≤ 50% of all beams or all beam angles) of beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter OR a shorter distance if the tumor abuts the chest or abdominal wall (i.e., to spare skin dose).

FFF photon beams are allowed if the institution has performed SBRT credentialing with FFF beams.

Treatment Technology

This protocol requires photon treatment. Techniques including 3DCRT, IMRT, VMAT are allowed. Delivery on LINACs, Tomotherapy, or CyberKnife are acceptable.

Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 3 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques, where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed. In addition, if the site has specifically commissioned the beams for smaller field sizes, and if these same beams have been employed in IROC Houston QA Center credentialing, they may reduce the minimum field aperture requirement to the size commissioned after pre-approval by the physics co-chairs.

All institutions must use heterogeneity correction dose calculation algorithms approved by the IROC Houston QA Center independent of the treatment planning technique. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

Stereotactic Targeting

For the purposes of this protocol, the term 'stereotactic' implies the targeting, planning, and directing of radiation beams along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable 'fiducials.' A fiducial may be external or internal to the patient's body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers OR reliably identifiable anatomy that is clearly visible on orthogonal kV imaging, including the tumor itself. In all cases, the relationship between the fiducial and the actual tumor position in real-time should be reliably understood for both planning and treatment.

Isocenter Placement

When using a gantry mounted linear accelerator for this protocol, the isocenter is defined as the common intersection point of gantry, collimator, and couch rotation for the treatment unit. For other types of treatment units (e.g., Tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter.

When treating multiple lesions, it is best to use multiple isocenters, each centered on a separate lesion, and to treat different targets on different days in order to decrease treatment time for a single day. For widely spaced lesions (over 10 cm apart), localization is improved when the isocenter is placed in the center of each target and image guidance is performed individually for each target. This is due to the limitation of most IGRT systems, which ignore necessary rotational corrections when table shift coordinates are derived. Some platforms, including Cyberknife and Tomotherapy, are inherently non-isocentric. These platforms take special account in the setup and treatment process to rigorously detect and account for rotations to avoid errors, making them exempt from the separate isocenter for each lesion requirement. For other platforms, the use of a single isocenter to treat multiple lesions in proximity to each other may be allowed if the

institution has successfully been credentialed by IROC Houston QA Center's phantom irradiation for SBRT treatment of 2 lesions with a single isocenter setup. Please contact the PIs directly before utilizing a single isocenter to treat multiple metastases.

Composite Dose Calculations

Composite plans must be generated to incorporate the dose to surrounding normal tissues from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance. Composite planning refers to dose summation from multiple treatment sites on a single CT scan that encompasses the relevant anatomy. Composite treatment planning is best accomplished by obtaining a planning CT dataset that incorporates all targets and relevant critical structures in the imaging study. If this is not possible due to restrictions on the size of the imaging study that can be managed by the treatment planning system, CT datasets should be divided into two parts and treatment fields should be adjusted so that dose spillage from the treatment of targets in one dataset to the next is minimal such that the dose contributions do not require summation. The two datasets should be obtained so that they have some amount of overlap that can be used to fuse the information using a rigid registration technique. The use of deformable registration to sum dose is not allowed. In general, it is best to perform CT scanning with the patient in the same position. This implies that, for example, all lesions planned on a gated CT scan must be treated with gating. If technical limitations are encountered in summing dose, contact the Study Chairs with questions regarding composite planning.

5.2.3 Localization, Simulation, and Immobilization

Patient Positioning (Immobilization)

Patients will be positioned in a stable pose conducive to allowing accurate reproducibility of the target position throughout treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV). Positioning patients directly on the couch and relying solely on image-guidance for reproducible set-up is strongly discouraged.

Simulation

All patients will undergo CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used), and be adequate to ensure contouring of all targeted metastases, as well as necessary organs at risk (OAR), defined below. High-resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm throughout. If a single CT scan cannot be obtained due to a large spatial separation between metastases (i.e., cervical and femoral metastases), or planning system slice number limitation, multiple CT scans are allowed provided that OAR are entirely encompassed in a single CT scan. CT imaging should be performed so that a composite dose distribution including all treated metastases can be created. Ideally, all metastases will be treated in one treatment position. When treating multiple metastases such as a lung and extremity, varying the treatment position may be necessary (i.e., simulation with arms up and arms to the side). Thus, more treatment positions can be used at the

discretion of the treating oncologist, but every effort should be made to obtain a composite distribution.

Use of Contrast Agents

The use of IV contrast will be required for liver metastases. For other metastases (central & peripheral lung, cervical/mediastinal, abdominal-pelvic, and spinal/paraspinal), the use of IV contrast is encouraged but will be left to the discretion of the treating physician. The use of other contrast agents is left to the discretion of the treating oncologist. Vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for planning. Duplicate planning datasets obtained prior to injection of intravenous contrast may be used for dose calculation.

Respiratory Motion Assessment and Management

All metastases with potential for respiratory motion should be evaluated by appropriate means including 4D CT scan, implanted fiducial marker, or fluoroscopy at the time of simulation.

Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any metastasis to be treated with motion > 5mm. A recommended approach would be to use an ITV technique for motion < 1cm, but for motion > 1cm (typically too large for a free breathing ITV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

If a treatment for multiple metastases (i.e., lung and spine) is designed on a CT scan employing motion management (i.e., abdominal compression), all metastases should be treated with the chosen motion management technique in order to generate an accurate composite dose calculation. (see Section 5.2.2)

Localization Using Daily IGRT

As an SBRT protocol, this study requires the use of IGRT. NRG Oncology defines IGRT as a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes also including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the Tomotherapy approach. Although all of these units are allowed, some might not be appropriate for some disease sites. For example, orthogonal imaging techniques result in overlapping structures that are not as easily visualized compared to 3D cone-beam approaches. Simple portal imaging approaches that do not use computer assistance are not considered suitable for this study.

When the treatment equipment does not include any device that allows direct visualization of anatomical structures using the treatment beam, the recommendations of AAPM Task Group Report 142 for testing the coincidence of the imaging and treatment reference points must be implemented. For example, verification of treatment and imaging isocenter coincidence must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

IGRT Requirements

The minimum IGRT requirement for each metastatic location is listed in Table 5-3. Volumetric imaging refers to 3D modalities (e.g., kV cone-beam, MV cone-beam, CT on rails), while orthogonal imaging refers to 2D modalities (e.g., kV OBI, ExacTrac). For volumetric imaging, appropriate CT window/level thresholds must be employed for registration at each metastatic location as outlined in Table 5-4. Additional IGRT may be employed at the discretion of the treating physician (i.e., orthogonal kV imaging prior to required volumetric imaging or volumetric imaging even if only orthogonal kV imaging is required). Note that when orthogonal kV imaging is employed for sites where respiratory motion is expected and not controlled via motion management techniques, care must be taken to ensure accurate targeting of the ITV within the treatment. For example, static kV imaging at an undetermined breath hold position would not be adequate IGRT for treating a free-breathing lung tumor.

Table 5-3

Metastatic Location	**Minimum IGRT Requirement**	
	No Fiducials	**With Fiducials****
Lung--Peripheral^{+}	Volumetric (3D)	Orthogonal kV (2D)
Lung—Central^{+}	Volumetric (3D)	Orthogonal kV (2D)
Mediastinal/Cervical LN	Volumetric (3D)	N/A
Liver^{+}	Volumetric (3D)	Orthogonal kV (2D)
Spinal	Orthogonal kV (2D)	Orthogonal kV (2D)
Osseous*	Orthogonal kV (2D)	N/A
Abdominal-pelvic^{+}	Volumetric (3D)	Orthogonal kV (2D)

***NOTE**: When osseous/rib metastases are classified into another metastatic location, follow the IGRT guidelines for that site.

****NOTE**: When a metastasis contains an implanted fiducial that is clearly visible on kV orthogonal or volumetric imaging, either method can be used.

$^{+}$**NOTE**: Registration to a soft tissue surrogate for the tumor is recommended for lung, liver, and abdominal-pelvic metastases for both 3D and 2D IGRT datasets.

Use of a shortened CT planning scan for registration may be important for IGRT systems that cannot handle a large number of CT slices. A subset of the planning CT scan can be

uploaded to the IGRT system for localization of each metastasis. The CT data should include the metastasis of interest plus at least 5cm superiorly and inferiorly. Please note that the composite dose must be calculated on a single CT scan encompassing all pertinent OAR (see Section 5.2.2)

5.2.4 Target Volumes

Metastasis Location Definition:
Each metastasis to be treated will be assigned to one of the seven "Metastasis Locations" as described below for determination of preferred radiation schedules as shown in Tables 5-1 and 5-2.

Metastatic Locations:
Lung Central: GTV within 2 cm of proximal bronchial tree as described in RTOG 0813/0915:
Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi) [See Figure 5-1]. Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol. A visual representation is shown below in Figure 5-1.

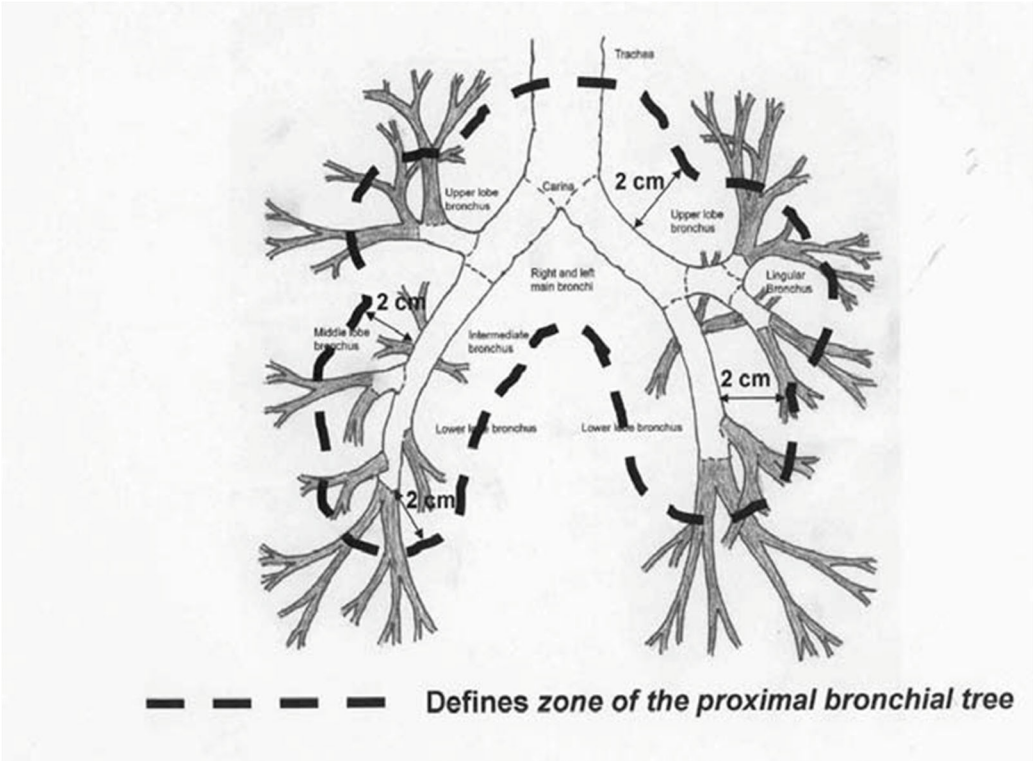


Figure 5-1

Lung Peripheral: Metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above.
Mediastinal/Cervical LN: Mediastinal: GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sternal notch. Cervival Lymph nodes: GTV occurring within cervical lymph node Levels I-VI and/or retropharyngeal spaces

- Sternal metastases will be assigned to the mediastinal/cervical lymph node location based on potential for normal tissue toxicity.

Liver: GTV arising within the liver.

- Rib metastases immediately adjacent to the liver will be assigned to the liver metastasis location based on potential for normal tissue toxicity.

