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NRG Oncology-Radiation Therapy Oncology Group Study 1014: 1-Year Toxicity Report From a Phase 2 Study of Repeat Breast-Preserving Surgery and 3-Dimensional Conformal Partial-Breast Reirradiation for In-Breast Recurrence.

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NRG Oncology RTOG 1014: 1 Year Toxicity Report From a Phase II Study of Repeat Breast Preserving Surgery and 3D-Conformal Partial Breast Re-Irradiation (3D-CRT PBrI) for In-Breast Recurrence

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Abstract

Purpose—NRG Oncology RTOG 1014 is a prospective phase II trial of 3D-CRT PBrI following repeat lumpectomy for in-breast recurrence following previous whole breast irradiation (WBI). The primary goal of the trial was to determine the associated toxicity, tolerance and safety of PBrI.

Materials and Methods—Eligibility criteria included in-breast recurrence occurring >1 year following WBI, <3cm, unifocal and resected with negative margins. PBrI was targeted to surgical cavity + 1.5 cm; prescription dose of 45 Gy in 1.5Gy BID for 30 treatments was used. The primary objective was to evaluate the rate of grade ≥3 treatment-related skin, fibrosis, and/or breast pain adverse events (AEs), occurring ≤1 year from re-treatment completion. A rate of ≥13% for these AEs in a cohort of 55 patients was determined to be unacceptable, 86% power, 1-sided α=0.07.

Results—Between 2010 and 2013, 65 patients were accrued and the first 55 eligible and with 1 year follow-up were analyzed. Median age is 68 years. 22 patients had DCIS and 33 invasive disease; 19 ≤1cm, 13 >1 to ≤2cm and 1 >2cm. All patients were clinically node-negative. Systemic therapy was delivered in 51%. All treatment plans underwent quality review for contouring accuracy and dosimetric compliance. All treatment plans scored acceptable for tumor volume (TV) contouring and TV dose volume analysis (DVA). Only 4 (7%) scored unacceptable for organs at risk (OAR) contouring and OAR DVA. Treatment-related skin, fibrosis, and/or breast pain AEs were recorded as grade 1 in 64%, grade 2 in 7% with only 1 (<2%) grade ≥3 and identified as grade 3 fibrosis of deep connective tissue.

Conclusion—PBrI with 3D-CRT following second lumpectomy for patients experiencing in-breast failures after WBI is safe and feasible with acceptable treatment quality achieved. Skin, fibrosis and breast pain toxicity was acceptable and grade 3 toxicity was rare.

Keywords

breast cancer; breast cancer trials; re-treatment; partial breast radiation therapy for breast cancer

Introduction

Breast conservation surgery (BCS) followed by whole breast irradiation (WBI) yields excellent in-breast control rates and is recognized as a standard of care option for local treatment of properly selected patients. Long term follow-up of patients treated with BCS and WBI finds that in-breast failure rates are approximately 10%.[1] Mastectomy is the acknowledged treatment of choice when encountering an in-breast failure following WBI. This has become accepted for reasons including the perception that mastectomy is the only logical next step, concerns over cosmetic outcomes following additional surgery and complication rates following additional radiotherapy. Published outcomes suggest that a mastectomy may not be the definitive answer, as chest wall failure rates following a mastectomy for in-breast failure after WBI range from 3–32%.[2–15] (Table 1) It is recognized that these are older series with variable follow up and that the stage at presentation, in-breast recurrence extent and surgical details are not available to allow modern perspective regarding anticipated chest wall recurrence rates. However, this suggests that exploration of alternative options is appropriate. Attempts at continued breast conservation are represented through the limited series of repeat BCS alone that have been reported with poor in-breast

control rates.[9,11,12,15,16] (Table 2) The lack of reported surgical margin status and description of imaging use make it difficult to extrapolate these results into present-day practice. Nevertheless, the rate of second in-breast failure is significant and consistent with results following lumpectomy only for primary disease. Whole breast irradiation in this setting is discouraged given the potential for serious late toxicity related re-irradiation of sensitive normal tissue such as lung and heart. The acceptance of partial breast irradiation as an alternative to whole breast irradiation in the setting of de novo breast conservation makes it a logical solution to apply to repeat breast conserving surgery in an attempt to reduce the 2nd in-breast recurrence rates to acceptable levels while avoiding excessive toxicity. Early and limited investigation of this approach has generated outcome data that suggests this may be an appropriate direction to pursue if continued breast conservation is preferred.[17–23] (Tables 1 and 2).

