ORIGINAL REPORT

Radiotherapy and Adjuvant Trastuzumab in Operable Breast Cancer: Tolerability and Adverse Event Data From the NCCTG Phase III Trial N9831

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ABSTRACT

Purpose

To assess whether trastuzumab (H) with radiotherapy (RT) increases adverse events (AEs) after breast-conserving surgery or mastectomy.

Patients and Methods

Patients with early-stage resected human epidermal growth factor receptor 2 (HER-2) –positive breast cancer (BC) were randomly assigned to doxorubicin (A) and cyclophosphamide (C), followed by weekly paclitaxel (T; AC-T-H or AC-TH-H). RT criteria (with or without nodal RT) were postlumpectomy breast or (optional) postmastectomy chest wall. RT of internal mammary nodes was prohibited. RT commenced within 5 weeks after T, concurrently with H. Analysis included 1,503 irradiated patients for RT-associated AEs across treatment arms. Rates of cardiac events (CEs) with and without RT were compared within arms.

Results

No significant differences among arms were found in incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia. A significant difference occurred in incidence of leukopenia, with higher rates for AC-T-H versus AC-T (odds ratio = 1.89; 95% CI, 1.25 to 2.88). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of CEs regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% v 5.9% with or without RT, respectively.

Conclusion

Concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs. Further follow-up is required to assess late AEs.

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INTRODUCTION

Approximately 15% to 25% of breast cancers (BCs) express human epidermal growth factor receptor 2 (HER-2) amplification.[1] Patients with HER-2–positive disease have greater risk for relapse and death.[2-5] Trastuzumab (Herceptin [H]; Genentech, Inc, South San Francisco, CA) is a recombinant, DNA-derived, monoclonal antibody that selectively binds to the extracellular domain of the HER-2 protein in BC cells. H was an effective part of adjuvant treatment for HER-2–positive BC in randomized trials by the North Central Cancer Treatment Group (NCCTG; N9831 trial) and the National Surgical Adjuvant Breast and Bowel Project (B-31 trial). Joint analysis of these studies showed statistically significant improvement in 4-year disease-free survival (92.6%; $P < .00001$) and overall survival (85.9%; $P < .0007$) in patients randomly assigned to H concurrently with paclitaxel (T) after doxorubicin and cyclophosphamide (AC) compared with patients randomly assigned to T alone after AC (89.4% and 73.1%, respectively).[6] However, in the N9831 trial, concurrent use of H produced a 3.7-year cumulative incidence of New York Heart Association class III or IV congestive heart failure (CHF) or cardiac death of 3.3% compared with 0.3% in the control arm.[7]

Because H is generally administered postsurgically for 12 months, patients receiving breast radiotherapy (RT) generally take it concurrently. Preclinical data suggest a radiosensitizing effect of H on BC cells, but whether it causes radiosensitization

of normal cells is unknown.[8] Adding RT to H raises concerns about increased adverse events (AEs), particularly cardiac toxicity, because adjuvant anthracyclines can be cardiotoxic with H.[2,9-14]

Limited published data exist concerning concurrent adjuvant RT and H.[7,15,16] To our knowledge, this is the largest study with the longest follow-up that systematically investigates potential RT and H interactions during adjuvant treatment. We report our assessment of documented AEs in the NCCTG phase III N9831 trial, focusing on the impact of RT on H-related toxicity and the impact of H on RT-associated toxicity.

PATIENTS AND METHODS

Study Design

Enrollment began in May 2000 (Fig 1), with trial coordination by the NCCTG in collaboration with the Eastern Cooperative Oncology Group, the Cancer and Leukemia Group B, and the Southwest Oncology Group. Primary goals were to evaluate whether H added benefit to adjuvant AC followed by T, to examine the disease-free survival impact of sequential versus concurrent H, and to compare the cardiac toxicity profile of the three regimens. Although not designed to assess RT impact on outcomes, this trial reviewed toxicities for all patients. RT delivery was not determined by random assignment. However, at initial random assignment, investigators declared whether patients would receive RT and, if so, the extent of the RT fields. RT was required after adjuvant chemotherapy after a breast-sparing procedure or mastectomy with ≥ four positive nodes.