Spinal: Metastases will be assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1 cm. Spinal metastases, shown in Figure 5-2 in black, can involve:

(a) The vertebral body only **OR**
(b) The vertebral body and pedicle **OR**
(c) Posterior elements only

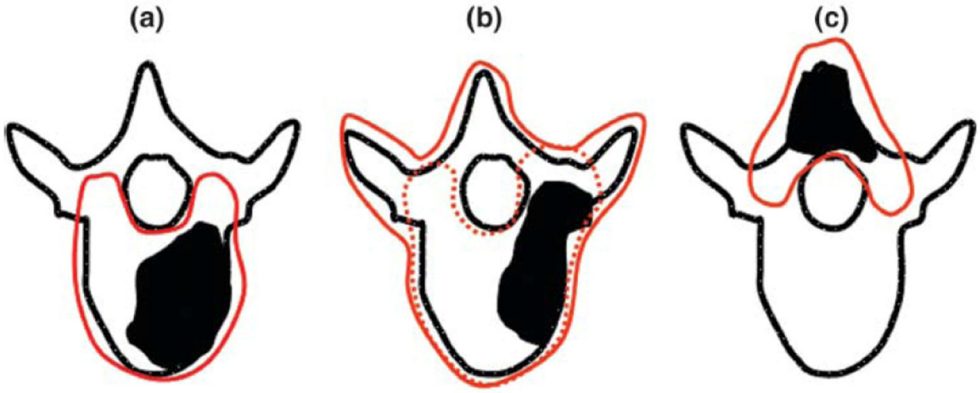


Figure 2: Diagram of Spine Metastasis and Target Volume

Figure 5-2

For each of these metastases, the PTV delineation will include:

(a) the involved vertebral body and both pedicles (solid red line in Figure 5-2a) **OR**

(b) a more generous delineation of the involved vertebral body and both pedicles (dashed red line in Figure 5-2b) **OR**

(c) the involved vertebral body, both pedicles, and the anterior and posterior elements of the spine (solid red line in Figure 5-2b) **OR**

(d) the spinous process and laminae (solid red line in Figure 5-2c)

- The target volume may be chosen at the discretion of the treating Radiation Oncologist based on the extent of tumor involvement.
- Spinal metastases with epidural extension will only be included if there is > 3 mm gap between the edge of the epidural metastasis and edge of the spinal cord.
- Metastases arising in the ribs within 1 cm of the edge of the vertebral body should be included in the spinal metastasis location, but osseous metastases planning guidelines are to be used.

Osseous: GTV arising within an osseous structure, part of the axial skeleton, not included in the spinal definition.

- Rib metastases that are within 1 cm of the vertebral bodies will be classified into the spinal metastasis location given the similar normal tissues at risk.
- Rib/scapular metastases within the thorax adjacent to lung parenchyma will be classified into the lung metastasis location given the similar normal tissues at risk.
- Rib/osseous metastases adjacent (≤ 1cm) to mediastinal or cervical structures will be classified into the mediastinal/cervical lymph node location given the similar normal tissues at risk.
- Rib metastases adjacent (≤ 1cm) to the liver will be classified into the liver location given the similar normal tissues at risk
- Rib metastases adjacent to the stomach/abdominal wall will be classified into the intra-abdominal location given the similar normal tissues at risk
- Sternal metastases will be considered part of the mediastinal/cervical lymph nodes location given the similar normal tissues at risk.

Abdominal-pelvic: GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly including the peritoneal and retroperitoneal spaces, not including liver, osseous, or spinal metastases.

Target Volume Definition Based on Metastatic Location:
Specific SBRT planning parameters depend on the location of the treated metastasis as well as mechanism used for motion management/evaluation. The table below defines appropriate planning CT window/leveling, recommended additional modality scans to be fused, as well as how to define the GTC, ITV, CTV, and PTV for each metastatic location. Only rigid registration will be permitted for multi-modality fusion. In general, the GTV is defined as the entirety of the metastasis as seen on planning CT scan aided by additional diagnostic imaging studies (i.e., PET/CT or MRI). Use of additional diagnostic studies is left to the discretion of the treating physician. The CTV=GTV; there is no margin added for microscopic extension. In general, either a helical CT or 4DCT will be

used for defining the GTV/ITV depending upon the tumor motion encountered, although both scans may be acquired at the time of simulation. Typically, the ITV is generated using either expiratory/inspiratory phase scans or from reconstructed maximum intensity projection (MIP) scans. Maximum/minimum intensity projections (MIP/MinIP) should be used with caution because the MIP reconstruction for lung or MinIP reconstruction for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP).

Table 5-4

	Metastatic Location						
Planning Parameter	**Lung Central**	**Lung Peripheral**	**Liver**	**Abdominal-pelvic**	**Mediastinal/ Cervical Lymph Nodes**	**Osseous**	**Spinal**
CT window/level	Pulmonary/ Mediastinal	Pulmonary/ Mediastinal	Hepatic	Soft tissue	Pulmonary/ Mediastinal	Bone/soft tissue	Bone/soft tissue
Additional Studies	PET/CT	PET/CT	PET/CT MRI	PET/CT MRI	PET/CT	PET/CT MRI	PET/CT MRI
Multiphase CT	N/A	N/A	N/A	Yes	N/A	N/A	N/A
Anatomy of focus for multi-modality fusion	Bony Anatomy	Bony Anatomy	Liver	Bony Anatomy	Bony Anatomy	Bony Anatomy	Bony Anatomy
GTV definition	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis
CTV definition	= GTV/ITV*	= GTV/ITV*	= GTV/ITV*	=GTV/ITV*	=GTV/ITV*$^{+}$	= GTV	= GTV
PTV axial expansion	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= PTV in RTOG 0631** (see Figure 5-2)
PTV craniocaudal expansion	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= PTV in RTOG 0631** (see Figure 5-2)

***NOTE:** A GTV to ITV expansion of greater than 1cm in any one direction is strongly discouraged and alternative respiratory management technique is suggested.

****NOTE:** When osseous/rib metastases are classified into other specific metastatic locations, the planning guidelines for that metastatic location should be used. If rib

metastases are grouped into the spinal metastasis location, then the metastasis should be contoured as defined for osseous metastases, but the prescription doses for the spinal region should be used.

+**NOTE:** Mediastinal lymph nodes should undergo motion assessment and an ITV should be generated to account for motion.

5.2.5 Treatment Planning

Note: also see Composite Dose Calculations in Section 5.2.2

Planning Techniques

General Considerations: A variety of planning techniques can be used to deliver SBRT for each metastasis. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7-13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed while treating small metastases with 3D-CRT.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span a total for all beams of 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90%, but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45 Gy/0.6 = 75 Gy when 45 Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

Dose calculations: All dose distributions shall include corrections for tissue heterogeneities. The approved algorithms to be used are found on the IROC Houston website (http://irochouston.mdanderson.org). All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

Successful treatment planning will require accomplishment of all of the following criteria; these criteria will be assessed on dose calculated independently for each metastasis (i.e., not from composite dose calculations):

1. Normalization: The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While

this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.

2. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV as shown in Figure 5-3. The prescription isodose surface selected MUST be ≥ 60% and ≤ 90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.
3. Target Dose Heterogeneity: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR (see Figure 5-3).
4. Critical Organ Doses: Respect all critical organ dose-volume limits listed in Section 5.2.6).
5. High-Dose Spillage:
    a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV. See Figure 5-3.
    b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end, the ratio of prescription isodose volume to PTV should be as small as possible.
        i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_5000 with the 5000 changing to reflect the prescription dose in cGy. Contours with identical doses should be distinguished according to the convention described in section 5.2.6.
        ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in Table 5-5. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple metastases, this ratio should be evaluated for dose calculated for a single metastasis at a time (i.e., not for composite dose). Additionally, the 50% isodose volume may be elongated deliberately in order to avoid OAR, thereby making it difficult to meet the guidelines in Table 5-5. This is acceptable as long as normal tissue constraints are met.

iii. Given that conformal tumor coverage is often more difficult to achieve in lung than in more homogeneous organs, these ratios should serve as a guide for liver, abdominal-pelvic, mediastinal/cervical metastases as well.

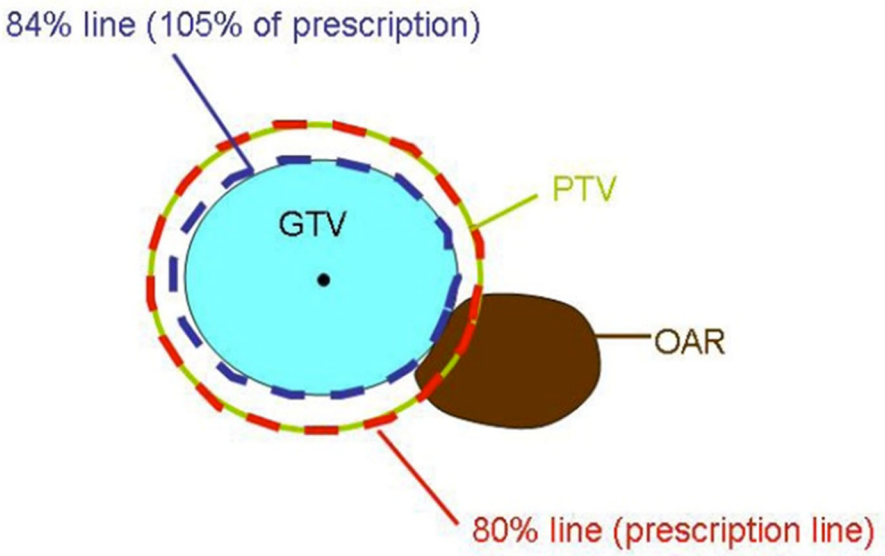
iv. Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected. These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm (see Section 5.2.2) results in the inability to meet a conformity ratio of 1:5

Table 5-5

PTV Volume (cc)	**Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%**	**Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose**
1.8	< 7.5	<57.0
3.8	< 6.5	<57.0
7.4	< 6.0	<58.0
13.2	< 5.8	<58.0
22.0	< 5.5	<63.0
34.0	< 5.3	<68.0
50.0	< 5.0	<77.0
70.0	< 4.8	<86.0
95.0	< 4.4	<89.0
126.0	< 4.0	<91.0
163.0	< 3.7	<94.0

NOTE: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

NOTE: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be used.



1. Prescription dose 50 Gy
2. Prescription isodose 80%
3. 105% of prescription dose 52.5 Gy (corresponds to 84% isodose line)
4. Maximum dose (normalization) at isocenter is 62.5 Gy

Figure 5-3

Planning Priorities

Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria without receiving a plan score of Deviation Unacceptable. In some circumstances, it may not be possible to meet all the ideal criteria, leading to plans in the Variation Acceptable range. Thus, suggested priority of planning goals in order of importance is:

1. Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints.
2. Meet dose "compactness" constraints including the prescription isodose surface coverage, high-dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the aim in using SBRT. Dose compactness should be assessed for plans based on treatment dose for a single lesion at a time. OAR dose constraints should be met based on composite dose planning as discussed in the last subsection of Section 5.2.2.

3. Meet critical structure constraints other than those listed in 1. The OAR constraints are last in priority (except for nervous system tolerance) because they are the least validated. The aim of a stereotactic plan is captured mostly

in the dose compactness criteria, thereby justifying their higher priority. As an example, in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation, even at the expense of a non-spinal cord normal tissue having acceptable deviation. Unacceptable deviations should be avoided in all cases.

4. In cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OAR (see Section 5.2.6), coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation . Please contact Study Team when this is done to ensure this is not scored as a Deviation Unacceptable.

5.2.6 Critical Structures

Note: All required structures must be labeled as listed below in Table 5-6 for digital RT data submission. Resubmission of data will be required if labeling of structures does not conform to the standard DICOM name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD. If multiple lesions named PTV_4500 exist, each should be labelled according to numerical order of the anatomical sites listed in 5.2.1 (e.g., "PTV_4500_1" is a peripheral lung lesion while "PTV_4500_4" is a liver lesion). If multiple lesions exit within a single anatomical site, each lesion can be distinguished by adding a letter to the end of the PTV name ("PTV_4500_1a" and "PTV_4500_1b").