Therefore, it is proposed that in properly selected patients facing an in-breast failure after initial lumpectomy and WBI, repeat BCS followed by partial breast re-irradiation (PBrI) could yield acceptable results. This manuscript is the first report from the NRG Oncology RTOG 1014 prospective phase II trial of 3D-conformal external beam (3D-CRT) PBrI following repeat lumpectomy for in-breast recurrence following previous WBI. The primary endpoint is to evaluate skin, breast, and chest wall adverse events (AEs) occurring within 1 year from the completion of re-irradiation and is the focus of this report. Additional endpoints of local recurrence, cosmesis, and circulating tumor cells require additional follow-up and will be reported in the future.

Materials and Methods

Eligibility Criteria

Protocol approval was received from the Institutional Review Board at each study site and informed consent was obtained from each patient prior to participation. Patient eligibility criteria were defined to select patients with low likelihood of extensive in-breast recurrence with the risk of microscopic disease confined to the immediate vicinity of the lumpectomy cavity. In-breast failures could represent either delayed failure of the original tumor or a new primary within the same breast. Eligibility criteria included unicentric breast lesions by MRI that were ≤ 3 cm and without evidence of skin involvement, which occurred one year or more following initial breast conserving therapy. Histologically, recurrent tumors were to be consistent with invasive ductal, medullary, tubular, mucinous, lobular or ductal carcinoma in situ. Documentation of a negative metastatic work-up was required for invasive recurrences by either whole body Positron Emission Tomography - Computed Tomography (PET/CT) or a combined CT of the chest, abdomen, pelvis and bone scan. Being ≥ 18 years old and having breast conserving surgery with anticipated acceptable cosmesis and obtaining negative histologic margins of resection, no tumor on ink (re-excision was permitted to achieve negative margins) were requisites. Based on a postoperative, pretreatment CT scan the target lumpectomy cavity needed to be clearly defined and the target lumpectomy cavity/whole breast reference volume <30% for study entry.

Axillary management was dependent on the in-breast recurrence histology and previous axillary surgery. Patients with 0–3 positive axillary lymph nodes without extracapsular

extension were eligible for enrollment. Axillary evaluation beyond a node negative clinical exam consisted of ultrasound, sentinel node evaluation and/or axillary node dissection (ALND) depending on histology and previous axillary surgery. Any suspicious areas were to be biopsied and if positive, followed with an ALND. Any patients presenting with a positive axillary clinical exam were required to undergo biopsy and if positive, follow with an ALND.

Target definition and dose delivery

Supine or prone treatment positioning was allowed and a treatment planning CT scan with required target volumes and organs at risk outlined on all CT slices was required. This included the clinical target volume (CTV), planning target volume (PTV) and PTV for Evaluation (PTV_EVAL), skin, ipsilateral and contralateral whole breast reference volume, thyroid, ipsilateral and contralateral lung, and heart (see Supplemental Appendix). The excision cavity was outlined based either on clear visualization on CT or, if placed, with the help of surgical clips. The CTV was defined by uniformly expanding the excision cavity volume by 15 mm with limitation to 5 mm from the skin surface and the posterior breast tissue extent (chest wall structures and pectoralis muscles were not included). The PTV provided a margin around the CTV to compensate for the variability of treatment setup and motion of the breast with breathing. The PTV was defined as a minimum of 10 mm around the CTV. The PTV_EVAL was generated and used for dose volume histogram analysis (DVA) constraints. The PTV_EVAL was defined as the PTV bounded and limited to exclude the first 5 mm of tissue under the skin and excludes any the PTV expansion beyond the posterior extent of breast tissue.

Dose delivery specifications included the use of 3D-CRT PBrI to begin within 9 weeks after last breast surgery. A total of 45 Gy was delivered in two fractions per day, each of 1.5 Gy, separated by at least six hours and given in fifteen consecutive working days for a total of 30 fractions and 45 Gy.