Patients

Inclusion criteria were a pathologic diagnosis of breast adenocarcinoma with immunohistochemical staining for HER-2 protein of 3+ intensity or amplification of the *HER2* gene by fluorescence in situ hybridization. Initially, node-positive disease was required. However, in May 2003, patients were included with HER-2–positive, axillary node–negative tumors with a diameter of more than 2 cm regardless of hormone receptor status or of more than 1 cm with hormone receptor–negative disease. Complete tumor removal and negative sentinel lymph node biopsy or complete axillary dissection were required. Exclusion criteria included active cardiac disease defined as prior myocardial infarction, history of documented CHF, current use of digitalis or β-blockers for CHF, history of arrhythmia or cardiac valvular disease requiring medications or considered clinically significant, current use of medications for arrhythmias or angina pectoris, current uncontrolled hypertension (diastolic blood pressure > 100 mmHg or systolic blood pressure > 200 mmHg), and clinically significant pericardial effusion.
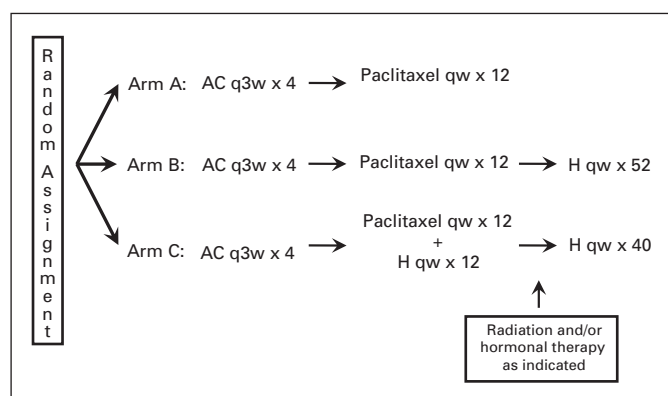

Fig 1. N9831 random assignment schema: H, trastuzumab in 4 mg/kg loading dose followed by 2 mg/kg; A, doxorubicin 60 mg/m²; C, cyclophosphamide 600 mg/m²; T, paclitaxel 80 mg/m²; HRT, hormone replacement therapy; RT, radiotherapy; qw, every week; q3w, every 3 weeks.

After release of the joint analysis of the N9831 and B-31 trials, AC-T and AC-T-H patients could begin concurrent treatment with H if the patient was receiving T or had completed T within the past 6 months.[17] Thus, patients randomly assigned on or after April 25, 2004, were eligible for crossover and were excluded from analysis; 2,393 patients were previously randomly assigned. Twenty-four patients cancelled before treatment, and 221 patients were ineligible (178 because central review failed to corroborate HER-2 positivity and 43 because of other eligibility violations), leaving 2,148 patients for analysis.

An RT report form documenting RT use and treatment parameters (fields, beam energy, dose, and RT-related AEs [type and grade]) was available for 2,008 patients. In this analysis, 140 patients who met entry criteria for cardiac event (CE) analysis but for whom these data were not available are assumed to have not received RT. Of note, additional analyses excluded patients without RT report forms, and conclusions were consistent with our results. All patients provided written informed consent.

RT

Whole-breast RT was required after segmental mastectomy, with a dose of 45.0 to 50.4 Gy in 25 to 28 fractions of 1.8 to 2.0 Gy. Boost dose to the primary tumor excision site was optional. RT to the chest wall was optional for mastectomy patients at the same dose specified for whole-breast RT with optional boost. RT to the supraclavicular and axillary nodal regions was also optional. Whole-breast and chest wall RT alone, without regional lymph node treatment, was administered to 82 patients (5%) and 312 patients (21%), respectively. RT guidelines excluded purposeful irradiation of internal mammary nodes (IMN) because of questionable patient outcomes and potential cardiac toxicity.[18] Nonetheless, 44 patients received IMN RT. RT was started within 5 weeks after T treatment, concurrently with H and any hormonal therapy. RT quality assurance was not available because simulation films, port films, and dosimetry data were not required. However, when IMN RT was deemed necessary, the dosimetry plan was reviewed by the NCCTG radiation oncology coinvestigator (T.M.P.) to ensure cardiac sparing.

