Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial

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Published at jco.org on May 1, 2017.

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Clinical trial information: NCT01417286.

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0732-183X/17/3518w-2037w/\$20.00

ABSTRACT

Purpose

Conventionally fractionated postmastectomy radiation therapy (PMRT) takes approximately 5 to 6 weeks. Data supporting hypofractionated PMRT is limited. We prospectively evaluated a short course of hypofractionated PMRT, in which therapy was completed in 15 treatment days.

Patients and Methods

We delivered PMRT at a dose of 36.63 Gy in 11 fractions of 3.33 Gy over 11 days to the chest wall and the draining regional lymph nodes, followed by an optional mastectomy scar boost of four fractions of 3.33 Gy. Our primary end point was freedom from any grade 3 or higher toxicities. We incorporated early stopping criteria on the basis of predefined toxicity thresholds.

Results

We enrolled 69 women with stage II to IIIa breast cancer, of whom 67 were eligible for analysis. After a median follow-up of 32 months, there were no grade 3 toxicities. There were 29 reported grade 2 toxicities, with grade 2 skin toxicities being the most frequent (16 of 67; 24%). There were two patients with isolated ipsilateral chest wall tumor recurrences (2 of 67; crude rate, 3%). Three-year estimated local recurrence-free survival was 89.2% (95% CI, 0.748 to 0.956). The 3-year estimated distant recurrence-free survival was 90.3% (95% CI, 0.797 to 0.956). Forty-one patients had chest wall reconstructions; three had expanders removed for infection before radiation therapy. The total rate of implant loss or failure was 24% (9 of 38), and the unplanned surgical correction rate was 8% (3 of 38), for a total complication rate of 32%.

Conclusion

To our knowledge, our phase II prospective study offers one of the shortest courses of PMRT reported, delivered in 11 fractions to the chest wall and nodes and 15 fractions inclusive of a boost. We demonstrated low toxicity and high local control with this schedule. On the basis of our data, we have designed a cooperative group phase III prospective, randomized trial of conventional versus hypofractionated PMRT that will activate soon.

J Clin Oncol 35:2037-2043. © 2017 by American Society of Clinical Oncology

INTRODUCTION

The efficacy of irradiating the chest wall and draining lymph nodes after mastectomy to improve locoregional control has been established by trials that compared mastectomy alone with mastectomy with postoperative radiation.¹⁻⁷ Most of these trials used older radiation techniques and orthovoltage x-rays. Other trials studied the efficacy and incremental benefit of postmastectomy radiation therapy (PMRT) in the presence of systemic therapy.⁸⁻²⁰ The Early Breast Cancer Trialists' Collaborative Group has collected primary data from every randomized trial of PMRT

in breast cancer and periodically reports analyses on the benefits and risks of radiation therapy in these patients. In the most recent report from 2014, PMRT in node-positive patients resulted in improved local control and breast cancer mortality,²¹ even in patients with N1 disease. These improvements were independent of the use of systemic therapy.

In standard chest wall irradiation, daily fraction sizes of 1.8 Gy or 2 Gy are commonly used and can be described as conventional. The linear quadratic model of fractionation effects has been used to describe the relationship between fraction size/total dose and tissue response.²² In this model, the therapeutic ratio of radiation

ASSOCIATED CONTENT

Appendix
DOI: <https://doi.org/10.1200/JCO.2016.70.7158>

DOI: <https://doi.org/10.1200/JCO.2016.70.7158>

therapy derives from differences in late-reacting normal tissues, such as fibroblasts versus rapidly proliferating tumor cells. The former are more sensitive to high dose per fraction, whereas the latter are less responsive to changes in fraction size. Thus, high cumulative doses of radiation are needed for tumor control, but daily fraction size has to be respectful of the fraction sensitivity of normal tissues in the treated volume. As a result, daily fractions of 1.8 to 2 Gy have been delivered over 4 to 8 weeks, building to a cumulative dose of 45 to 80 Gy.²²