Table 5-6

Standard Name	***Description***
Group 1: Lung - Peripheral	
PTV_4500_1 or PTV_3000_1	For peripheral lung tumors.
GTV_4500_1 or GTV_3000_1	For peripheral lung tumors
PTV_20_1	PTV with 2cm expansion
NonPTV_1	External minus PTV
NonPTV_20_1	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should

	be contoured
Heart	Heart
External	Body surface
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Liver	Liver
BileDuct	Bile duct
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Group 2: Lung - Central	***Description***
PTV_5000_2	For central lung tumors
GTV_5000_2	For central lung tumors
PTV_20_2	PTV with 2cm expansion
NonPTV_2	External minus PTV
NonPTV_20_2	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney

Kidney_L	Left Kidney
Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 3: Mediastinal/Cervical Lymph Node	***Description***
PTV_5000_3	For mediastinal and cervical lymph node tumors.
GTV_5000_3	For mediastinal and cervical lymph node tumors.
PTV_20_3	PTV with 2cm expansion
NonPTV_3	External minus PTV
NonPTV_20_3	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 4: Liver	***Description***

PTV_4500_4 or PTV_3000_4	For liver tumors.
GTV_4500_4 or GTV_3000_4	For liver tumors.
PTV_20_4	PTV with 2cm expansion
NonPTV_4	External minus PTV
NonPTV_20_4	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
ChestWall	Chest wall
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Femurs	Both Femurs
Duodenum	Duodenum
Bladder	Bladder
Liver	Liver
BileDuct	Bile duct
Ureter	Ureter
Bowel	Large and Small Bowel
Group 5: Spinal/Paraspinal	***Description***
PTV_2000_5 or PTV_3000_5 or PTV_3500_5	For spinal/paraspinal tumors.
GTV_2000_5 or GTV_3000_5 or GTV_3500_5	For spinal/paraspinal tumors.
NonPTV_5	External minus PTV
NonPTV_10_5	External minus PTV_10 (PTV with a 1 cm expansion)
NonPTV_20_5	External minus PTV_20 (PTV with a 2.0 cm expansion)
SpinalCord	Spinal cord
SpinalCord_Prt	A portion of the spinal cord contoured near a target
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
CaudaEquina	Cauda equine
SacralPlexus	Sacral plexus
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchialTree	Carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
BronchTree_20	Proximal bronchial tree expanded by 2cm

ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Liver	Liver
BileDuct	Bile duct
Duodenum	Duodenum
Bowel	Large and Small Bowel
Rectum	Rectum
Bladder	Bladder
Femurs	
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 6: Osseous	***Description***
PTV_2000 _6 or PTV_3000 _6 or PTV_3500 _6	For non-spinal osseous tumors.
GTV_2000_6 or GTV_3000 _6 or GTV_3500 _6	For non-spinal osseous tumors.
NonPTV _6	External minus PTV
NonPTV_10 _6	External minus PTV_10 (PTV with a 1 cm expansion)
NonPTV_20 _6	External minus PTV_20 (PTV with a 2.0 cm expansion)
SpinalCord	Spinal cord
SpinalCord_Prt	A portion of the spinal cord contoured near a target
BrachialPlexus	Brachial plexus
CaudaEquina	Cauda equine
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
SacralPlexus	Sacral plexus
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchialTree	Carina, right and left main bronchi, right and left upper lobe bronchi,

	intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
BronchTree_20	Proximal bronchial tree expanded by 2cm
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Liver	Liver
BileDuct	Bile duct
Duodenum	Duodenum
Bowel	Large and Small Bowel
Rectum	Rectum
Bladder	Bladder
Femurs	
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 7*: *Abdominal-pelvic metastases (lymph node/adrenal gland)	***Description***
PTV_4500 _7	For abdominal-pelvic tumors.
GTV_4500 _7	For abdominal-pelvic tumors.
PTV_20 _7	PTV with 2cm expansion
NonPTV _7	External minus PTV
NonPTV_20 _7	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
CaudaEquina	Cauda equina
SacralPlexus	Sacral plexus
ChestWall	Chest wall
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Stomach	Stomach
Kidney_R	Right Kidney

Kidney_L	Left Kidney
Kidneys	Total kidneys
Femurs	Both Femurs
Duodenum	Duodenum
Bladder	Bladder
Liver	Liver
BileDuct	Bile duct
Bowel	Large and Small Bowel

Planning SBRT Near Prior Radiotherapy Volumes

The toxicity of delivering SBRT to multiple metastases in close proximity to prior conventionally fractionated external beam radiotherapy (EBRT) volumes is not known. Therefore, overlap of protocol treatment SBRT isodoses with prior fractionated external beam volumes must be minimized (see Section 3.3.5).

Organs at Risk

For all metastases-specific organs at risk (OAR) must be contoured. The specific OAR to be contoured will depend on the location of metastases to be treated. The contour of structures that have a lumen (bronchus, trachea, esophagus, etc.) will include both the "wall" and the "lumen" to result in a cylindrical structure. In general, OAR within 3 cm of any single metastasis should be contoured. To identify these OARs, all PTVs will be expanded by 3cm and any OAR that overlaps with PTV + 3cm must be contoured.

Lung Central/Lung Peripheral/Mediastinal/Cervical Lymph Node metastases:

- Proximal tracheobronchial tree (as defined by Timmerman et al. 2006)
- Lungs, left/right/combined
- Heart
- Great vessels
- Trachea
- Esophagus
- Spinal cord
- Chest wall
- Brachial plexus
- Skin
- Liver
- Bile duct
- Kidney, left/right
- Larynx
- Stomach
- Rib

Liver/Abdominal-pelvic metastases:

- Heart
- Stomach
- Duodenum
- Spinal cord

- Kidney, left/right
- Bowel
- Rectum
- Bladder
- Skin
- Lungs, left/right/combined
- Liver
- Bile duct
- Chestwall
- Sacral plexus
- Cauda equine
- Femurs

Spinal Metastases:

- For all spinal metastases, the partial spinal cord volume as per RTOG 0631 should be defined as follows: the partial spinal cord should be contoured starting from 5-6 mm above the superior extent of the target volume to 5-6 mm below the inferior extent of the target volume.
- For thoracic and cervical spinal metastases, follow guidelines for pulmonary/ mediastinal/cervical metastases depending upon nearby organs at risk.
- For lumbar metastases, follow guidelines for abdominal-pelvic metastases.

Osseous Metastases:

- OAR for osseous metastases will depend on the location of the osseous metastasis.

NOTE: OAR listed above should be contoured in their entirety if a portion of that organ is located within 3 cm of the osseous metastases.

Contouring of Normal Tissue Structures

In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal ending at L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Cauda Equina

Starting at the conus (end of spinal cord, typically around L1 or L2), include the entire spinal canal into the sacrum to the filum.

Sacral Plexus

Include the nerve roots from L5 to S3 on each side from the neuroforamina to the

coalescing of the nerves at the obturator internus muscle.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, lumen, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamine on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If PTV of all metastases are more than 10 cm away from the brachial plexus, this structure need not be contoured.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base), for purposes of contouring, will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa, and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as the proximal bronchial tree.

- *Proximal Trachea*
  Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV for lung metastases or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.
- *Proximal Bronchial Tree*
  The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides, as indicated in Figure 5-1. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower

lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as "proximal bronchial tree GTV," not as part of the "proximal bronchial tree."

Whole Lung
Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

Proximal Bronchial Tree Plus 2 cm
As part of determining if lung metastases are central or peripheral, adhering to the eligibility of the zone of the proximal bronchial tree, the RTOG SBRT protocols defined an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this structure, the patient is eligible for this protocol. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment planning software to ensure protocol compliance.

Skin
The external contour of the patient will be contoured. The skin OAR will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Great Vessels
The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right-sided tumors, the vena cava will be contoured, and for left-sided tumors, the aorta will be contoured.

Non-adjacent Wall of a Structure
For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV. These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

Stomach
The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum
The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Bowel (Large/Small)
The bowel should be contoured from the ileocecal area to include the ascending, transverse, descending, and sigmoid colon as one structure.

Rectum
The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus should be contoured.

Bladder
This organ will be contoured as bladder wall exclusive of urinary contents.

Kidney (renal cortex)
Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex).

Liver
The entire liver minus the GTV targets should be contoured.

Bile ducts
To contour the bile ducts, use the portal vein from its juncture with the splenic vein to its right and left bifurcation in the liver (as a surrogate to identify the bile ducts).

Femoral Heads
The ball of the head and socket joint should be contoured.

Rib
Ribs within 5 cm of the PTV should be contoured by outlining the cortical bone including the intramedullary space. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

PTV + 2 cm
As part of the QA requirements for "low-dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible, this

structure should be constructed as a single contour that is 2 cm larger than the PTV.

Other Structures
The constraints tables above contain other structures. These are required if the structure is within 3 cm of the PTV.

Critical Organ Dose-Volume Limits
Composite dose distributions of organs at risk are critical to understand toxicity following SBRT. Composite dose plans including all treated metastases and organs at risk must be submitted, as well as individual SBRT plans, to evaluate protocol compliance. To facilitate composite planning, dose to all metastases should be calculated on a single CT scan simultaneously with in-plane resolution of at least 2 x 2 x 3mm. If this is not possible, composite plans should be generated incorporating the dose from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance.

Tables 5-7, 5-8 and 5-9 list maximum dose limits to a point or volume within several critical organs based on the dose fractionation schema (one, three or five fractions) assigned based on metastatic tumor location.

NOTE: If a point (0.03 cc) inside an OAR has > 5 Gy total dose contribution on the composite plan from multiple treatment sites, it is strongly suggested that the same dose scheme be used to treat all sites.

NOTE: If different dose schemes are used in a given patient, dose limits to OAR receiving > 1 Gy contribution from treatment of individual metastases will be evaluated according to the table with the lowest number of treatment fractions (e.g., Table 5-7 for a single fraction will be used to assess OAR limits when a patient is treated with 1 and 5 fraction dose schemes).

Planning priorities for Organs at Risk:
The spinal cord doses are absolute limits, and treatment delivery that exceeds these limits will constitute an unacceptable deviation. However, some OAR (i.e., the esophagus, trachea, bronchi and heart within the lung) may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning must be accomplished so that there is no hot spot within that organ, even if that organ is part of the GTV/PTV, i.e., that no part of any serial OAR receives more than 105% of the prescribed dose (deviation unacceptable). In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. For parallel OAR, exceeding the doses in the tables (5-7, 5-8, 5-9) by more than 110% of the prescribed dose will be considered an unacceptable deviation.

For non-spinal cord OAR with known sensitivity to high doses of radiation (including the bowel, esophagus, and stomach) included within a PTV or immediately adjacent to PTVs, a prescription dose at the lower end of acceptable variation should be used. Additionally, every effort should be made to cover the GTV with the prescription dose while ensuring rapid falloff to the organ at risk. Coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation. Every effort should be made to cover 100% of the GTV by the prescription dose at the lower end of acceptable variation. Since the tumor and normal tissue may not allow strict avoidance, the larger volume limits will not be scored as unacceptable deviations if exceeded.

The total allowable doses over either a 1, 3, or 5 fraction treatment regimen are based on the schema assigned and are listed in Tables 5-7, 5-8 and 5-9.

For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 6 Gy/fraction).

NOTE: No studies of OAR limits for multiple metastases have been reported in the literature. Thus, organ limits from previously developed protocols, as shown in Tables 5-7, 5-8 and 5-9 below, will be utilized.

Table 5-7 **OAR Per Protocol Dose Limits for Single Fraction SBRT**

Serial Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Spinal Cord	<0.35 cc	10	Myelitis (RTOG 0915/Timmerman)
	<10% partial spinal cord	10	Myelitis (RTOG 0631)
	<1.2 cc	8	Myelitis (Timmerman)
	<0.03 cc	14	Myelitis (0915/Timmerman)
Ipsilateral Brachial Plexus	<0.03 cc	17.5	Neuropathy (0915/Timmerman)
	<3 cc	14	Neuropathy (0915/Timmerman)
Cauda Equina	<0.03 cc	16	Neuritis (RTOG 0631/Timmerman)
	<5 cc	14	Neuritis (RTOG 0631/Timmerman)
Sacral Plexus	<0.03 cc	18	Neuropathy

			(RTOG 0631)
	<5 cc	14.4	Neuropathy (RTOG 0631/Timmerman)
Trachea and Ipsilateral Bronchus*	<0.03 cc	20.2	Stenosis/Fistula (0915/Timmerman)
	<4cc	17.4	Stenosis/Fistula (Timmerman)
Esophagus*	<0.03 cc	15.4	Stenosis/Fistula (RTOG 0631)
	< 5 cc	11.9	Stenosis/Fistula (RTOG 0915/ RTOG 0631/ Timmerman)
Heart/Pericardium	<0.03 cc	22	Pericarditis (RTOG 0631/Timmerman)
	<15 cc	16	Pericarditis (RTOG 0631/Timmerman)
Great vessels	<0.03 cc	37	Aneurysm (RTOG 0915/RTOG 0631/ Timmerman)
	<10 cc	31	Aneurysm (RTOG 0915/RTOG 0631/ Timmerman)
Skin	<0.03 cc	27.5	Ulceration (Timmerman)
	< 10 cc	25.5	Ulceration (Timmerman)
Stomach	<0.03 cc	22	Ulceration/fistula (Timmerman)
	< 5cc	17.4	Ulceration/fistula (Timmerman)
Duodenum*	<0.03 cc	17	Ulceration (Timmerman)
	<5 cc	11.2	Ulceration (RTOG 0631/Timmerman)
	<10 cc	9	Ulceration (Timmerman)
Bowel*	<0.03 cc	29.2	Colitis/Fistula (Timmerman)
	<20 cc	18	Colitis/Fistula (Timmerman)
Rectum*	<0.03 cc	44.2	Proctitis/Fistula (Timmerman)
	<3.5 cc	39	Proctitis/Fistula (Timmerman)

	<20 cc	22	Proctitis/Fistula (Timmerman)
Bladder	<0.03 cc	25	Cystitis/Fistula (Timmerman)
	<15 cc	12	Cystitis/Fistula (Timmerman)
Ureter	<0.03 cc	35	Stenosis (Timmerman)
Penile bulb	<3 cc	16	Impotence (Timmerman)
Femoral heads	<10 cc	15	Necrosis (Timmerman)
Bile duct	<0.03 cc	30	Stenosis (Timmerman)
Renal Hilum/vascular trunk	<15 cc	14	Malignant Hypertension (Timmerman)
Rib	<0.03 cc	33	Pain or Fracture (Timmerman)
	<5 cc	28	Pain or Fracture (Timmerman)
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Lung (total)	<37% lung volume	8	Pneumonitis (Timmerman)
	<1500 cc	7	Basic lung function (Timmerman)
	<1000 cc	7.6	Basic lung function (Timmerman)
Total kidney	<200 cc	9.5	Basic Renal Function (Timmerman)
Liver	<700 cc	11	Liver function (Timmerman)

NOTE: Doses to serial OAR up to and including105% of the dose prescribed to the PTV will be scored as Variation Acceptable. Doses to parallel OAR up to 110% of the values listed in the table will be score as Variation Acceptable. Doses above these values will be scored as Deviation Unacceptable.