RT-Related AEs and Cardiac Assessment

Cardiac function was assessed before registration by physical examination and multiple-gated acquisition scanning or two-dimensional echocardiogram and then monitored regularly ≤ 3 months after the last study dose.[19] Study entry required a left ventricular ejection fraction (LVEF) greater than or equal to the institutional lower limit of normal. For use of H after completion of AC, LVEF had to meet or exceed the lower limit of normal with a decrease of less than 16% from baseline. Patients were monitored for CHF signs and symptoms. Per protocol, continuing or stopping H in asymptomatic patients was determined by LVEF change from baseline. Permanent discontinuation was required for asymptomatic decreases in LVEF that did not recover after two successive 4-week treatment holds or for confirmed CHF defined as symptomatic CHF with objective findings by multiple-gated acquisition scan or echocardiogram or by ECG and chest radiograph. Reports of CEs, which were defined as cardiologist-confirmed CHF or probable cardiac death (sudden death without documented cause) or definite cardiac death (as a result of CHF, myocardial infarction, or documented primary arrhythmia), were submitted to the NCCTG within 14 days. Standard expedited AE reporting was also used. In addition, National Cancer Institute Common Toxicity Criteria (version 2.0) were used to assess RT patients for acute RT-related AEs.[20]

Statistical Analysis

All grades of acute RT-related AEs were reported on RT report forms. Analysis included all eligible patients who received RT according to the treatment arm assigned at random assignment. Each AE was summarized by grade and arm. Incidences of each AE (Common Toxicity Criteria grades ≥ 1 and ≥ 3), the relative frequency of early RT discontinuation, and the relative frequency of at least one RT interruption were compared across arms using logistic regression containing one predictor variable for arm. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test, and significance was assessed with the Wald χ^2 statistic for overall arm effect followed by a 95% CI of the odds ratio (OR) comparing each H arm to the AC-T arm. Subsequent

logistic modeling added age, RT type (whole breast v postmastectomy), regional lymphatic RT (yes v no), RT side (left v right), and hormone receptor status as predictor variables. Results with respect to arm remained consistent; thus, univariate models are presented.

For each treatment arm, the relative frequency of patients with confirmed CHF or CEs after completion of T therapy was summarized for those receiving or not receiving RT or with unknown RT status. Using the method of Fine and Gray,[21] we estimated the cumulative CE incidence in the presence of competing risks (ie, documented BC recurrence, contralateral BC, second primary cancer, or noncardiac death) after completion of T therapy for RT patients and all other patients. The interaction term (between arm and RT status) in a proportional hazards model for the subdistribution of a competing risk also included main effects for arm and RT status, which tested the interaction between H and RT regarding CEs.

With repeat CE analyses excluding patients with unknown RT status, results (data not shown) were essentially unchanged. Using the same analyses, we compared left-sided RT patients with all other patients and, among RT patients, compared patients who received purposeful IMN RT with those who received none.

CE analysis included all eligible patients alive on study without CEs or documentation of BC recurrence, contralateral BC, or second primary cancer at completion of T. Inclusion criteria for CE analysis also included adequate cardiac functioning after AC treatment to be eligible for H. On February 16, 2007, data were frozen for analysis (median follow-up time, 3.7 years; range, 0 to 6.5 years).

RESULTS

Analyses focused on the following two areas: the impact of H on RT-related AEs and the impact of RT on H-related cardiac toxicity. Thus, patients included in these two analyses differ.

Analysis of RT-Related AEs

Of the 2,148 patients, 1,503 (70%) received adjuvant RT, 505 (23.5%) received none, and 140 (6.5%) had unknown RT status.

Of the 1,503 RT patients, 780 (52%) received right-sided RT, and 723 (48%) received left-sided RT. Table 1 lists demographic and RT characteristics.