Interestingly, most breast cancers behave differently from other, rapidly proliferating tumors. Breast cancer cells seem to possess fraction sensitivities similar to normal tissues; thus, the primary rationale for prolonged fractionation is not applicable. The reported alpha/beta ratio (the linear quadratic parameter describing how sensitive cells are to high fractional doses) for breast cancer is approximately 4 Gy, which is quite low and similar to normal tissues.²³ For this reason, shorter and more convenient schedules have been studied. These hypofractionated (HF) schedules are now considered an acceptable, and even preferred, standard of care in the adjuvant, intact-breast population.

The largest randomized trials to study HF were the UK START A and B trials. The START A trial randomly assigned women with pT1-3a, pN0-1 breast cancer after either lumpectomy or mastectomy (15%) to one of three radiation treatment arms, with treatment time remaining constant, spanning 5 weeks.²⁴ The control arm was standard fractionation (50 Gy in 25 fractions) versus 39 Gy in 13 fractions versus 41.6 Gy in 13 fractions. Simultaneously, the START B trial randomly assigned women who had undergone a lumpectomy or mastectomy (8%) with pT1-3a, pN0-1 breast cancer to standard fractionation in 5 to 6 weeks versus 40 Gy in 15 fractions over 3 weeks.²⁵ There was no difference in locoregional recurrence in either the START A or B trials,²⁶ and late breast changes seemed to be better with HF. Still, data for the PMRT setting are lacking, and hypofractionation is not routinely considered because of potential toxicity, particularly when irradiating regional lymph nodes and patients who have undergone breast reconstruction.

Here, we report our bi-institutional trial of HF PMRT, describing the safety of this approach using modern radiation techniques. Our results were used as preliminary data for a successor phase III randomized trial of HF PMRT getting set to launch nationally through the Alliance for Clinical Trials in Oncology, A221505.

PATIENTS AND METHODS

Trial Design/Patient Eligibility

We conducted a prospective, single-arm phase II trial (NCT01417286) using a novel fractionation schedule for PMRT in women > 18 years of age with stage IIA to IIIC invasive breast cancer. We also included women with locally advanced breast cancer who received neoadjuvant chemotherapy, regardless of final pathologic stage. We arbitrarily defined locally advanced breast cancer as tumors > 3 cm and/or clinically node-positive breast cancer on exam or diagnostic imaging. We did not exclude patients if they had high-risk features, such as T4 disease, lymphovascular invasion, close margins, young age, hormone-receptor negativity, or an extensive intraductal component. Reconstructed chest walls, implants, or temporary expanders were allowed. Our primary hypothesis was that HF PMRT

resulted in toxicities that were similar to those reported for conventionally fractionated PMRT. Our intent was to complete the experimental therapy in 15 fractions over 3 weeks.

Radiation Treatment Planning and Technique

We delivered a chest wall dose of 36.63 Gy in 11 fractions of 3.33 Gy delivered 5 days per week, 1 fraction per day (equivalent dose in 2-Gy fractions [EQD₂] of 45 Gy, using linear quadratic formalism and an alpha/beta ratio of 4, alpha value of 0.3, T_{pot} value of 13 days, and initial time lag of 14 days).²⁷ Patients who received an optional chest wall boost were treated with four fractions of 3.33 Gy delivered once daily (EQD₂, 15 Gy). Computed tomography–based treatment planning was mandatory (1463 days from last surgery or last cycle of chemotherapy), with the treatment planning scan including the entire chest. Radiation treatment began within 21 to 63 days from last surgery or last cycle of chemotherapy. Standard chest wall tangential fields were used while limiting dose to deeper structures per standard of care. The heart was required to be excluded from the primary beam using blocks or other techniques (breath hold), with no part of the heart receiving more than 2 Gy per fraction. A planning target volume for the chest wall was encouraged but not required at the time this study was initiated, and a graphical review of the plan at the discretion of the treating physician was considered acceptable. Dose homogeneity within the treatment volume was required to be within 90% to 115% of the prescription dose. If matched photon/electron fields were used, a maximum dose of 120% was allowed but could not exceed a volume of 2 mL. The draining lymph node basins were treated with a supraclavicular field ± a posterior axillary boost using the same treatment schedule. Nodal volumes were contoured and evaluated for coverage; internal mammary coverage was left to the discretion of the treating physician. Use of chest wall bolus was allowed. The brachial plexus, particularly the axillary component, is not visible on computed tomography scan and was not contoured. A max dose exceeding 107% was not allowed in the supraclavicular/axillary volume to constrain brachial plexus dose. Optional chest wall boosts were delivered with an electron beam to a margin on the chest wall scar. Wedges, bolus material, field-in-field, and electronic compensation were allowed to achieve dose homogeneity.