Table 5-8 **OAR Dose Limits for 3 fraction SBRT**

Serial Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Spinal Cord	<0.03 cc	22.5	Myelitis (Timmerman)

	<1.2 cc	13	Myelitis (Timmerman)
Ipsilateral Brachial Plexus	< 0.03 cc	26	Brachial Plexopathy (Timmerman)
	<3 cc	22	Brachial Plexopathy (Timmerman)
Cauda Equina	<0.03 cc	25.5	Neuritis (Timmerman)
	<5 cc	21.9	Neuritis (AAPM TG-101)
Sacral Plexus	<0.03 cc	24	Neuropathy (AAPM TG-101)
	<5 cc	22.5	Neuropathy (AAPM TG-101)
Trachea and Ipsilateral Bronchus*	<0.03 cc	30	Stenosis/Fistula (Z4099)
	<5cc	25.8	Stenosis/Fistula (Timmerman)
Esophagus*	<0.03 cc	27	Stenosis/Fistula (Timmerman 2006 /RTOG 0618)
	<5cc	17.7	Stenosis/Fistula (Z4099)
Heart/Pericardium	<0.03cc	30	Pericarditis (Z4099)
	<15 cc	24	Pericarditis (Z4099)
Great vessels	<0.03cc	45	Aneurysm (Z4099)
	<10 cc	39	Aneurysm (Z4099)
Skin	<0.03cc	33	Ulceration (Z4099)
	<10cc	31	Ulceration (Timmerman)
Stomach	<0.03cc	30	Ulceration/Fistula (Timmerman)
	<10cc	22.5	Ulceration/Fistula (Timmerman)
Duodenum*	<0.03cc	24	Ulceration (Timmerman 2006)
	<10cc	15	Ulceration (Timmerman 2006)

Bowel*	<0.03 cc	34.5	Ulceration (Timmerman)
	<20cc	24	Colitis/Fistula (Z4099)
Rectum*	<0.03 cc	49.5	Ulceration (Timmerman)
	<3.5 cc	45	Proctitis/Fistula (Timmerman)
	< 20 cc	27.5	Proctitis/Fistula (Timmerman)
Bladder	0.03cc	33	Cystitis/Fistula (Timmerman)
	<15 cc	16.8	Cystitis/Fistula (AAPM TG-101)
Ureter	<0.03 cc	40	Stenosis (Timmerman)
Penile bulb	< 3cc	25	Impotence (Timmerman)
Femoral heads	<10 cc	24	Necrosis (Timmerman)
Bile duct	< 0.03 cc	36	Stenosis (Timmerman)
Renal hilum/vascular trunk	<15 cc	19.5	Malignant Hypertension (Timmerman)
Rib	< 0.03 cc	50	Pain or Fracture (Timmerman
	<5 cc	40	Pain or Fracture (Timmerman
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Lung (total)	<15% lung volume	20	Pneumonitis/Lung Function (RTOG 0618)
	< 37% lung volume	11	Pneumonitis (Timmerman)
	<1500 cc	10.5	Basic Lung Function (Z4099)
	<1000 cc	11.4	Pneumonitis (Z4099)
Total Kidney	<200cc	15	Basic Renal Function (Timmerman)
Liver	<700 cc	17.1	Basic Liver function (Timmerman

			2006/Z4099)

***NOTE:** Every effort should be made to avoid circumferential irradiation.
NOTE: Doses to serial OAR up to and including 105% of the dose prescribed to the PTV will be scored as Variation Acceptable. Doses to parallel OAR up to 110% of the values listed in the table will be score as Variation Acceptable. Doses above these values will be scored as Deviation Unacceptable

Table 5-9 **OAR Dose Limits for 5 fraction SBRT**

Serial Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Spinal Cord	<0.03 cc	28	Myelitis (Timmerman)
	<0.35 cc	22	Myelitis (Timmerman)
	<1.2 cc	15.6	Myelitis (Timmerman)
Ipsilateral Brachial Plexus	< 0.03 cc	32	Brachial Plexopathy (RTOG 0813)
	<3 cc	30	Brachial Plexopathy (RTOG 0813)
Cauda Equina	<0.03 cc	32	Neuritis (AAPM TG-101)
	<5 cc	30	Neuritis (AAPM TG-101)
Sacral Plexus	<0.03 cc	32	Neuropathy (AAPM TG-101)
	<5 cc	30	Neuropathy (AAPM TG-101)
Trachea and Ipsilateral Bronchus*	<0.03cc	40	Stenosis/Fistula (Timmerman)
	<5cc	32	Stenosis/Fistula (RTOG 0813)
Esophagus*	<0.03cc	35	Stenosis/Fistula (Timmerman)
	<5 cc	27.5	Stenosis/Fistula (RTOG 0813)
Heart/Pericardium	<0.03 cc	38	Pericarditis (Timmerman)
	<15 cc	32	Pericarditis (RTOG 0813)
Great vessels	<0.03 cc	53	Aneurysm (Timmerman)
	<10 cc	47	Aneurysm (RTOG 0813)

Skin	< 0.03cc	38.5	Ulceration (Timmerman)
	< 10cc	36.5	Ulceration (Timmerman)
Stomach	< 0.5cc	35	Ulceration/Fistula (Timmerman)
	< 5cc	26.5	Ulceration/Fistula (Timmerman)
Duodenum*	< 0.5 cc	30	Ulceration (RTOG 1112)
	< 5 cc	18.3	Ulceration (Timmerman 2006)
Bowel*	< 0.03 cc	40	Ulceration (Timmerman)
	<20 cc	28.5	Colitis/Fistula (Timmerman)
Rectum*	<0.03 cc	55	Ulceration (Timmerman)
	<3.5 cc	50	Proctitis/Fistula (Timmerman)
	<20 cc	32.5	Proctitis/Fistula (Timmerman
Bladder	< 0.03	38	Cystitis/Fistula (Timmerman)
	<15 cc	20	Cystitis/Fistula (Timmerman)
Ureter	< 0.03 cc	45	Stenosis (Timmerman)
Penile Bulb	<3 cc	30	Impotence (Timmerman)
Femoral head	<10 cc	30	Necrosis (Timmerman)
Bile Duct	<0.03 cc	41	Stenosis (Timmerman)
Renal hilum/Vascular Trunk	<15 cc	23	Malignant Hypertension (Timmerman)
Rib	<0.03 cc	57	Pain or Fracture (Timmerman)
	<5 cc	45	Pain or Fracture (Timmerman)
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Lung (total)	< 37% lung volume	13.5	Pneumonitis (Timmerman)
	< 1500 cc	12.5	Basic Lung Function (RTOG 0813)

	< 1000 cc	13.5	Pneumonitis (RTOG 0813)
Total Kidney	< 200cc	18	Basic Renal Function (Timmerman)
Liver	<700 cc	21	Basic Liver Function (Timmerman)

***NOTE**: Every effort should be made to avoid circumferential irradiation.

NOTE: Doses to serial OAR up to and including 105% of the dose prescribed to the PTV will be scored as Variation Acceptable. Doses to parallel OAR up to 110% of the values listed in the table will be score as Variation Acceptable. Doses above these values will be scored as Deviation Unacceptable.

Rib/Chest Wall Dose Constraints

Recent reports have highlighted that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication. Tumor location, particularly when located peripherally, will enhance the potential risk for chest wall toxicity. While target coverage should not be compromised to limit dose to the rib/chest wall, every effort should be made to minimize dose to this OAR.

5.2.7 Documentation Requirements

Treatment Interruptions

In general, treatment interruptions should be avoided by preventative medical measures and supportive therapies. Treatment breaks, including indications, must be clearly documented on the treatment record.

Sites will record dose-volume values for all required structures on this datasheet. The datasheet must be completed and submitted with the digital RT data via TRIAD for review.

5.2.8 Compliance Criteria

Treatment Duration

Treatment Duration will be defined per metastasis

Per Protocol:

- Single Fraction Treatment: SBRT should be completed within 6 weeks of randomization/registration
- 3 fraction treatment: All 3 fractions of SBRT should be completed within 3 weeks of first SBRT dose and within 6 weeks of randomization/registration
- 5 fraction treatment: All five fractions of SBRT should be completed within 3 weeks of first SBRT dose and within 6 weeks of randomization/registration

Acceptable Variation: Treatment completing > 3 but < 4 weeks
Unacceptable Deviation: Treatment completed > 4 weeks

PTV Dosimetry Compliance

Tables 5-1 and 5-2 describe acceptable variations in the protocol prescription dose (dose covering 95% of the PTV). These criteria should be evaluated for each metastasis independently (i.e., while suppressing dose from all other metastases), particularly for metastases treated on separate days. This may not be possible for metastases treated on the same day using a single plan (e.g., VMAT). Prescription doses outside of the variation acceptable range will be scored as Deviation Unacceptable. Scoring of PTV coverage will be: acceptable if ≥ 95%, variation acceptable if 70-95%, deviation unacceptable if < 70%.

Organ at Risk Dosimetry Compliance

Critical structure doses should be based on composite dose distribution when more than one met is treated (as stated in Section 5.2.6). Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints. Any dose to spinal cord, cauda equina, sacral plexus above that listed in Tables 5-7, 5-8, and 5-9 will be considered an unacceptable deviation. For all other OAR, when OAR dose criteria provided in Section 5.2.6 cannot be accomplished by following planning priorities outlined in Section 5.2.5, doses to serial OAR of more than 105% of the dose prescribed to the PTV will be scored as Deviations Unacceptable. Doses to parallel OAR exceeding 110% of the dose prescribed to the PTV will be scored as unacceptable deviations. Doses in the range between the numbers in the tables and unacceptable deviation will be considered acceptable variations.

5.2.9 Radiation Therapy Adverse Events

All Radiation Therapy AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Adverse events related to SBRT for the treatment of metastases are dependent on the location of the metastases treated, as well as from exposure of surrounding normal tissues.

For all treated metastases, fatigue is likely to occur and should be transient, lasting < 8 weeks. Other adverse events are likely to be related to the specific metastatic location receiving SBRT.

Lung (Central and Peripheral), Mediastinal/Cervical Lymph Node Metastases:

Cardiac and Pericardial Injury

Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of SBRT a number of possible side-effects can be seen.

Gastrointestinal/Esophageal Injury

The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases.

Central Airway/Bronchial Injury
This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease, while the actual tumor may be stable or shrinking.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 4; MedDRA, v. 12.0.

Lung Injury
Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has not been as dose-limiting as in conventionally fractionated, large-field RT, but it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence**.**

Given that larger volumes of lung may be irradiated in this protocol compared to SBRT for primary tumors, it is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary hygiene. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Liver/abdominal-pelvic metastases
Very likely (80-90%): Patients may experience fatigue (which generally goes away after the radiation therapy is completed), skin irritation, redness, itchiness, discomfort, temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms.

Less likely (30%): Patients may experience nausea, vomiting (during therapy) – more common if stomach or gastrointestinal tract irradiated, gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility

following therapy (may require medications or surgery) (<10% permanent changes), chest wall pain, and rib fracture (< 10%).

Less likely, but serious (<20%): Patients may experience radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the Liver; non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease. In addition, permanent thrombocytopenia (<1%) may lead to bleeding, and kidney injury (<1%) may lead to changes on imaging and more rarely the need for medication.

Spinal metastases

Radiation Myelitis

Given the proximity and position of the spinal cord in relation to the radiosurgery target, every effort should be made to minimize the radiation dose to the spinal cord. Radiation myelitis is a subacute or chronic clinical syndrome after radiation. The symptoms may include paresthesia, sensory changes, and motor weakness including paralysis. There is no active treatment for radiation myelitis; therefore, it is important to prevent any injury to the spinal cord. Corticosteroids are used when clinical symptoms develop.

Radiation Esophagitis

Patients with thoracic spine treatment will likely develop esophageal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. There are no long-term adverse events reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal esophagus. The consequences of esophageal toxicity, e.g., swallowing difficulty, dysphagia, cough, dehydration, and fistula, should be documented.

Radiation Laryngitis or Pharyngitis

Patients with cervical spine treatment will likely develop laryngopharyngeal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. No long-term laryngopharyngeal toxicity has been reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal larynx and pharynx. The consequences of toxicity, e.g., swallowing difficulty, dysphagia, cough, dysphonia dehydration, and fistula, should be documented.

Tracheal Injury

Although no cases of tracheal injury have been reported with spine radiosurgery, it is prudent to minimize the radiation spillage in the normal trachea. The consequences of tracheobronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should be documented.