Postlumpectomy RT was administered to 703 patients (46.8%), and postmastectomy RT was administered to 800 patients (53.2%). The median RT whole-breast dose was 50 Gy (range, 22.5 to 60.4 Gy). Postmastectomy RT with photons was delivered to 746 patients (median dose, 50.4 Gy; range, 18 to 64.4 Gy), and RT with electrons was delivered to 71 patients (median dose, 50 Gy; range, 3.6 to 60.4 Gy). A boost dose was administered to 641 postlumpectomy patients (median dose, 14 Gy; range, 0.2 to 26 Gy) and to 443 postmastectomy patients (median dose, 10 Gy; range, 0.1 to 25.0 Gy). Of 1,503 adjuvant RT patients, 1,126 (74.9%) and 499 (33.2%) had supraclavicular and axillary nodal irradiation, respectively. Although IMN RT was not permitted per protocol, 44 patients (2%) received it, with post hoc assessment of IMN, cardiac, and pulmonary dose distributions by one reviewer. In all cases, an electron beam was used predominantly or exclusively, resulting in dose-volume characteristics qualitatively similar to those expected without IMN. These results are from an acute time period (from RT initiation to 90 days after completion).

There were no statistically significant differences across the three treatment arms in incidence of grade ≥ 1 RT-related AEs, except leukopenia (Table 2). Leukopenia was more common with AC-T-H compared with AC-T (OR = 1.89; 95% CI, 1.25 to 2.88), driven primarily by increases in grade 1 and 2 leukopenia. The incidence of grade ≥ 3 RT-related AEs was low in all three treatment arms (Table 2). At least one RT interruption was reported for 126 (24.2%), 133 (24.6%), and 115 patients (26.3%) in arms AC-T, AC-T-H, and AC-TH-H, respectively (OR for AC-T-H v AC-T = 1.02; 95% CI, 0.77 to 1.35; OR for AC-TH-H v AC-T = 1.11; 95% CI, 0.83 to 1.49). Of 2,346

Table 1. Demographic and RT Characteristics of Patients Receiving RT in N9831 Trial

Characteristic	AC-T (n = 521)		AC-T-H (n = 543)		AC-TH-H (n = 439)		Total (N = 1,503)		P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age at random assignment, years									.92
Mean	48.7		49.0		49.1		48.9		
Standard deviation	9.72		10.32		9.77		9.95		
Median	49		49		49		49		
Range	24-77		19-79		25-79		19-79		
ER status at initial diagnosis									.86
Positive	284	54.5	297	54.7	233	53.1	814	54.2	
Negative	237	45.5	246	45.	206	46.9	689	45.8	
PgR status at initial diagnosis									.47
Positive	218	41.8	226	41.6	177	40.3	621	41.3	
Negative	303	58.2	315	58	259	59.0	877	58.3	
Unknown	0	0	2	0.4	3	0.7	5	0.3	
Type of RT									.96
Whole-breast RT	115	22.1	106	19.5	91	20.7	312	20.8	
Whole-breast plus regional lymphatic RT	133	25.5	146	26.9	112	25.5	391	26.0	
Postmastectomy chest wall	26	5.0	31	5.7	25	5.7	82	5.5	
Postmastectomy chest wall plus regional lymphatic RT	247	47.4	260	47.9	211	48.1	718	47.8	
Side treated with RT									.51
Right	280	53.7	273	50.3	227	51.7	780	51.9	
Left	241	46.3	270	49.7	212	48.3	723	48.1	

Abbreviations: RT, radiotherapy; AC, doxorubicin and cyclophosphamide; T, paclitaxel; H, trastuzumab; ER, estrogen receptor; PgR, progesterone receptor.
*P values were determined using an analysis of variance F-test for age and χ^2 tests for all other variables.

Table 2. Incidence of RT-Related Adverse Events (grade $\geq$ 1 and $\geq$ 3)