Statistical Analysis

The primary aim/end point of this study was to ensure that the total serious toxicity rate (greater than grade 2, Common Terminology Criteria for Adverse Events [version 4]) from the experimental fractionation, at any time point, was similar to standard PMRT. This composite end point included both acute and late toxicities. The background serious toxicity rate from standard regimens was estimated to be 3%.²⁸ Our goal was to ensure a serious toxicity rate from the HF scheme of below 9% with 80% power, using a 10% level one-sided test of proportions. To meet this requirement, we needed to accrue 67 patients. With five or more toxicity events among 67 patients, we rejected the hypothesis that the upper limit of the 90% CI of the true serious toxicity rate is below 9%. The exact significance level of this discrete variable test is .0508, and the exact power is 0.732. The power was computed using standard methods for a binomial distribution. We used the Wilson method for computing the CI.²⁹ The Wilson CI was calculated using the binconf function in the R package Hmisc.³⁰ We used a fixed sample size of 67 patients with locoregional recurrence as a secondary outcome of interest. For up to five recurrences out of 67 patients, we can say with 90% confidence that the true recurrence rate would be between 3.7% and 14.5%. For a small, institutional phase II trial, we felt this was an acceptable upper threshold for noninferiority in a cohort that included patients with high-risk features (the corresponding rate is approximately 11% in the highest risk group from the Early Breast Cancer Trialists' Collaborative Group analysis³¹).

Disease control end points were dated from the diagnosis date. Chest wall reconstruction complications did not contribute to the primary end point of toxicity and were scored as group 4 if they resulted in removal or complete failure of the reconstruction.³¹ They were scored as group 3 if an

unplanned surgical intervention was required for the reconstruction. However, routine fat grafting or in-office minor procedures were excluded from the group 3 definition.

The study was to be stopped early if, at any time, we became more than 80% sure that the > grade 2 toxicity rate exceeded 9%. A stopping rule table was generated consisting of posterior probabilities that the true toxicity level exceeded 9%, assuming a uniform prior on a binomial distribution.

All time intervals were calculated from the date of diagnosis. Nonparametric estimates of the survival or recurrence-free distributions or recurrence (failure) distribution were obtained by life table methods (Kaplan-Meier estimate of survival function). Tests were declared statistically significant if the calculated *P* value was $\leq .05$. All tests used two-sided *P* values. Acute toxicities were scored using Common Terminology Criteria for Adverse Events (version 4). Late toxicities were scored using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer scale. The study and the informed consent was reviewed by the Rutgers Cancer Institute of New Jersey's Institutional Review Board and approved. The first patient was enrolled at Rutgers Cancer Institute of New Jersey (R-CINJ) in December 2010. The Huntsman Cancer Institute (HCI) in Utah was brought on as a participating site, and the HCI Institutional Review Board approved the study, with minor modifications for local context. The first patient from HCI was enrolled in August 2012. The Office of Human Research at the R-CINJ oversaw patient accrual and safety monitoring, inclusive of site visits to HCI. The study was supported by the R-CINJ's Core Center Support Grant (P30CA072720).