Radiation Pneumonitis
There have been no reported cases of symptomatic radiation pneumonitis with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the lung tissue. It is strongly recommended to use radiation beams directed from the posterior to avoid passage of radiation through the lungs. Patients with symptoms of pneumonitis will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary hygiene. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Compression Fracture of Treated Vertebra
Radiation doses in excess of 19 Gy for a single fraction are associated with higher rates of vertebral body compression (Saghal 2013). In this protocol, doses per fraction this high are not used, so that the estimated rate of vertebral body compression fracture following spinal metastases treatment should be approximately 10%.

Other Adverse Events
Short-term or long-term injury to the kidney or upper airway has not been reported. If other severe adverse events occur, details should be documented.

Osseous:
Erythema, desquamation and alopecia are common side effects from radiation therapy for osseous metastases; other effects are determinate on location of metastasis, and may include pain, edema and neuralgia.

5.3 Surgery (Arm 2)

For patients receiving surgery, surgery must occur within 6 weeks of study entry.

5.3.1 Technique, timing, other

Breast cancer metastases must be proven pathologically prior to surgical resection. All surgical resections will be approached with intent of an R0 resection (rendering the patient with no evidence of measureable disease and pathologic negative margin). If surgical resection of a given metastasis is incomplete with gross or microscopic residual (i.e. positive margins) the treating team is encouraged to deliver additional therapy including completion resection, conventionally fractionated radiation therapy, or systemic therapy as appropriate. Given the lack of data in the post-operative setting SBRT should NOT be delivered to the incomplete resection site. If a metastases undergoes a biopsy only at the time of surgery, SBRT would be allowed per protocol.

Approach to surgery will be based upon the treating surgeon. An open, laparoscopic, or thorascopic approach is acceptable. Surgery that may result in major morbidity and/or mortality is discouraged, i.e. major pancreatic resection or pneumonectomy. If at time of surgery, an R1 resection is the best outcome, then if possible the surgery should be aborted. Standard pre-operative and post-operative evaluation is required.

5.3.2 Surgery Adverse Events

Surgical morbidity and mortality must be recorded and reported. Any adverse event from surgery within 30-days must be reported. Morbidities include, but are not limited to hemorrhage, re-operation, infection, bile leak, persistent air leak, anastomotic leak/dehiscence, and poor wound healing.

5.4 General Concomitant Medication and Supportive Care Guidelines (1/12/16)

5.4.1 Permitted Systemic Therapy

Experimental therapeutics need to have a wash out period and must be discontinued 30 days prior to SBRT therapy being administered or surgery performed.

Participants may receive continuing standard of care systemic therapy management for their disease as follows: All hormonal therapy and bone supportive therapy may be continued during SBRT and around surgical procedures with interruption only as needed for routine surgical care [ie: NPO]. Tamoxifen is recommended to be held for 1 week before and after any major surgical procedure due to the increased thrombosis risk. The ongoing use of biologic therapy with trastuzumab, pertuzumab, and lapatinib is permitted concurrent with SBRT and around surgical procedures with interruptions only as needed for routine surgical care. Administration of ado-trastuzumab emantasine, palbociclib and everolimus should follow the chemotherapy guideline listed in Section 5.4.3.

5.4.2 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Anticonvulsants if indicated for reasons other than brain metastasis.
- For patients with liver and/or abdominal-pelvic metastases (as well as any other patient at the discretion of the treating oncologist) anti-emetics may be given prior to each fraction of SBRT to prevent nausea.
- For patients with lung (central or peripheral) and/or mediastinal/cervical lymph node metastases to be treated with radiation, corticosteroid premedication can be used at the discretion of the treating oncologist (in which case, its use needs to be reported.
- Anticoagulants as indicated for thrombotic disease. These must be held or bridged for patients undergoing surgical ablation according to routine surgical practice.
- Antidiarrheal as indicated by symptomatic diarrhea.
- Routine post-operative bowel regimens.
- Analgesic premedication to avoid general discomfort during simulation and treatment is recommended when appropriate.
- Routine anesthetics and post-surgical pain management.
- Hematopoietic growth factors should not be used during SBRT protocol therapy. G-CSF or pegylated G-CSF may have been given as part of prior chemotherapy as indicated by standard parameters, but ANC must be recovered to entrance values for the protocol without ongoing support.
- Herbal products are at the treating physicians' discretion and should be captured on the concomitant medication forms.

- Nutritional supplementation may be administered per standard indications and should be captured on the concomitant medication forms.
- Highly active antiretroviral therapy (HAART) is permitted for HIV affected individuals.
- Aspirin, non-steroidal anti-inflammatory, or other medications known to affect bleeding risks should be held for one week prior to any surgical study procedures, according to routine surgical guidelines.
- Routine use of blood products in the peri-operative time frame is permitted according to standard procedures.

5.4.3 Prohibited Systemic Therapy

Cytotoxic chemotherapy and select biologics, including palbociblib, everolimus and ado-trastuzumab-emantasine, are not permitted during the administration of protocol specific ablative SBRT or surgery (Arm 2). Cytotoxic chemotherapy/select biologics should be held prior to the initiation of protocol specified SBRT or surgical procedure following standard surgical pre-operative guidelines [long enough for bone marrow function to be recovered from any anticipated nadir (i.e. 14-21 days for 14-28 day cycles of scheduled chemo, 7 days for weekly regimens)]. Patients on palbociclib must have drug held long enough to permit neutrophil count to be greater than 1000, platelets greater than 100 and no requirement for ongoing blood transfusions. Patients on ado-trastuzumab emantasine should be held until platelets are 75 or greater. Cytotoxic chemotherapy may not overlap the SBRT and can be resumed 28 days after completion of protocol-specified SBRT and after the collection of blood for CTC has been completed, provided standard of care guidelines for bone marrow and/or liver function are met. Resumption of chemotherapy should not occur earlier than 28 days after completion of surgery and CTC collection or the recovery of any post-operative complications that would be worsened by re-initiation of chemotherapy (ie: infection, non-healing wound, bleeding). It is recommended that the decision to re-initiate chemotherapy be made jointly between the treating Radiation Oncologist and/or Surgeon and Medical Oncologist according to standard practices. The use of bevacizumab for patients on this study is prohibited. Patients may have received bevacizumab in the adjuvant setting or prior to study enrollment, as long as the last dose was 30 days or more prior to study enrollment. Patients should not resume bevacizumab as part of systemic breast cancer treatment as part of their post-ablative or ongoing SOC protocol therapy. Use of bevacizumab for subsequent treatment regimens after disease progression is at the discretion of the patients treating physicians.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6,
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Not applicable to this study

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Not applicable. Standard of care therapy will be given as appropriate for the patient's disease subtype at the discretion of the treating physician.

7.2 Adverse Events and Serious Adverse Events (14-JUN-2018)

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, 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, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Expedited Reporting of Adverse Events (9/16/16)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

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

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology by phone, 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. For instructions to submit supporting documentation, contact NRG Oncology at 1-215-574-3191.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Adverse Events For Arm 2: Any Phase Study Utilizing Radiation Therapy (including chemoRT studies)[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (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 or subject 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		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 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 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

For Arm 1: Any Phase Study Utilizing a Commercial Agent[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (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 or subject 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.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 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 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Not applicable

7.3.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.3.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g.,

treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. 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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.4 Routine Reporting Requirements for Adverse Events (14-JUN-2018)

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

8. REGISTRATION AND STUDY ENTRY PROCEDURES (21-SEP-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types:

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster;
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the site-protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (21-SEP-2022)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW)

for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

- IRB/REB Approved Informed Consent (International sites only: English and native language versions*)
  *Note: International and Canadian Institutions must provide certification/verification of IRB/REB IEC consent translation to NRG Oncology (described below).

Downloading Site Registration Documents:
Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;

- Click on *Protocols* in the upper left of the screen

- Enter the protocol number in the search field at the top of the protocol tree; or
- Click on the By Lead Organization folder to expand, then select *NRG*, and protocol number *NRG-BR002*.

Protocol-Specific Requirements for Protocol NRG-BR002 Site Registration:

- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.
- For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.
- Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.
- IRB/REB approved consent (International and Canadian sites only: English and native language versions*)
- **Note:** International and Canadian sites must submit an English version of the consent form to NRG Regulatory (Regulatory-PHL@nrgoncology.org) for review prior to submission to local IRB/REB/IEC. Certification/verification of IRB/REB/IECconsent translation must be provided with submission to CTSU (described below).

Non-English Speaking Canadian and International Institutions:

*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB/IEC approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Officeusing the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Porta,l log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements (21-SEP-2022)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution and NRG Oncology when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. This document must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated. IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: http//irochouston.mdanderson.org**	
	Treatment Modality	**Key Information**

	SBRT	IMRT	
Facility Questionnaire	✓	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to http://irochouston.mdanderson.org/questionnaires/
Credentialing Status Inquiry Form	✓	✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	✓	✓	An IROC Houston anthropomorphic phantom must be successfully completed (if the institution has not previously met this credentialing requirement)if the institution plans to deliver SBRT with IMRT. Credentialing for IMRT allows the institution to also use 3D-CRT SBRT, but credentialing for 3D-CRT SBRT does not allow the institution to use IMRT. Flattening-filter-free (FFF) photon beam delivery, Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually. Instructions for requesting and irradiating the phantom are available on the IROC Houston website under credentialing (http//irochouston.mdanderson.org),
IGRT Verification Study	✓	✓	Submit a series of daily treatment images along with a spreadsheet of IGRT data from 2 anonymized cancer patients treated with SBRT to the appropriate site (1. lung/liver and 2. spine). The anonymized data must come from a patient treated with an identical motion management strategy (i.e., gating, breath-hold, abdominal compression, motion tracking), as used with the phantom irradiation.
	✓	✓	
Credentialing Issued to:			
Institution	✓	✓	IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

NRG does not have a single, specific credentialing method for stereotactic body radiotherapy (SBRT). SBRT credentialing consists of a combination of other existing credentialing steps. SBRT requires the use of image-guided radiotherapy (IGRT) with its associated credentialing requirement. **Therefore, IGRT credentialing is also required for this protocol** .

Since SBRT can be used for various sites in the body, treatment technique credentialing must include some method of addressing motion when lesions in or near the thorax are treated. **Credentialing of individual treatment modalities is required for this**

protocol.

However, institutions need to credential for only the most complex modality they intend to use. The increasing complexity level for treatment modalities is three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric arc therapy (VMAT). Treating with flattening-filter-free (FFF) photon beam, Tomotherapy or the CyberKnife requires separate credentialing. The selected treatment technique(s) have to be coupled with the motion management technique that will be used by the institution. Taken together, the various required credentialing steps can be considerable. However, the number of steps can be reduced through a process of "grandfathering" institutions with appropriate previous credentialing. Please contact the Imaging and Radiation Oncology Core (IROC) Houston for more information.

NOTE: If the institution wishes to utilize a single isocenter setup to treat multiple lesions, which is discouraged (see Section 5.2.2) for lesions more than 10cm away, the SBRT credentialing must be performed with two lesions (lung and spine) in the lung SBRT phantom provided by IROC Houston. Furthermore the phantom must be irradiated in the same manner (i.e., utilizing a single isocenter to treat both the lung and spine metastases concurrently) and with appropriate motion management.

8.2.1 Digital Radiation Therapy Data Submission Using Transfer of Images, and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

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

RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment (12-AUG-2021)

Patient registration can occur only after evaluation for eligibility 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.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- 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 and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

9. DRUG INFORMATION

Not applicable to this study

10. PATHOLOGY/BIOSPECIMEN (11-JUL-2018)

See detailed specimen collection/processing/shipping instructions on the NRG-BR002 protocol page of the CTSU website. Instructions are also provided with all kits.

Patients must be offered the opportunity to consent to optional specimen collections. If the patient consents to participate, the site is required to submit the patient's specimens as specified in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Funding for the following studies has been generously provided from two sources:

Ralph R. Weichselbaum, MD
Daniel K. Ludwig Distinguished Service Professor & Chair
Director, Ludwig Center for Metastasis Research
Ludwig Center for Metastasis Research
924 E. 57th Street
Chicago IL 60637-5419

And

Peter Kuhn
3430 S. Vermont
Suite #106
Los Angeles, CA 90089

Optional Study #1: Whole Blood Collection for Translational Research: Circulating Tumor Cells (CTCs) See the NRG-BR002 protocol page of the CTSU website for further details on collection logistics.
Consenting patients will have 7.5 ml of whole blood drawn by phlebotomy or through a central venous access device into a "CellSave" tube (included with NRG-BR002 kits) to collect and quantify CTCs (see below for collection timepoints). Because the

analytes for this study degrade rapidly, only specimens drawn Mon-Wed, and shipped overnight no later than Thursday to MD Anderson Cancer Center will be accepted (see address below).