Field arrangements were at the discretion of the physician and determined through 3D-treatment planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient was based on analysis of the volumetric dose including DVA of the PTV_EVAL and critical normal tissues. Dose calculations with tissue inhomogeneity correction were used. Photon field combinations (with or without electrons), and field within a field treatment approaches were accepted.

Quality assurance and rapid review

All cases were electronically submitted to the Image-Guided Therapy Quality Assurance Center (ITC) for review with final evaluation by one of the radiation oncology protocol investigators and judged as 1-per protocol, 2-variation acceptable or 3-deviation unacceptable. Quality assurance (QA) rapid reviews were to be done on the first case from each site before the start of treatment, unless previously participating on RTOG partial breast irradiation (PBI) protocols. The subsequent cases submitted to ITC were reviewed in a timely fashion with feedback of protocol guideline compliance to the participating institution as needed. QA reviews for all cases were completed prior to this report.

Toxicity Assessment

Treatment related toxicity is documented with use of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute. Protocol stipulates evaluation and recording of any AEs occurring during radiation therapy, at 6 weeks from the start of treatment and then at regular intervals to follow (every 3 months for 1 year, every 4 months for 2 years, every 6 months for 2 years and then annually).

Statistics

The primary objective of this study was to evaluate the rate (p) of grade ≥ 3 treatment-related skin, fibrosis, and breast pain AEs, as graded by CTCAE version 4.0, occurring within 1 year from the completion of re-irradiation. Based on a rate of 4% for these AEs from first line PBrI treatment in RTOG 0319, the investigators determined that a rate of 13% or more for these AEs with re-irradiation would be unacceptable (H_0: p ≤ 13% vs H_1: p >13%). A sample size of 55 evaluable patients (eligible and started protocol treatment) provided the following: 86% power to conclude that the treatment has an unacceptable rate of the specified AEs, if the true AE rate is at least 13%, and 93% probability to not conclude that the treatment has an unacceptable rate of the specified AEs, if the true AE rate is ≤ 4%. Adjusting this figure by 10% to allow for patients determined to be ineligible, that did not start protocol treatment, or lack data, a total sample size of 61 patients was required for this study.

If 5 or more, out of 55 evaluable patients, experience the treatment-related AEs specified above, then that rate would be considered unacceptable and the treatment not be considered further; otherwise the treatment-related AE rate would be acceptable and the treatment considered for further study.

Results

This NRG Oncology RTOG 1014 was opened in June 2010 and completed accrual in June 2013. In this 3 year time period, 34 RTOG members and affiliates/satellites participated, enrolling a total of 65 patients. Of those enrolled patients, 58 were determined to be ultimately eligible and received protocol treatment. As per protocol, this analysis is confined to the first 55 eligible patients who completed treatment and achieved 1 year of follow-up.

The overall compilation of pre-treatment patient and tumor characteristics are represented in Table 3. The median age is 68 years old (min-max: 44–86). The majority of cases consisted of invasive histology, 60% (n=33), with 40% (n=22) represented by ductal carcinoma in situ (DCIS). The invasive tumors were small (n=19 ≤1cm, n=13 >1 to ≤2cm, and n=1 >2cm) and the majority low to intermediate grade (69%) with only 31% high grade lesions. All tumors were tested for estrogen and progesterone receptors and 76.4% were estrogen positive and 56% progesterone positive. Her2 testing was not available for 11 patients, but in those tested 8 (18%) were positive with 36 (82%) negative. All patients were clinically node negative with 25% pathologically confirmed node negative. See Table 4 for axillary assessment details. The mean time between treatment for the initial breast disease and the in-breast failure was 14.9 years (median=14.0 years, min-max: 1.6–27.7). Systemic therapy was

delivered in 51% of patients, with systemic chemotherapy alone in 6 (10.9%) patients, hormone therapy alone in 21 (38.2%) patients, and both systemic chemotherapy and hormonal therapy in 1 (1.8%) patient.