RESULTS

We enrolled 69 women between December 2010 and December 2014 with Stage II to IIIa breast cancer. Twenty-three patients were enrolled at R-CINJ, and 46 patients were enrolled at HCI. Two enrolled patients became ineligible after enrollment and were replaced to reach the intended sample size of 67. One developed an infected postmastectomy seroma that spontaneously began draining after a single fraction of PMRT. The adverse event was not attributable to the radiation. The patient recovered and was treated with conventional fractionation. A second patient was enrolled but did not meet dosimetric constraints for the heart and was treated off protocol with 42.56 Gy in 16 fractions. Table 1 lists the clinical characteristics of the patient population. Median follow-up for our cohort of patients was 32 months, with a range of 26.6 to 35.3 months. Median age of our cohort was 54 years, with a range of 33 to 77 years. Forty-six percent of patients were ≤ 50 years of age. Thirty-three patients (49%) underwent neoadjuvant chemotherapy, of whom 10 (30%) had a pathologic complete response in the breast only and five (16%) had a pathologic complete response in both the breast and nodes. Of 27 patients with initially involved nodes (clinical or pathologically-proven) receiving neoadjuvant therapy, five (19%) converted to node negative. All but two patients in our study received an optional mastectomy scar boost.

Toxicities

Grade 1 toxicities were not captured in the study, because we expected most patients to have grade 1 skin toxicity. There were 29 reported grade 2 toxicities, with grade 2 skin toxicities being the most frequent (16 of 67 patients; 24%). Table 2 lists the treatment-related toxicities. Grade 2 fatigue occurred in five patients. There

Table 1. Patient Characteristics

Characteristic	No.	%
Age, years	54 (median)	
≤ 40	11	16
41-50	20	30
51-60	8	12
61-70	22	33
> 70	6	9
Final stage*		
IIA	14	21
IIB	25	37
IIIA	22	33
IIIB	4	6
IIIC	2	3
Histology		
IDC	62	93
ILC	5	7
Grade		
I	10	15
II	18	27
III	38	57
ECE		
No	35	52
Yes	18	27
Unknown	14	21
LVSI		
No	33	49
Yes	27	40
Unknown	7	10
ER positive	51	76
PR positive	45	67
HER2 positive†	15	22
ER negative/PR negative/HER2 negative	9	13
Neoadj chemo	33	49
Anthracycline based	21	57
Taxane based (no anthracyclines)	9	24
Other	3	8
Adj chemo	37	55
Anthracycline-containing regimen	24	65
Taxane based	12	33
No chemo received	5	7
Both neoadj and adj chemo	8	12
Adj tamoxifen (ER/PR positive)	22 (of 53)	42
Adj AI (ER/PR positive)	23 (of 53)	43
Both	1	1
No endocrine therapy (ER/PR positive)	8	15
Pre-therapy nodal biopsy (neoadj patients)		
Negative	2	
Positive	19	
Convert to pathologic CR nodes from positive nodes	5 (of 27)	19
Pathologic CR, breast only	10 (of 33)	30
Pathologic CR, both	5 (of 33)	15
No nodal evaluation (T3N0)	1	1
Sentinel node only	10	15
Axillary dissection	56	84
Range of nodes dissected	3 to 29	
Median No. of nodes	12.5	
Range positive	0 to 16	
Median positive	2	
Breast reconstruction		
Yes	41	59
No	28	41

Abbreviations: Adj, adjuvant; AI, aromatase inhibitor; chemo, chemotherapy; CR, complete response; ECE, extracapsular extension; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVSI, lymphovascular space invasion; neoadj, neoadjuvant; PR, progesterone receptor.

*Higher of pathologic or prechemotherapy clinical stage.

†100% of patients with HER2-positive disease received HER2-directed therapy.