NOTE: Samples for CTC analysis must be drawn on a Monday, Tuesday or a Wednesday in "CellSave" blood collection tubes containing EDTA and a stabilizer (Immunicon Corporation), must be clearly labeled with patient study number, type of sample, and date collected, and it must be shipped to UT MD Anderson Cancer Center overnight no later than Thursday so samples can be received and processed by Friday of the same week.

Specimens are being collected to determine whether a blood test could predict who will benefit from ablation of metastatic disease, and to better understand the biology that drives metastases.

(see Section 2.2 for further details).

- Required Forms: ST form.
- CTC tubes, kits and special CTC shipping supplies will be supplied with the Banking Kits (optional Study#3) from the NRG Oncology Biospecimen Bank-San Francisco (NRGBB-SF). Please allow 5-10 days for delivery as kits are shipped to sites by Fed Ex ground
- Shipping days: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American)**.**
- Shipping costs: Sites will receive BR002 specific Fed Ex account and reference number in the kits provided with instructions from the NRBB-SF. *Please contact wwoodward@mdanderson.org; 713-563-2363 with any questions regarding this process*

Submit Cell Save tube materials by FedEx priority overnight for CTC analysis (**labeled NRG-BR002**) directly to:

Dr. Carol Hall
UT MD Anderson Cancer Center
Dept of Surgical Oncology
1515 Holcombe Blvd
CRB T4.3932
Houston , TX 77030
713-563-8898/FAX 713-794-4830

Notify both Dr. Carol Hall (cshall@mdanderson.org) and Dr. Wendy Woodward (wwoodward@mdanderson.org) by e-mail on the day of submission with the following information: **(1)** that a sample is being submitted with the NRG case number; **(2)** the overnight shipping carrier and tracking number, and **(3)** e-mail and phone number of contact person.
For questions regarding Kits, contact:
NRG Oncology Biospecimen Bank- San Francisco

415-476-7864/FAX 415-476-5271 NRGBB@ucsf.edu			
Specimen Type	**Collection Time Points**	**Collection Information and Requirements**	**Shipping**
Whole Blood for CTCs: 7.5ml whole blood in a "CellSave" tube (Drawn Mon-Wed only)	(1)Pre-treatment (2) Post treatment: **Arm 2**:4 wks. post SBRT **OR Arm 1**:3 months post registration (3) At disease progression (if applicable)	Single tube at room temperature	Ambient temperature via overnight carrier no later than Thursday Ship to UT MD Anderson; contact the lab before shipping

Optional Study #2: Plasma Collection for Translational Research: ctDNA analysis See the NRG-BR002 protocol page of the CTSU website for further details on collection logistics.
A special plasma tube manufactured by Streck (tiger lid, 7-10 mL) will be drawn at the same time points as the CTC collection into a "Streck" tube (provided by NRG Oncology Biospecimen Bank-SF with special NRG-BR002 kits) for eventual ctDNA cell-free analysis, high-content single cell liquid biopsy (HD-SCA), and mathematical correlation to clinical data. This tube must be filled in after the "CellSave" tube in Optional Study #1. If no other tube is collected at the time points of CTC collection, then the first 2 mL of blood must be drawn into another tube (not "Streck") and discarded. Then, proceed to draw blood into the "Streck" tube. The "Streck" tube should be shipped to The Kuhn-Hicks Laboratory at USC (see address below). • Required Forms: ST form. • Streck tubes will be supplied with the special Streck shipping kit from the NRG Oncology Biospecimen Bank-SF. Each kit is for one timepoint. Please allow 5-10 days for delivery as kits are shipped to sites by Fed Ex ground • Shipping days: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American)**.** Shipping costs: Fed ex account information will be provided with each special Streck kit instruction packet from the NRGBB-SF. *Contact the Kuhn lab at* (kuhnlab@usc.edu) *for Streck kit collection or shipping information.*

Submit "Streck" tube ctDNA materials (**labeled NRG-BR002**) directly to:

Peter Kuhn
c/o USC Michelson Hall
Kuhn-Hicks Laboratory
1002 Childs Way, MCB 310
Los Angeles, CA 90089-3502

Notify Dr. Wendy Woodward (wwoodward@mdanderson.org) and Dr. Peter Kuhn's lab (kuhnlab@usc.edu) by e-mail on the day of submission with the following information: **(1)** that a sample is being submitted with the NRG case number; (2) date/time of draw; **(3)** the shipping carrier and tracking number, and **(4)** e-mail and phone number of contact person.

For questions call Xiomara Villasenor at 213-740-9614 (xvillase@usc.edu) or the Kuhn Lab (213-740-9945, kuhnlab@usc.edu); Or Dr. Woodward (713-563-2363) to coordinate labels addressed to USC.

NOTE: Guidelines for the shipment of ctDNA/"Streck" tube:
The Biospecimen bank kit will include instructions with Fed Ex account information and a special shipping container for shipping the Streck tube. This includes a white, two part "cassette" to hold the blood tube, an air pillow bag, a Paksense probe for temperature monitoring, and a blue shipping cardboard box.

- Open the blue shipping box to extract a silver air pillow bag that contains the white cassette. Open the white cassette and extract a 2-layer plastic tube holder.
- Place the filled ambient Streck tube inside the smaller plastic holder, place the lid. Insert smaller plastic holder into the larger plastic holder, place the lid.
- Prepare the Paksense temperature monitoring probe: Peel off the plastic cover over the back of the glue dot that is found in the back of the Paksense probe. Place the Paksense, glue dot down in the insert inside one side of the white cassette. Activate the Paksense probe by pressing the Start button for 2 seconds, then release. A green light should now be blinking.
- Place the 2-layer plastic tube holder containing the specimen inside the white cassette and snap the two halves together.
- Place the white cassette inside the air pillow bag. It will be a tight fit.
- Place the air pillow bag into the blue cardboard shipping box with the ST Form. No need to use the sticky seal; just fold it over.
- Verify the FedEx label is addressed to the Kuhn lab at USC and Biohazard label is visible. Contact your local Fed-Ex representative for pick-up.
- Send shipment notification email to kuhnlab@usc.edu.

Specimen Type	**Collection Time Points**	**Collection Information and Requirements**	**Shipping**
PLASMA (ctDNA): 7-10 mL	(1)Pre-treatment	Collect blood in special Streck tube.	Blood in special Streck tube sent in

of anticoagulated whole blood in tiger lid "Streck" tube	(2) Post treatment: **Arm 2**:4 wks. post SBRT OR **Arm 1**:3 months post registration (3) At disease progression (if applicable)	Do not process.	ambient temperature controlled special shipper via overnight carrier for 10:30am delivery (Ship to Kuhn Lab at USC by overnight courier-contact Kuhn lab before shipping)

Optional Study #3: Specimen Collection for Tissue Banking

See the NRG-BR002 protocol page of the CTSU website for further details on collection logistics.

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's previously collected diagnostic specimens as specified in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Specimens are being collected for future translational research projects and being submitted to the NRG Oncology Biospecimen Bank- San Francisco for banking

- Required Forms: ST form, pathology reports. All forms must be completely filled out with an NRG Label including the Study #, Case #, NRG Institution number or Institution NCI ID, and patient initials. The pathology accession number must remain visible on the pathology report but all other PHI information must be redacted/removed.
- Kits are available for Frozen biospecimens from the NRG Oncology Biospecimen Bank-San Francisco
- Detailed Processing and shipping instructions are provided on the protocol webpage
- Shipping days for Frozen Specimens: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American). We are unable to accept shipments on Saturdays or holidays.
- Shipping costs: One Prepaid Fed Ex label is provided for batch shipping the Frozen biospecimens for banking specimens for each case in the kits.
- Ship all Biospecimens for Optional Study #3 for banking to:

  NRG Oncology Biospecimen Bank- San Francisco
  UCSF Dept of Radiation Oncology
  2340 Sutter Street- Room S341
  San Francisco, CA 94115
  415-476-7864

For questions about banking biospecimens contact:
NRG Oncology Biospecimen Bank- San Francisco
NRGBB@ucsf.edu
415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Representative H&E stained slides of the primary tumor	Pre-treatment: obtained as part of routine diagnostic procedures.	H&E stained slide. Can be a duplicate cut slide, does not have to be the diagnostic slide.	Slide shipped ambient to the NRGBB-SF
A paraffin-	Pre-treatment:	Paraffin-embedded	Block or punch

embedded tissue block or one 3mm punch from the block of the primary tumor taken before initiation of treatment	obtained as part of routine diagnostic procedures.	tissue block or punch. Must match the H&E being submitted.	block shipped ambient to the NRGBB-SF. Ship with a cold pack during warmer weather to avoid wax from melting
Representative H&E stained slides of the metastatic tumor	Pre-treatment: obtained as part of routine diagnostic procedures.	H&E stained slide. Can be a duplicate cut slide, does not have to be the diagnostic slide	Slide shipped ambient to the NRGBB-SF
A paraffin-embedded tissue block or one 3mm punch from the block of the **metastatic** tumor taken before initiation of treatment when available	Pre-treatment: obtained as part of routine diagnostic procedures.	Paraffin-embedded tissue block or punch from block must match the same tissue block as the H&E being submitted	Block or punch block shipped ambient to the NRGBB-SF. Ship with a cold pack during warmer weather to avoid wax from melting
Representative H&E stained slides of the metastatic tumor	At Progression: obtained as part of routine diagnostic procedures.	H&E stained slide. Can be a duplicate cut slide, does not have to be the diagnostic slide	Slide shipped ambient to the NRGBB-SF
A paraffin-embedded tissue block or one 3mm punch of the metastatic tumor taken at the time of progression if available	At progression: if obtained as part of routine diagnostic procedures.	Paraffin-embedded tissue block or punch from block	Block or punch block shipped ambient to the NRGBB-SF. Ship with a cold pack during warmer weather to avoid wax from melting
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier to the NRGBB-SF

PLASMA (for banking): 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier to the NRGBB-SF
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #3 (purple/lavender top) and mix	Pre-treatment; **note**: If site missed this collection time point they may collect whole blood for DNA at a later time point but must note this on the ST Form.	Frozen whole blood samples containing 1.5-2 ml per aliquot in 2ml cryovials (3)	Whole blood sent frozen on dry ice via overnight carrier to the NRGBB-SF

11. SPECIAL STUDIES (NON-TISSUE)

None

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

Arm 2 Pre Treatment Review

A full 3D dosimetry plan PRE-TREATMENT REVIEW for the first patient registered for each disease site category treated at the institution on this protocol must be submitted to TRIAD for review PRIOR TO DELIVERY of radiation treatment. If the institution has previously treated patients with the same disease site on NRG-BR001 then a pre-treatment review is not necessary. If the initial case at the institution treats a single metastasis with SBRT, the institution will also be required to submit their first multiple metastases case to be treated with SBRT for pre-treatment review PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The plan(s) will be reviewed centrally by the PIs, and feedback regarding protocol compliance will be forwarded to the participating institution. Based on the results of any of the reviews described above, a request for additional pre-treatment reviews might be necessary. In general, the treatment plan for subsequent patients enrolled at a site will not be required to be centrally reviewed prior to treatment, but will be reviewed for protocol compliance at a later date. Allow 3 business days for the results of the pre-treatment review process. The pre-treatment review process will not start until all required data is submitted to TRIAD.

RT Quality Assurance Review

The Radiation Oncology Co-Chairs will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. The Radiation Oncology Co-Chairs will perform ongoing reviews after complete data for each cohort of 20 enrolled cases has been received at NRG Oncology. These reviews will be on going.

12.2 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Nora Jaskowiak, M.D., will perform a Quality Assurance Review on a continuous basis for patients randomized to Arm 2 that receive surgery as part of their ablative treatment. After NRG Oncology Statistics and Data Management Center (SDMC) has received complete data for each Arm 2 case enrolled that receives surgery, Dr. Jaskowiak will perform a review. Documents reviewed will be the Pre-operative H&P, the Operative Report, the Pathology Report from the surgical procedure, and the Discharge Summary from the surgical admission. In addition, all surgical SAEs will be reported in an expedited manner and reviewed regularly by the Surgical PI. Dr. Jaskowiak will utilize the expertise of other surgical oncologists, thoracic surgeons, and Orthopedic oncologic surgeons (at the University of Chicago and Duke Medical Center) if sub-specialty quality issues arise. If concern arises about surgical quality upon review, Dr. Jaskowiak will directly communicate with both the PI and surgeon at the institution, with possible intervention, if deemed appropriate.

13. DATA AND RECORDS

13.1 Data Management/Collection (12-AUG-2021)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to 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. Site staff 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. If an eLearning is required and has not yet been taken, the link to

the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

13.2 Summary of Data Submission (9/16/16)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.2 and 7.3. for information about expedited and routine reporting.

For reporting of second primary cancers or other report forms available in Rave: Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

Summary of Data Submission: Refer to the protocol-specific website.

See Section 8.4.2 for TRIAD account access and installation instructions.