Adverse Event	% of Patients			P*†	AC-T v AC-T-H*		AC-T v AC-TH-H*	
	AC-T (n = 521)	AC-T-H (n = 543)	AC-TH-H (n = 439)		OR	95% CI	OR	95% CI
Grade $\geq$ 1								
Radiation dermatitis	84	84	85	.79	0.97	0.69 to 1.34	1.09	0.76 to 1.55
Pneumonitis or pulmonary infiltrates	0.6	1.1	1.1	.59	1.93	0.48 to 7.75	1.97	0.47 to 8.31
Dyspnea	1.9	2.4	2.3	.86	1.25	0.55 to 2.88	1.18	0.49 to 2.87
Cough	2.9	2.4	2.3	.81	0.83	0.39 to 1.76	0.78	0.35 to 1.75
Radiation dysphagia (esophageal)	1.6	1.5	2.7	.30	0.96	0.36 to 2.58	1.79	0.72 to 4.42
Leukocytes	7.2	12.8	10.3	.01	1.89	1.25 to 2.88	1.47	0.93 to 2.32
Neutrophils or granulocytes	3.7	6.5	5.0	.12	1.81	1.02 to 3.21	1.37	0.73 to 2.57
Grade $\geq$ 3								
Radiation dermatitis	5.6	5.9	4.3	.51	1.06	0.63 to 1.78	0.76	0.42 to 1.38
Pneumonitis or pulmonary infiltrates	—	0.2	—	—	—	—	—	—
Dyspnea	0.6	—	—	—	—	—	—	—
Cough	—	—	—	—	—	—	—	—
Radiation dysphagia (esophageal)	—	—	—	—	—	—	—	—
Leukocytes	0.2	0.6	1.1	.23	2.87	0.30 to 27.69	5.91	0.69 to 50.78
Neutrophils or granulocytes	0.2	—	0.5	.78	—	—	2.35	0.21 to 25.98

Abbreviations: RT, radiotherapy; AC, doxorubicin and cyclophosphamide; H, trastuzumab; T, paclitaxel; OR, odds ratio.
*Based on a logistic regression model of the given adverse event containing a single predictor variable (arm: AC-T v AC-T-H v AC-TH-H).
†Wald χ^2 P value for overall arm effect.

total treatment interruptions, 79 (3%) were related to skin reactions ranging from dry desquamation to grade 3 moist desquamation, two (0.04%) were related to dysphagia, and one (0.04%) was related to pericarditis. The rest were unrelated to RT toxicity and included holiday breaks (n = 191; 8%), machine malfunctions (n = 81; 4%), patient choice (n = 63; 3%), and miscellaneous causes. Early RT discontinuation was higher in the AC-T arm (15 patients; 2.8%) with RT alone versus the AC-T-H (three patients; 0.6%) and AC-TH-H (six patients; 1.4%) arms when RT was initiated during H (OR for AC-T-H v AC-T = 0.19; 95% CI, 0.05 to 0.65; OR for AC-TH-H v AC-T = 0.47; 95% CI, 0.18 to 1.22). Discontinuations were a result of skin reactions (n = 11), patient choice (n = 5), metastatic disease (n = 3), and unknown reasons (n = 5).

Analysis of CEs

CEs were analyzed for 1,938 patients, of whom 1,418 (73.2%) received adjuvant RT, 450 (23.2%) received no RT, and 70 (3.6%) had unknown RT status. Comparison of RT patients with all other patients in each arm revealed no significant differences by age, hormone receptor status, and use of hypertensive medications.

Table 3 and Figure 2 show CE frequency and cumulative incidence by arm and RT status. Six patients who experienced CHF between T and RT are included in the RT group, although CHF predated RT. The proportional hazards model showed that the interaction between arm and RT status was not significant (P = .21).[21] RT status was also not significant (hazard ratio of RT yes v no/unknown = 0.7; 95% CI, 0.1 to 8.2); however, arm was significant (main effect, P = .04; HR for AC-T-H v AC-T = 4.9; 95% CI, 0.6 to 41.9; HR for AC-TH-H v AC-T = 11.1; 95% CI, 1.4 to 87.4). Similar results were observed for left-sided RT patients compared with all other patients (interaction, P = .37; Fig 3).

IMN RT

Among the 1,418 patients who received adjuvant RT included in the CE analysis, 44 patients received purposeful IMN RT with no apparent increase in cumulative incidence of CEs; however, sample sizes were small (Table 4). Careful planning was used to exclude or minimize cardiac irradiation. Also, there was no increased incidence of pneumonitis after IMN RT (data not shown).