Table 2. Treatment-Related Grade 2 Toxicities

Toxicity	No.	%
Skin	16	24.0
Fatigue	5	7.5
Pain	3	4.5
Lymphedema	3	4.5
Subcutaneous	1	1.4
Other*	1	1.4

*Hot flashes.

were no grade 3 toxicities in the treatment cohort. All toxicities were acute and have resolved, with the exception of the three patients with grade 2 lymphedema and one patient with grade 2 fibrosis.

Disease Control

There were two instances of isolated locoregional recurrence as first site of failure, both of which occurred on the chest wall (two of 67; crude rate, 2.9%). Three-year estimated local recurrence-free survival was 89.2% (95% CI, 74.8% to 95.6%, Fig 1). One patient received salvage treatment and is alive without evidence of disease. There were five distant relapses (crude rate, 7.5%). The 3-year estimated distant recurrence-free survival was 90.3% (95% CI, 79.7% to 95.6%; Appendix Fig A1, online only). The 3-year estimated overall survival was 92.0% (95% CI, 78.9% to 97.1%)

Chest Wall Reconstruction and Complications

Forty-one patients (61%) had a breast reconstruction or temporary expander (one patient had a prior augmentation implant that was used for immediate reconstruction). Table 3 lists details on the timing and types of breast reconstructions. Six patients had temporary expanders (TEs) but did not complete reconstruction. Five of these patients had TEs removed for infection, while one was removed electively for patient preference to

not complete reconstruction. We did not score the elective removal as a complication. Of the five removed for infection, three were removed before RT. Of these, two went on to have a deep inferior epigastric pedicle flap reconstruction after all therapy was complete, and one was not reconstructed. Two patients had TEs removed because of infection after RT, with no further reconstruction attempted.

Twelve of 41 patients (29%) had group 4 reconstruction complications (removal of prosthesis or flap failure; Table 4). Infection-related failures dominated the picture, with a total of 11 failures due to infection (five of these were the TE removals because of infections (mentioned previously) and six permanent implants were removed because of infection). One implant was removed because of cosmetic failure. Excluding the three TEs removed before RT was administered, the removal/failure rate with possible attribution to the experimental therapy was 24% (9 of 38). Three of 38 patients (8%) had a group 3 complication (unplanned surgical intervention). One patient had skin necrosis requiring a flap correction, one patient had a symmetry revision on the contralateral side, and one patient required debridement for infection and nonhealing. An additional patient required capsulectomy before RT, which was not counted as a complication; she did not experience a post-RT complication. Thus, the total, all-cause group 3 and 4 reconstruction complication rate attributable to RT was 32%. Acellular dermal matrix was used with 21 patients, six of whom had reconstruction complications.

DISCUSSION

To the best of our knowledge, this is the first dedicated trial of HF PMRT reported from North America and the first such trial ever reported using currently available planning and delivery techniques. Our fractionation scheme, 36.63 Gy in 11 fractions of 3.33 Gy followed by a boost, seems to be safe and effective with low toxicity. The locoregional and distant relapse rates were comparable to several randomized trials. Our study used one of the shortest schedules of PMRT reported to date.

Prior reports of HF PMRT are difficult to interpret or non-contributory because (1) the schedules were empirically derived, (2) the hypofractionation was modest, (3) the radiation techniques were outdated by current standards, or (4) any combination of these. Still, these prior reports bore important lessons for us in the design of this trial, especially pertaining to the risks of regional nodal irradiation.

Stoll et al³² from Melbourne reported on 117 patients treated between 1958 and 1962 with PMRT using 4 MeV photons to 6,300 rads (approximately 63 Gy) in 12 fractions, including regional nodes. Their 1966 report documented an unacceptable neuropathy rate of 73%. A similar study from Sweden on 71 patients treated from 1963 to 1965 with cobalt-60 teletherapy to 44 Gy in 11 daily fractions with three matching nodal fields also reported dismally poor results.^{33,34} At 34 years, the risk of fibrosis was 86% and neuropathy was 63%. The EQD₂ (alpha/beta, 2) for the Australian study can be estimated at 114 Gy and 76 Gy for the Swedish study using linear quadratic conversion. Thus, the brachial plexopathy

Fig 1. Kaplan-Meier survival estimate for local recurrence-free survival in 67 patients treated with experimental schedule. At 50 months, there were five patients at risk. Three of these were censored; one of the two remaining patients had a local recurrence.