Summary dose information is shown in Supplemental Table 1. Median PTV_EVAL volume is 242cc (min-max: 33.8–951.2cc), median ipsilateral breast volume is 1064cc (min-max: 102.5–3103.4cc), and the median PTV_Eval volume/ipsilateral breast volume is 22% (min-max: 7.7–49.3%). Overall contouring and dosimetric compliance was judged as exceptionally good with rare unacceptable variations. Details of dose constraint criteria and the ability to meet these constraints are shown in Table 5. Tumor volume contours were scored as per protocol in 52 (94.5%) cases, 3 (5.5%) cases were scored as acceptable variations and there were no unacceptable scores. Organs at risk (OAR) contours were scored as per protocol in 38 (69.1%) cases, 13 (23.6%) as acceptable variations, and only 4 (7.3%) cases scored as unacceptable variations. High quality of treatment planning was confirmed through the dose volume analysis (DVA) score of tumor volume analysis and OAR. Tumor volume DVA were scored as per protocol in 54 (98.2%) cases, 1 (1.8%) as acceptable variation, and there were no unacceptable scores. OAR DVA were scored as per protocol in 45 (81.8%) cases, 5 (9.1%) as acceptable variations, and 5 (9.1%) cases as unacceptable variations. In review of the cases with unacceptable variation scores, 5 cases total were identified, 4 scoring unacceptable variation on both OAR contouring and OAR DVA and 1 scoring acceptable variation on OAR contouring and unacceptable variation on OAR DVA.

Treatment-related skin, fibrosis, and/or breast pain AEs are the primary endpoint for this phase II protocol. In the first 55 patients evaluable, these specific AEs were recorded as grade 1 in 64%, grade 2 in 7% with only 1 (<2%) grade 3. There were no grade 4 or 5 AEs reported. The skin and subcutaneous tissues disorders represented the majority of the reported grade 1 and grade 2 events. The documented grade 3 AE was represented by fibrosis of deep connective tissue (Table 6). Since there were fewer than 5 grade ≥ 3 treatment-related skin, fibrosis, and breast pain AEs, the treatment-related AE rate is considered to be acceptable.

Discussion

This trial demonstrates acceptable toxicity and safety of a second breast conservation using lumpectomy and partial breast re-irradiation for management of in-breast recurrence following initial breast conservation where whole breast irradiation was delivered. Several publications have previously reported small experiences that describe early outcome results following repeat breast conservation and partial breast re-irradiation.[18–23] Each experience has contributed to the overall understanding of this approach and helped to support the initiation of NRG Oncology RTOG 1014. One of the first experiences reported is from France where investigators offered repeat breast conservation treatment only to women that either refused mastectomy or when mastectomy was contraindicated.[21] Treatment of the in-breast failure consisted of re-resection followed by partial breast brachytherapy using 30Gy total dose delivered with low dose rate multicatheter brachytherapy (MCB). The study included 15 patients with a mean tumor size of 2.4 cm. Following this focused treatment, a

second in-breast recurrence was encountered in 26% (n=4 patients) at a mean follow-up of 48 months. Major sequelae were reported in 3 patients. Of these 3, one patient with skin necrosis was treated with local wound care and one patient had a mastectomy performed.

Resch, et al, followed years later in 2002 with an additional small study. In this experience, 17 patients were treated after encountering an in-breast failure following breast conserving therapy that included WBI.[22] Nine patients followed local resection with 40–50 Gy partial breast treatment delivered with multicatheter technique. The remaining eight patients received repeat WBI to 30Gy followed by 12.5Gy delivered to a partial breast target with MCB. There were four second recurrences reported with a mean follow up of 50 months. Interestingly, all were within the group treated with repeat WBI and MCB. Toxicity was acceptable with only grade 1–2 fibrosis encountered.

Deutsch, et al., from the University of Pittsburgh Medical Center, published a study of repeat irradiation for in-breast tumor recurrence after prior lumpectomy and whole breast irradiation using external beam radiotherapy after re-resection.[23] Thirty-nine patients were treated in this study, 31 invasive and 8 non-invasive diseases. All patients underwent resection of the recurrence to achieve negative pathologic margins with 15% of cases reported to ultimately have resection margins that were positive. Following local resection, external beam re-irradiation to the operative bed with 50 Gy in 25 fractions was delivered. At a median follow-up of 52 months, a second local in-breast recurrence was encountered in 20.5% of patients. Contralateral breast cancer occurrence in this cohort study was also 20.5%. There were no reports of radiation-induced necrosis.