13.3 Data Quality Portal (21-SEP-2022)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms. DQP Form Status, and DQP Reports modules

13. 4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (12Jul2017)

14.1.1 Stratification

Patients will be stratified before randomization with respect to the following: number of metastases (1 vs. > 1), hormone receptor status (ER and/or PR positive vs. ER and PR negative), Primary Breast HER2 Status (positive vs. negative), and First-line standard systemic therapy (Yes vs. No).

14.1.2 Randomization

This study will use a permuted-block randomization with a 1:1 allocation. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

14.1.3 Total Accrual

Ph II-R: 128

Ph III: 360 patients (including the 128 already accrued in the Ph II-R portion).

14.1.4 Justification of Design:

This study will be an integrated phase II/III interim analysis trial, proposed by Hunsberger et al (2009). This efficient design allows the patients from the Ph II-R portion of the trial to be included in the Ph III portion of the trial, given the Ph II-R results provide a go signal for continuation to the Ph III.

14.2 Study Endpoints

14.2.1 Primary Endpoints

Ph II-R: Progression-free survival (failure: progression or death due to any cause)

Ph III: Overall survival (failure: death due to any cause)

14.2.2 Secondary Endpoints

- Existing metastasis control
- Appearance of new metastases
- Adverse Events
- Evaluating impact of ablative therapy on circulating tumor cells (CTCs) in oligometastatic breast cancer patients
- Exploring clinically relevant technological parameters per Section 1.2

14.3 Primary Objectives Study Design (12-AUG-2021)

14.3.1 Primary Hypothesis and Endpoints

The primary objectives for the study are to evaluate if ablation (through Stereotactic Body Radiotherapy (SBRT) or surgical resection of all known metastases) in oligometastatic breast cancer patients will (i) show a sufficient signal for improvement in progression-free survival (PFS) to warrant (ii) full accrual to a Phase III superiority trial with OS as the primary endpoint.

Phase II-R Portion
The primary endpoint hypothesis is that ablative therapy will provide a signal for improved PFS from 10.5 months to 19 months, corresponding to a hazard ratio (HR) of 0.55 (experimental/control).

Phase III Portion
The primary endpoint hypothesis is that ablative therapy will improve overall survival from 28% to 42.5% at 5-years, corresponding to a HR of 0.67 (experimental/control).

14.3.2 Definitions of Primary Endpoints and How These Will Be Analyzed

Progression-free survival (PFS) will be estimated by the Kaplan-Meier method (1958), with PFS failure defined as: progression of initial/treated metastases (see Section 4), appearance of new metastases, or death due to any cause. The distribution of PFS estimates between the two arms will be compared using the log rank test (Mantel 1966). PFS time will be measured from the date of randomization to the date of first PFS failure or last follow-up. Imaging will be every 3 months for 2 years or until progression. After 2 years, imaging will be lengthened to every 6 months or until progression. After 5 years without progression, imaging per best clinical practice is recommended.

Overall survival (OS) will be estimated by the Kaplan-Meier method (1958). The distribution of OS estimates between the two arms will be compared using the log rank test (Mantel 1966). OS time will be measured from the date of randomization to the date of death or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS.

Analysis for Reporting the Initial Treatment Results

Ph II-R Portion
This major analysis will occur after at least 69 PFS failure events have been observed. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary endpoint of PFS

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a 1-sided significance level of 0.15. If there is a

signal of an improvement in PFS, the results will not be reported, but rather will be interpreted as a "Go Signal" for continuation on to the full accrual of the Ph III portion of the trial. If there is not a signal of an improvement in PFS, then the results will be interpreted as a "No-Go Signal," accrual will be stopped, and the trial will be reported.

Ph III Portion

This major analysis will occur after at least 231 OS failure events (deaths) have been observed. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a 1-sided significance level of 0.025. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms (e.g. age, gender, race, etc.). Where feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

14.3.3 Sample Size and Power Calculations:

Justification for selected PFS and OS Estimates

For Arm I, the PFS and OS estimates are derived from a number of studies employing single or poly agent chemotherapy. Studies were selected that defined the number of metastatic lesions as to best approximate the population proposed in this trial, as shown in Table 2-1.

For Arm II, the effect of metastasis-directed ablative therapy (either surgery or radiotherapy) on the progression-free and overall survival of breast cancer patients was estimated based on available series, as shown in Table 14-1. As can be seen in these series the median PFS is reported to be at least 14 months, and the 5-year overall survival for those with limited metastases (Greenberg 1996, Albain 2009) is >40%. These effect sizes are selected based on the available literature. A large effect must be seen in order to integrate the finding of this trial into the standard practice for patients with limited metastatic breast cancer.

Table 14-1 Selected Retrospective Studies of Ablative Metastasis-Directed Therapy in Breast Cancer Patients

Study	Number of patients	Metastasis Directed Therapy	ER/PR Positive	Her 2 Neu Positive	≤2 Metastases	Median PFS	Median OS	5 year OS

		Type (Location)				(months)	(months)	
Milano et al.(2009)	40	SBRT (all body sites)	63%	Not Stated	71%	23	Not Reached	59%
Abbott et al.(2012)	86	Surgery (liver)	69%	37%	62% solitary	14.2	57	43.6%
Adam et al.(2006)	85	Surgery (liver)	82%	Not Stated	Median=2 (37% solitary)	20 months (no extrahepatic disease)	46	41%
Friedel et al. (all patients) (2002)	467	Surgery (lung)	Not Stated	Not Stated	66% solitary	Not Stated	35	35%
Friedel et al. (1 metastasis) (2002)	308	Surgery (lung)	Not Stated	Not Stated	100%	Not Stated	42	44%
Planchard et al.(2004)	125	Surgery (lung)	45% (of those available	Not Stated	Median=1	Not Stated	50	45%

Phase II-R Portion

One-hundred and sixteen evaluable patients will provide 92% power to detect a signal for improved median PFS from 10.5 months to 19 months (HR=0.55), with a 1-sided type I error of 0.15. To adjust for ineligible/lost patients, a total of 128 patients will be required for the Ph II-R portion of the study.

Phase III Portion

An additional 208 evaluable patients, for a total of 324 evaluable patients, will be required to definitively determine if ablative therapy improves 5-year overall survival from 28% to 42.5% (HR=0.67), with 85% power and a one-sided type I error of 0.025. To adjust for ineligible/lost patients in the Ph III portion, the total accrual to the trial (to address the Ph III question) will be 360 patients (including the 128 that were already accrued in the Ph II-R portion).

This integrated phase II/III design has 78% power for the overall survival analysis under the global alternative hypothesis, while having 0.025 (1-sided) probability of concluding a positive effect on overall survival under the global null hypothesis.

Sample Size Consideration for Translational Research

Primary Objective

It is expected that 80% of the trial population will have signed consent to participate in

the tissue/specimen component of the study and will have usable baseline material based on collection from RTOG 10-14. Based on the SWOG 0500 data and the differences in patient selection in this trial excluding those who progress on standard chemotherapy, we expect that among patients with available specimens, 75% will have <5 CTCs per 7.5ml of blood at baseline. Based on the proposed PFS event rates in two treatment arms and the results from Cristofanilli (2004), the projected monthly event rates for patients with <5 CTCs per 7.5ml of blood and ≥5 CTCs per 7.5ml of blood at baseline are 0.0368 and 0.0943 correspondingly. Under other general assumptions of the main trial (accrual time, total follow-up time) and assuming a two-sided probability of type I error of 0.05, the sample size of 116 evaluable patients, accrued in the Phase II-R portion, will be sufficient to detect such a difference with a statistical power of 88%. Similarly, based on the proposed OS event rates in two treatment arms and the results from Cristofanilli (2004) the projected monthly event rates for patients with <5 CTCs per 7.5ml of blood and ≥5 CTCs per 7.5ml of blood at baseline are 0.0148 and 0.0265 correspondingly. The total sample size of 324 evaluable patients will be sufficient to provide a statistical power of at least 93% to detect such a difference. The estimation is based on the simple unstratified log-rank test and provides the conservative approximation for the purpose of the primary analysis for the transactional susbstudy (Akazawa, 1997; Schoenfeld, 1983)

Selected Secondary Objectives

To evaluate whether <5 CTCs per 7.5ml of blood is a predictive marker for improved PFS (OS), a statistical test for interaction between baseline CTCs and treatment will be performed. Table 14-2 provides the statistical power to detect a presence of interaction under previously described assumptions except for the different effect of treatment in the <5 and ≥ 5 CTCs per 7.5ml of blood subgroups. We assume a two-sided test is performed at the alpha = 0.05 level.

Table 14-2 Statistical power to evaluate whether <5 CTCs per 7.5ml of blood at baseline is a predictive marker for improved PFS and OS

Endpoint	The effect of treatment (HR)		Interaction effect size (HR <5 CTCs / HR ≥5 CTCs)	Power
	<5 CTCs	≥5 CTCs		
PFS	0.20	0.96	0.21	0.64
	0.25	0.91	0.28	0.50
	0.30	0.85	0.35	0.37
	0.35	0.79	0.44	0.25
	0.40	0.73	0.55	0.16
OS	0.50	0.97	0.52	0.53
	0.53	0.92	0.58	0.40
	0.55	0.88	0.62	0.31
	0.57	0.85	0.67	0.24
	0.60	0.80	0.75	0.14

Non-Compliance with Randomized Treatment

Treatment other than the treatment arm to which the patient was randomized is not permitted per the protocol and will be considered non-compliant. However, as this will not prevent treatment crossovers (patients receiving the treatment to which they were not randomized) from occurring and the primary endpoint analyses will be done based on the arm to which the patient was randomized, the rate of treatment crossovers will be closely monitored.

Tables 14-3a and 14-3b show the impact for 5% and 10% crossover from the control arm to the experimental arm for the Ph II-R and Ph III portions respectively. If the crossover rate falls between 5% and 10%, NRG Oncology will discuss with NCI the potential of amending the trial in order to adjust for this crossover, so as to maintain the original study parameters. If the crossover rate reaches or exceeds 10%, NRG Oncology will discuss with NCI the feasibility of continuing the trial.

Table 14-3a: Impact of Crossover from Control Arm to Experimental Arm for Ph II-R

Crossover Rate	Adjusted Experimental Median PFS Rate	Power Given Crossover (95% by Design)	Increase in Accrual Time to Maintain Original Parameters
5%	18.3	93%	2.5 mths
10%	17.6	91%	6 mths

Table 14-3b: Impact of Crossover from Control Arm to Experimental Arm for Ph III

Crossover Rate	Adjusted Experimental 5-yr OS Rate	Power Given Crossover (85%)	Increase in Accrual Time to Maintain Original Parameters
5%	41.6%	81%	6.5 mths
10%	40.8%	76%	15 mths

14.4 Study Monitoring of Primary Objectives (9/16/16)

Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables

- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoints, PFS/OS, or any secondary endpoints, with the exception of reporting of adverse events.

Futility Testing at the Completion of the Ph II-R Accrual

It is projected that at the time of the Ph II-R accrual completion, 74% of the 84 required Ph II-R primary endpoint (PFS) events will have occurred. At this time, a futility analysis will be performed. If the HR ($\lambda_{ablation}/\lambda_{standard\ of\ care}$) is < 1 then accrual will continue during the additional time needed for the full Ph II-R analysis; otherwise, accrual will be stopped, pending the results of the full Ph II-R analysis.

Significance Testing for Early Termination and/or Reporting of the Primary Endpoint (OS) of the Ph III Portion of the Trial

Assuming that the trial continues on to the full Ph III portion, two interim significance tests of treatment difference are planned, using the Haybittle-Peto (Lan 1983; O'Brien 1979) rule for efficacy and the Freidlin-Korn (Freidlin 2002) rule C for futility. The timing of the interim analyses will be based on OS failure events, as described in Section 14.2.1. The maximum number of OS events required for the study is 231. Under the alternative hypothesis that ablative therapy will increase 5-year OS from 28% to 42.5%, the projected number of events and the nominal significance levels for rejecting the H0 or the H1 for the interim analyses are shown in the table below:

Table 14-4: Nominal Significance Levels for Interim Analyses

Interim Analysis	Number of Events	Efficacy: Reject H0 if p (H0) ≤	Futility: Reject H1 if Z (H1) ≤
#1	69	≤ 0.001	-0.92
#2	173	≤ 0.001	0.05

At each planned interim analysis, the one-sided p-value from the log-rank test assessing treatment efficacy with respect to OS will be compared to the nominal significance level in Table 14-4 above. If the computed p-value is less than or equal to the nominal significance level boundary for rejecting the H0 (efficacy), then accrual to the trial will be stopped (if applicable) and it will be concluded that the OS with ablative therapy (Arm 2) is significantly higher than palliative standard of care (Arm 1) and the results will be reported. If the Z-score is less than or equal to the nominal critical value for rejecting the H1 (futility), then accrual to the trial will be stopped (if applicable) and the fact that it cannot be concluded that the OS with ablative therapy (Arm 2) is significantly higher than palliative standard of care (Arm 1) will be reported. Otherwise, if neither boundary is crossed, accrual to the trial and/or follow-up (as applicable) will continue to the next scheduled analysis.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment blinded efficacy results will be reported to the NRG Oncology DMC, following the required number of events for the planned interim analysis.