Table 3. Timing, Type, and Fate of Patients Undergoing Reconstruction

Timing	Type of Reconstruction	No.	Procedure	
Pre-RT procedures	Temporary expander placement	34	Removed before RT for infection	3
			Removed after RT for infection	2
			Elective removal for patient preference (abandon reconstruction)	1
			Converted to implant	8
			Converted to LAT flap	2
			Converted to LAT Flap plus implant	9
			Converted to DIEP flap	8
			Converted to DIEP flap plus implant	1
	Immediate implant	2		
	Prior augmentation implant used for immediate reconstruction	2		
Post-RT procedures	LAT flap plus implant reconstruction TRAM	2 1		

Abbreviations: DIEP, deep inferior epigastric pedicle; LAT, latissimus dorsi; RT, radiation therapy; TRAM, transverse rectus abdominus muscle flap.

rate is hardly surprising, given that the plexus tolerance is estimated at 54 to 59 Gy. Similar, older studies with clear overdosing are listed in [Table 5](#).

In contrast, studies in which the EQD₂ is within known tolerances of critical structures predictably do not report high toxicity rates. Appendix [Table A1](#) (online only) lists reports in which tolerances were within limits and toxicities were low. For example, the UK START trials²⁴⁻²⁶ enrolled 4,400 patients in the A and B trials; 513 of these patients were postmastectomy, and 479 patients received regional RT (of whom 201 and 278 were randomly assigned to HF schedules, respectively; overlap among these two groups was not reported). The investigators reported equal lymphedema rates and a single patient with brachial plexopathy from the UK Start A trial (from the 41.6 Gy treatment arm).²⁵ Clearly, hypofractionation is safe when linear quadratic parameters are accounted for.

With a median follow-up of 32 months, we have not seen any brachial plexopathies; however, we will monitor these patients closely because reports have shown potentially long latency periods before manifestation of plexopathy.³⁵ A companion trial at our institution has completed enrollment with this fractionation in a cohort of patients who underwent lumpectomy and was recently

reported.³⁶ We believe there is little reason to doubt the radiobiologic parameters of efficacy and toxicity that have now been established by large in-human studies, thanks to the effort of Yarnold et al²⁵—indeed, these are more robustly tested and described in breast cancer than in any other human malignancy. Still, we do not believe these shorter schedules should be used routinely off study, particularly among women with breast reconstruction.

On the basis of the results reported here, we have designed a randomized phase III trial of HF PMRT in which we will test the safety of a shorter schedule (42.56 Gy in 16 fractions) when directly compared with conventional fractionation (Alliance A221505, Phase III Randomized Trial of Hypofractionated Post-Mastectomy Radiation With Breast Reconstruction). Notably, all women in this trial will have breast reconstruction or intent for ultimate reconstruction. The overall grade 3 or 4 reconstruction toxicity of 32% seen in our cohort may seem high but is in line with previously published complication rates.^{37,38} The primary end point of Alliance A221505 is reconstruction complication rate, but secondary end points will include lymphedema, toxicities including brachial plexopathy, recurrence-free survival, and end points for health costs/economics. As such, this important trial will prospectively resolve two important and

Table 4. Chest Wall Reconstruction Complications

Complication	No.	Notes	%
Group 4 reconstruction complications*			
TE removed for infection <i>after</i> RT	2	No reconstruction after TE failure	5
Permanent implant removed for infection	6		15
Permanent implant removed for cosmetic failure	1	Salvage with DIEP flap reconstruction	3
Total	9		24
Group 3 reconstruction complications†			
Skin necrosis	1	Requiring bilateral skin flaps	3
Debridement for infection/healing	1	DIEP flaps requiring debridement	3
Revision for symmetry	1		3
Total	3		8

Abbreviations: DIEP, deep inferior epigastric pedicle; TE, temporary expander.