Chadha, et al, published an additional experience from Beth Israel Medical Center in New York City, NY.[20] This phase I/II study evaluated the role of partial breast MCB following local resection of a local recurrence/new primary following standard WBI. Fifteen patients were treated post lumpectomy with low dose rate brachytherapy utilizing a total of 30Gy for the first six patients and 45Gy for the subsequent nine patients. Median follow-up was 36 months. They reported only one re-recurrence, and therefore, an overall in-breast control rate of 89%. No grade 3 or 4 toxicities reported.

In an additional small study published by Trombetta, et al., balloon based brachytherapy was used to deliver PBrI after local resection for in-breast failure following BCS and WBI.[19] Eighteen patients were included in this study and reported with a mean follow up of 39.6 months. Results were again encouraging with only 2 patients recorded as having an in-breast re-recurrence and 2 patients with infection of which one required a mastectomy.

The largest study that has been published on this subject is the multicenter GEC-ESTRO European trial (The Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO).[18] This experience of 217 patients was reported in 2013 with a mean follow up of 3.9 years. All patients had previously been treated with BCS and WBI and documented to have an in-breast failure. Repeat treatment on this trial consisted of local resection of the recurrent disease and MCB. They reported a 5-year actuarial re-recurrence rate of only 5.6% with limited grade 3–4 complications (11%).

The published literature corroborates the hypothesis of this trial that local resection followed by partial breast re-irradiation could be an appropriate alternative treatment approach to mastectomy for the local management of an in-breast failure following BCS and WBI. The growing experience in the use of 3D-CRT PBI and that it is widely available, reproducible, and could reliably deliver a homogeneous dose to previously irradiated tissue confirmed that this method needed to be studied in this setting. Furthermore, the established treatment guidance with existing outcome data from the previously successful RTOG 0319 phase II protocol provided a platform from which to build.[24,25] To further reduce the risk of grade 3 tissue toxicity, a hyperfractionated dose regimen was decided upon. This provided the opportunity to use a dose fractionation scheme modeled after the head and neck re-treatment experience − 1.5 Gy bid X 30 treatments and a total of 45 Gy.[26–28] The intent was to assure the highest level of disease control and low risk of toxicity with optimal cosmetic outcome. Therefore, dose homogeneity and the dose fractionation scheme were believed to be optimized.

Conclusion

Initial AE data from NRG Oncology RTOG 1014 investigating PBrI with 3D-CRT following second lumpectomy for patients experiencing in-breast failures after lumpectomy and WBI suggests promising outcome and supports continued investigation. Despite previous whole breast irradiation, PBrI delivered with 3D-CRT is well tolerated and at the 1-year follow-up interval is found to be safe and feasible with acceptable treatment quality achieved. In the RTOG 0319 phase II protocol, 3D-CRT was used in an accelerated fashion (3.85Gy bid X 10 delivered in 5 days) for primary breast conserving therapy for early stage breast cancer and reported a grade 3 toxicity event rate of 4%. In this trial of PBrI in patients with in-breast failure after WBI, a protracted hyperfractionated course of treatment was utilized. The fractionation scheme applied in this protocol was based on previous re-treatment experiences, however, it is recognized that alternative fractionation schemes may be appropriate. Grade 1 skin, fibrosis and breast pain was documented in a large number of patients as expected, however, grade 2 toxicity was infrequent at 7% and grade 3 toxicity was rare at <2%. This initial report suggests that the primary hypothesis, local resection followed by PBrI for an in-breast failure following WBI is safe and feasible, is correct. Further follow up is necessary for confirmation of long-term safety and to address the ability to achieve in-breast disease control with an acceptable long term cosmetic outcome and the ability to avoid mastectomy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

NRG Oncology RTOG 1014 is a phase II trial investigating partial breast re-irradiation (PBrI) with 3D-CRT following second lumpectomy for patients experiencing in-breast failures after whole breast irradiation (WBI). At the 1 year follow up interval, PBrI delivered with 3D-CRT technique is found to be well tolerated, safe and feasible with acceptable treatment quality achieved.