14.5 Accrual Considerations (14-JUN-2018)

14.5.1 Accrual Rate

Patient accrual is projected to be 4 cases per month. Assessment of accrual compliance will be based on the NCI Ph II-R and Ph III accrual rules and will be monitored by the NRG Oncology DMC. It is projected that approximately 11 months of follow-up post the Ph II-R accrual will be required to reach the number of events in order to assess the Ph II-R endpoint of PFS and determine if the trial will continue to the full Ph III accrual. Given the number of patients required for the Ph III portion of the trial and the fact that the projected monthly accrual is only 4, accrual will not be halted following accrual to the Ph II-R portion of the trial. A futility analysis will be performed at the completion of the Ph II-R accrual, as described in Section 14.4. Assuming that futility boundary is not crossed, full accrual to the Ph III portion of the trial will be determined following the results of the Ph II-R analysis, as described in Section 14.3.2.

14.5.2 Accrual Goal

Ph II-R: 128
Ph III: 360 patients (including the 128 already accrued in the Ph II-R portion).

14.5.3 Study Accrual Duration

Ph II-R: Based on the projected accrual of 4 cases/month, the Ph II-R portion of the trial should complete accrual in ~ 2.5 years.

Ph III: If the trial continues to the full Ph III accrual, that accrual should complete in ~4.5 years from the end of the Ph II-R accrual.

14.5.4 Estimated Duration for Completion of Primary Endpoint:

Ph II-R: Approximately 1 year from completion of the Ph II-R accrual.

Ph III: Approximately 6 years from determination of the Ph II-R results.

14.6 Secondary or Exploratory Elements (including correlative science aims)

14.6.1 Statistical Analysis Plan for Translational Research

Primary endpoint/analysis

The prognostic effect of the initial presence of CTCs at baseline on PFS (OS) will be evaluated using the Cox proportional hazards model, controlling for treatment effect and stratification factors. The hypothesis tests will be two-sided and will use an alpha level of 0.05 to determine significance.

Secondary endpoints/analyses

The interaction between treatment effect and the initial presence of CTCs at baseline on PFS (OS) will be evaluated in the Cox model, which will include an indicator for

treatment group, an indicator for presence of CTCs (≥5 per 7.5ml of blood), and their interaction term. The analysis will be adjusted for the stratification factors.

The effect of change in CTC count from CTC ≥ 2 per 7.5ml of blood at baseline to CTC=0 at follow-up after initial treatment on PFS (OS) will be evaluated using the Cox proportional hazards model, controlling for treatment effect and stratification factors. The analyses will be conditional on a patient's event-free survival up to post-treatment evaluation. The interaction between treatment effect and change in CTC count will be evaluated in the Cox model, which will include an indicator for treatment group, an indicator for change of CTCs, and their interaction term. The analysis will be adjusted for the stratification factors.

For the analyses related to the circulating tumor DNA, the levels of ctDNA will be dichotomized at the median level. If at the time of the analysis the data published suggests alternative cutoffs to be more clinically relevant, we would revise our plan prior to analysis. The prognostic effect of dichotomized ctDNA on PFS (OS) will be evaluated using the Cox proportional hazards model, controlling for treatment effect and stratification factors. In addition, the presence of the interaction between treatment effect and dichotomized ctDNA will be evaluated (predictive effect). Spearman rank correlation coefficient will be used to correlate the levels of CTCs and ctDNA.

All secondary analyses will be performed at 0.05 level.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Treated Metastasis Progression: is the clearance and subsequent recurrence or the development of new metastases in the treated area. The rates of treated metastases control for the experimental arm will be reported overall and by the following factors: tumor receptor status (ER, PR, HER-2), use of chemotherapy, protocol treatment (surgery vs. SBRT), and number of metastases (solitary metastasis vs. 2 metastasis).

Appearance of New Metastases

Failure for this endpoint will be the appearance of any new metastases. The cumulative probability of new metastases in the presence of competing failure events will be estimated by the cumulative incidence method (Kalbfleish 1980). The cumulative incidence distributions between the two arms will be compared using Gray's test (Gray 1988). The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with the incidence of new metastases, including tumor receptor status (ER, PR, HER-2), use of chemotherapy, protocol treatment (surgery vs. ablative therapy), and number of metastases (solitary metastasis vs. 2 metastasis).

14.7 Gender/Ethnicity/Race Distribution (21-SEP-2022)

Women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interactions between race/ethnicity and treatment have been considered. The projected non-White and Hispanic/Latino accrual rates are too low for any meaningful treatment comparisons.

DOMESTIC

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	6	0	0	0	**6**
Asian	11	0	0	0	**11**
Native Hawaiian or other Pacific Islander	0	0	0	0	**0**
Black or African American	25	0	0	0	**25**
White	224	0	25	0	**249**
More than one race	10	0	5	0	**15**
TOTAL	**276**	**0**	**30**	**0**	**306**

FOREIGN

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	0	0	0	**0**
Asian	2	0	0	0	**2**
Native Hawaiian or other Pacific Islander	1	0	0	0	**1**
Black or African American	3	0	0	0	**3**
White	44	0	3	0	**47**
More than one race	1	0	0	0	**1**
TOTAL	**51**	**0**	**3**	**0**	**54**

REFERENCES

Abbott, D.E., et al., Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery*, 2012. 151(5): p. 710-6.

. Adam, R., et al., Is liver resection justified for patients with hepatic metastases from breast cancer? *Annals of surgery,* 2006. 244(6): p. 897-907; discussion 907-8.

Akazawa, K., et al., Power of Logrank Test and Cox Regression Model in Clinical Trials with Heterogeneous Samples. *Statistics in Medicine*, 1997. 16: p. 583-597

Albain, K.S., et al., Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*, 2008. 26(24): p. 3950-7.

Albain, K.S., et al., Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet*, 2009. 374 (9707): p. 2055-63.

Alix-Panabières, C. et al., Circulating tumor cells and circulating tumor DNA. *Annu Rev Med*, 2012. 63: p. 199-215.

Bergh, J., et al., Clinical and pharmacokinetic study of sunitinib and docetaxel in women with advanced breast cancer. *Breast*, 2012. 21(4): p. 507-13.

Bidard, FC., et al., Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma. *Int J Cancer*, 2014. 134(5): p. 1207-13.

Cleeland C.S., et al. Pain Outcomes in Patients with Advances Breast Cancer and Bone Metastases. *Cancer*, 2013; 119: 832-838

Cristofanilli M, B.G., Ellis MJ, *et al* .Circulating Tumor Cells, Disease Progression and Survival in Metastatic Breast Cancer. *N Engl J Med* , 2004; 351, 781-791.

Demaria, S., et al., Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys*, 2004. 58(3): p. 862-70.

Dewas, S., et al., Stereotactic body radiation therapy for liver primary and metastases: the Lille experience. *Cancer Radiother*, 2012. 16(1): p. 58-69.

Fisher, B. Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res*. 1980; 40: 3863-3874.

Fong, Y., et al., Liver resection for colorectal metastases. *J Clin Oncol*, 1997. 15(3): p. 938-46.

Formenti, S., et al., Abscopal response in irradiated patients: results of a proof of priniciple trial. *Int J Radiat Oncol Biol Phys,* 2008. 72(S1): p. S6-7.

Freidlin B, Korn EL. A comment on futility monitoring. *Controlled Clinical Trials*. 2002;23:355-366.

Friedel, G., et al., Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic *Surgery*, 2002. 22(3): p. 335-44.

Fumagalli, I., et al., A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases. *Radiat Oncol*, 2012. 7: 164.

Gianni, L., et al., *AVEREL:* Arandomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. *J Clin Oncol*, 2013. **31**(14): p. 1719-25.

Greenberg, P.A., et al., Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol*: official journal of the American Society of Clinical Oncology, 1996. 14(8): p. 2197-205.

Halsted, W.S., *I.* The Results of Radical Operations for the Cure of Carcinoma of the Breast. *Ann Surg*, 1907. 46(1): p. 1-19.

Heitzer, E., et al., Circulating tumor cells and DNA as liquid biopsies. *Genome Med*, 2013. 5(8): p 73.

Hellman, S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol*. 1994; 12 :2229-2234.

Hellman, S, Weichselbaum, RR. Oligometastases. *J Clin Oncol*. 1995; 13:8-10.

Hunsberger S, Zhao Y,Simon R, et al. A comparison of phase II study strategies. *Clin Cancer Res*. 2009;15:5950-5955

Hurvitz, S.A., 0.0.0. A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing advanced breast cancer that progressed during prior trastuzumab and taxane therapy. *Breast Cancer Res Treat,* 2013. 141(3): p. 437-46.

Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing

risk. *Ann Stat.* 16:1141-1154, 1988.

Kalbfleish JD, Prentice RL: The statistical analysis of failure time data. New York, NY, *John Wiley & Sons*. 1980.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Stat Assoc*. 1958;53: 457-81,

Karnoub, A.E., et al., Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature*, 2007. 449(7162): p. 557-63.

. Kocher, M., et al., Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*:*official journal of the American Society of Clinical Oncology*, 2011. 29(2): p. 134-41.

Lan KKG, DeMets ER. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70: 659-663.

Lewis, S.L., et al., An International Survey of Definitive SABR for Extracranial Limited Metastases. *Int J Radiat Oncol Biol Phys*, 2013. 87(2): p. S605

. *Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. International Registry of Lung Metastases. J Thorac Cardiovasc Surg*, 1997. 113(1): p. 37-49.
Maclean, J. et. al., Multi-disciplinary management for patients with oligometastases to the brain: results of a 5 year cohort study. *Radiat Oncol*, 2013. 8: 156.

.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother. Rep* 1966:50: 163-70,

McDonald, ML, Deschamps, C, Ilstrup, DM, et al. Pulmonary resection for metastatic breast cancer. *The Annals of thoracic surgery.* 1994. 58:1599-1602.

Milano, M.T., et al., Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys*, 2012. 83(3): p. 878-86.

Milano, M.T., et al., Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat*, 2009. 115(3): p. 601-8.

Miller, G., et al., Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg, 2007.* 205(2): p. 231-8.

Muss, H.B., et al., Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med*, 2009. 360(20): p. 2055-65.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.

Planchard, D., et al., Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer*, 2004. 100(1): p. 28-35.

Pockaj, B.A., et al., Metastasectomy and surgical resection of the primary tumor in patients with stage IV breast cancer: time for a second look? *Annals of surgical oncology*, 2010. 17(9): p. 2419-26.

Postow, M.A., et al., Immunologic correlates of the abscopal effect in a patient with melanoma.
N Engl J Med, 2012. 366(10): p. 925-31.

Rusthoven, K.E., et al., Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases. *J Clin Oncol,* 2009a. 27(10): p. 1579-84.

Rusthoven, K.E., et al., Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases. *J Clin Oncol*, 2009b. 27: p. 1572-1578

Salama, J.K., et al., Stereotactic body radiotherapy for multisite extracranial oligometastases: Final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer*, 2012. 118(11): p. 2962-70.

Schoenfeld, D.A., Sample-Size Formula for the Proportional-Hazards Regression Model. Biometrics, 1983.39(2): p. 499-503

Simpson, R., et al., Pulmonary resection for metastaic breast cancer. *Aust NZ J Surg,* 1997. 67(10): p. 717-9.

Stamell, E.F., et al., The Abscopal Effect Associated With a Systemic Anti-melanoma Immune Response. *Int J Radiat Oncol Biol Phys*, 2012.

Staren, E.D., et al., Pulmonary resection for metastatic breast cancer. *Archives of surgery*, 1992. 127(11): p. 1282-4.

Tanvetyanon, T., et al., Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol,* 2008. 26(7): p. 1142-7.

Tawfik, H., Y. Rostom, and H. Elghazaly, All-oral combination of vinorelbine and capecitabine as first-line treatment in HER2/Neu-negative metastatic breast cancer. *Cancer Chemother Pharmacol*, 2013. 71(4): p. 913-9.

Timmerman, R., et al., Excessive toxicity when treating central tumors in a phase II study

of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*, 2006. 24(30): p. 4833-9.

Tree, A.C., et al., Stereotactic body radiotherapy for oligometastases. Lancet Oncol, 2013. 14(1): p. e28-37.

Torok, J., et al., Stereotactic body radiation therapy for adrenal metastases: a retrospective review of a noninvasive therapeutic strategy. *Future oncology*, 2011. 7(1): p. 145-51.

Valastyan, S., et al., A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. *Cell,* 2009. **137**(6): p. 1032-46.

Vlastos, G., et al., Long-term survival after an aggressive surgical approach in patients with breast cancer hepatic metastases. *Ann Surg Oncol*, 2004. 11(9): p. 869-74.

Wronski, M., et al., Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. *J Neurosurg*, 1995. 83(4): p. 605-16.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 1974: 27: 365-75,