*Loss of implant/reconstruction.

†Unplanned surgical intervention.

Table 5. Studies in Which the EQD₂ to Structures Exceeded Known Tolerances

First Author	Period	Patients, No.	RNI Dose (Gy)	Fractions	EQD ₂	Plexopathy Rate, %	Median Follow-Up, Years
Stoll ³²	1958-1962	117, PMRT	63	12	114.2	73	2.5
Johansson ³³	1963-65	71, PMRT	57	17	76.3	63	34
Bajrovic ³⁹	1980-1993	140, RNI	52.0	20	59.8	14	8
Bates ⁴⁰	1968-1974	411, PMRT	35	6	68.5	NR	10
			50	12	77.1	NR	Lymphedema 30 vs 12%
Baillets ⁴¹	1984-1989	230, RNI not reported	23	4	44.6	NR	4 (min) Fibrosis 18 vs 9%
Rodger ⁴²	1979-1982	484, PMRT and RNI	45	10	66.4	1	10
	1982-1984	289, PMRT and RNI	45	20	43.8	1	

NOTE. Alpha/beta ratio of 2 Gy assumed for normal tissues in EQD₂ calculations.

Abbreviations: EQD₂, 2-Gy equivalent dose; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradiation.

outstanding questions in the adjuvant therapy of breast cancer: (1) what is the rate of breast reconstruction complications with hypofractionation (and conventional fractionation for that matter), and (2) how safe is hypofractionation for the regional nodal volume.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Rutgers Cancer Institute of New Jersey's Core Center Support Grant No. P30CA072720 and Breast Cancer Research Foundation Grant No. BCRF-16-064 (B.H.).

Prior Presentation

Presented in part at the annual San Antonio Breast Cancer Symposium, San Antonio, TX, on December 10, 2014.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/iffc.

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Consulting or Advisory Role: Elekta

Research Funding: Elekta (Inst), Cianna Medical (Inst)

Matthew M. Poppe

No relationship to disclose

Sharad Goyal

No relationship to disclose

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Consulting or Advisory Role: Merit Medical Systems (I)

Travel, Accommodations, Expenses: Merit Medical Systems (I)

Thomas Kearney

No relationship to disclose

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Appendix

Fig A1. Kaplan-Meier survival estimate for distant recurrence-free survival in 67 patients treated with experimental schedule.

Table A1. Studies in Which the EQD₂ to Structures Remained Within Tolerance of Critical Structures

First Author	Period	Patients, No.	RNI Dose (Gy)	Fractions	EQD ₂ (Gy)	Plexopathy Rate, %	Median Follow-Up
Ragaz ¹⁸	1979-1986	318 (164 PMRT)	35	16	37	0	20
Powell (Radiother Oncol 18:213-220) ⁴³	1982-1984	338	45	15	(56)	6	5.5
		111	54	30	51	1	
Owen (Lancet Oncol 7:467-471) ⁴⁴	1986-1998	290 (2/3rd hypofx)	42.9	13	47-49	0	8
			39				
Haviland ²⁶	1998-2002	479 (278 hypofx)	40	13-15	47-49	1 (< 1)	9.3
			42.9				
			39				

NOTE. Alpha/beta ratio of 2 Gy was assumed for normal tissues in EQD₂ calculations.

Abbreviations: BC, British Columbia; EQD₂, 2-Gy equivalent dose; hypofx, treated on hypofractionated arm; PMRT, postmastectomy radiation therapy; RMH/GOC, Royal Marsden Hospital/Gloucestershire Oncology Centre.