Table 1

Chest wall failure rates following mastectomy for in-breast failure following lumpectomy and WBI

	No. of pts	Med. F/U (mo's)	Chest wall re-recurrence rate (%)	5-yr OS rates (%)
Clarke, et al, 1985	12	26	27	-
Recht, et al, 1989	65	32	9	-
Kurtz, et al, 1989	43	53	12[a]	53
Forquet, et al, 1989	39	63	-	73
Fowble, et al, 1990	52	25	-	84
****	41	60	-	59
Osborne, et al, 1992	46	28	31	76
Abner, et al, 1993	106	39	7	79
Cajucom, et al, 1993	25	52	32	65
Dalberg, et al, 1998	65	156	19	-
Salvadori, et al, 1999	134	73	4	70
Doyle, et al, 2001	112	44	3	83
Huang, et al, 2002	118	84	20	52[b]

Abbreviations: No., number; Med., median; F/U, follow-up; mo's, months; yr, year; OS, overall survival

[a] chest wall and regional failures

[b] true recurrences

Table 2

In-breast re-recurrence rates following repeat lumpectomy only for in-breast failure following lumpectomy and WBI

	No. of pts	Med. f/u (mo's)	In-breast re-recurrence rate (%)	5-yr OS (%)
Kurtz, et al, 1991	55	51	27	-
Abner, et al, 1993	16	39	31	81
Dalberg, et al, 1998	14	156	50	-
Voogd, et al, 1999	16	52	38	-
Salvador, et al, 1999	57	73	19	85

Abbreviations: No., number; Med., median; F/U, follow-up; mo's, months; yr, year; OS, overall survival

Table 3

First 55 Evaluable Patients: Patient and Tumor Characteristics

Patient or Tumor Characteristic	n	%
Age (years)		
Median	68	
Min - Max	44 – 86	
Q1 – Q3	59 – 73	
Race		
Asian	1	1.8
Black or African American	8	14.5
White	45	81.8
Unknown	1	1.8
Zubrod Performance Status		
0	52	94.5
1	3	5.5
Histology		
DCIS	22	40.0
Invasive Histologies	33	60.0
Size - largest dimension		
≤ 0.5 cm	6	18.2
>0.5 to ≤ 1.0 cm	13	39.4
>1.0 to ≤ 2.0 cm	13	39.4
>2.0 cm	1	3.0
Histology Grade		
Low grade	8	14.5
Intermediate grade	30	54.5
High grade	17	30.9
Stage (AJCC 7th Edition)		
Stage 0	21	38.2
Stage I	33	60.0
Stage IIA	1	1.8
Estrogen Receptor Status		
Positive	42	76.4
Negative	13	23.6
Progesterone Receptor Status		
Positive	31	56.4
Negative	24	43.6
Her2 Status		
Not applicable/Not done	11	20.0
Positive	8	14.5
Negative	36	65.5

Q1 = first quartile; Q3 = third quartile

Table 4

First 55 Evaluable Patients: Information on Sentinel Lymph Nodes and Axillary Nodes (n=55)

Node Information	n	%
Invasive Lesions	(n=33)	
No SLNB/No ALND	13	39.4
SLN not identified/No ALND	8	24.2
Yes SLNB/No ALND	9*	27.3
Yes SLNB/Yes ALND	3*	9.1
DCIS	(n=22)	
No SLNB/No ALND	18	81.8
No SLNB/Yes ALND	1*	4.6
SLN not identified/No ALND	2	9.1
Yes SLNB/Yes ALND	1*	4.6

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

*All node negative

Table 5

Dose Constraints for Critical Structures and Scoring

Structure	Score	Criteria	n (%)
PTV	**Per Protocol**	>90% of the prescription isodose surface covers >90% of the PTV_EVAL. Maximum dose does not exceed 110% of the prescription dose.	54 (98.2%)
	Variation Acceptable	All specified PTV-EVAL dosimetric coverage goals fall within 5% of the guidelines. Maximum dose is 110%–120% of the prescription dose.	1 (1.8%)
	Deviation Unacceptable	If the PTV-EVAL dosimetric coverage goals exceed 5% of the guidelines. Maximum dose exceeds 120% of the prescription dose.	0 (0.0%)
Ipsilateral Breast	**Per Protocol**	<60% of the whole breast reference volume should receive ≥50% of the prescribed dose and <35 % of the whole breast reference volume should receive the prescribed dose. The whole breast reference volume is defined as per Supplemental Appendix.	45 (81.8%)
	Variation Acceptable	60–65% of the whole breast reference volume should receive ≥50% of the prescribed dose	7 (12.7%)
	Deviation Unacceptable	>65% of the whole breast reference volume should receive ≥50% of the prescribed dose	3 (5.5%)
Contralateral Breast	**Per Protocol**	< 3% of the prescribed dose to the contralateral breast	52 (94.5%)
	Variation Acceptable	3–5% of the prescribed dose to the contralateral breast	2 (3.6%)
	Deviation Unacceptable	>5% of the prescribed dose to the contralateral breast	1 (1.8%)
Ipsilateral Lung	**Per Protocol**	< 15% of the lung received 30% of the prescribed dose	50 (90.9%)
	Variation Acceptable	15–20% of the lung received 30% of the prescribed dose	5 (9.1%)
	Deviation Unacceptable	>20% of the lung received 30% of the prescribed dose	0 (0.0%)
Contralateral Lung	**Per Protocol**	< 15% of the lung received 5% of the prescribed dose.	55 (100.0%)
	Variation Acceptable	15–20% of the lung received 5% of the prescribed dose.	0 (0.0%)
	Deviation Unacceptable	>20% of the lung received 5% of the prescribed dose.	0 (0.0%)
Heart (n=1, missing)	**Per Protocol**	Right-sided lesions: < 5% of the heart received 5% of the prescribed dose. Left-sided lesions: <40% of the prescribed dose to the V5	52 (96.3%)
	Variation Acceptable	Right-sided lesions: 5–10% of the heart should receive 5% of the prescribed dose Left-sided lesions: 40–45% of the prescribed dose to the V5	1 (1.9%)
	Deviation Unacceptable	Right-sided lesions: >10% of the heart received 5% of the prescribed dose Left-sided lesions: >45% of the prescribed dose to the V5	1 (1.9%)
Thyroid (n=1, missing)	**Per Protocol**	Maximum point dose of 3% of the prescribed dose.	54 (100.0%)
	Variation Acceptable	>3–5% of the prescribed dose	0 (0.0%)
	Deviation Unacceptable	>5% of the prescribed dose	0 (0.0%)

Table 6

Number of Patients with an Adverse Event by System Organ Class and Grade Definitely, Probably, or Possibly Related to Protocol Treatment Occurring ≤ 1 Year from the Completion of Reirradiation in the First 55 Evaluable Patients

	Grade				
System Organ Class Term	**1**	**2**	**3**	**4**	**5**
Worst Skin, Fibrosis, and Breast Pain	35	4	1	0	0
INFECTIONS AND INFESTATIONS	2	1	1	0	0
Breast infection	0	1	0	0	0
Skin infection	2	0	0	0	0
Soft tissue infection	0	0	1	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16	2	2	0	0
Dermatitis radiation	14	1	0	0	0
Seroma	2	1	2	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	19	3	1	0	0
Back pain	0	1	0	0	0
Chest wall pain	1	0	0	0	0
Fibrosis deep connective tissue	10	1	1	0	0
Generalized muscle weakness	1	0	0	0	0
Joint range of motion decreased	1	0	0	0	0
Superficial soft tissue fibrosis	9	2	0	0	0
NERVOUS SYSTEM DISORDERS	1	0	0	0	0
Paresthesia	1	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	13	6	0	0	0
Breast atrophy	3	6	0	0	0
Breast pain	14	0	0	0	0
Reproductive system and breast disorders - Other	1	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	32	3	0	0	0
Dry skin	1	0	0	0	0
Erythema multiforme	3	0	0	0	0
Pruritus	3	0	0	0	0

System Organ Class Term	Grade 1	2	3	4	5
Skin and subcutaneous tissue disorders - Other	6	0	0	0	0
Skin atrophy	2	0	0	0	0
Skin hyperpigmentation	25	2	0	0	0
Skin hypopigmentation	1	0	0	0	0
Skin induration	10	1	0	0	0
Telangiectasia	2	0	0	0	0
VASCULAR DISORDERS	4	0	1	0	0
Hot flashes	1	0	0	0	0
Lymphedema	3	0	1	0	0

Skin, Fibrosis, and Breast Pain Adverse Events