Table 3. Cardiac Events After Completion of T by RT Status

Cardiac Event	AC-T (n = 664)		AC-T-H (n = 708)*		AC-TH-H (n = 566)*		Overall (N = 1,938)		
	RT: Yes	RT: No or Unknown	RT: Yes	RT: No or Unknown	RT: Yes	RT: No or Unknown	RT: Yes	RT: No or Unknown	Total
Patients, No.	483	181	522	186	413	153	1,418	520	1,938
Confirmed CHF, No.	1	1	14*	4	7*	9	22*	14	36
Cardiac deaths, No.	1	0	0	1	0	1	1	2	3
Cardiac events, No.	2	1	14*	5	7*	9	23*	15	38

NOTE. See Figure 2 for 3-year cumulative incidence rates.
Abbreviations: RT, radiotherapy; AC, doxorubicin and cyclophosphamide; T, paclitaxel; H, trastuzumab; CHF, congestive heard failure.
*Two patients in the AC-T-H arm and four patients in the AC-TH-H arm had a cardiac event between the end of T therapy and the initiation of RT. These six patients are included in the RT category; however, the cardiac events are not attributable to RT because of their timing.
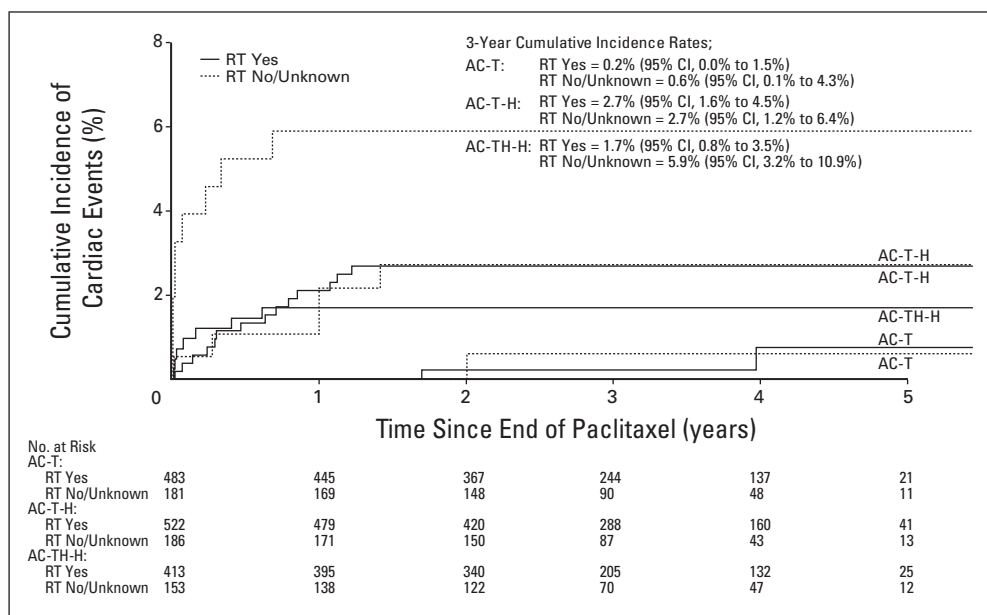
Fig 2. Cumulative incidence plots of cardiac events after completion of paclitaxel (T) therapy by treatment arm and radiotherapy (RT) status (yes v no/unknown). A, doxorubicin; C, cyclophosphamide; H, trastuzumab.

DISCUSSION

Randomized trials have shown the benefit of adjuvant H in HER-2–positive BC.[1,17,22-24] In the National Surgical Adjuvant Breast and Bowel Project B-31 trial, RT was administered with H after chemotherapy. In the Herceptin Adjuvant trial, H was administered 6 weeks after RT. In the Finnish Herceptin trial, RT was administered after chemotherapy. No RT details are available for the Breast Cancer International Research Group 006 study. No study provided information on tolerability and AEs of RT with H. To our knowledge, our analysis is the first using prospectively collected data within a large-scale randomized clinical trial to examine AEs of H combined with RT.

RT for BC causes potential acute and long-term AEs. The risk of acute RT-related pneumonitis is reportedly ≤ 5% with modern RT techniques.[25-27] Risk of pneumonitis may increase with sequential or concurrent T and rarely with H.[17,28-32] Taghian et al[31] reported a statistically significant increase in incidence of RT pneumonitis after adjuvant or neoadjuvant AC with or without concurrent or sequential T. The pneumonitis rate was 14.6% with T versus 1.1% without T. However, in 189 patients treated with four versus eight cycles of fluorouracil, doxorubicin, and cyclophosphamide, no significant difference in pneumonitis was found with T (5.0% v 4.5%, respectively; $P = 1.0$).[33] The incidence of pneumonitis was low in all three treatment arms. Grade 3 RT-related pneumonitis developed in only one patient in the sequential H arm.
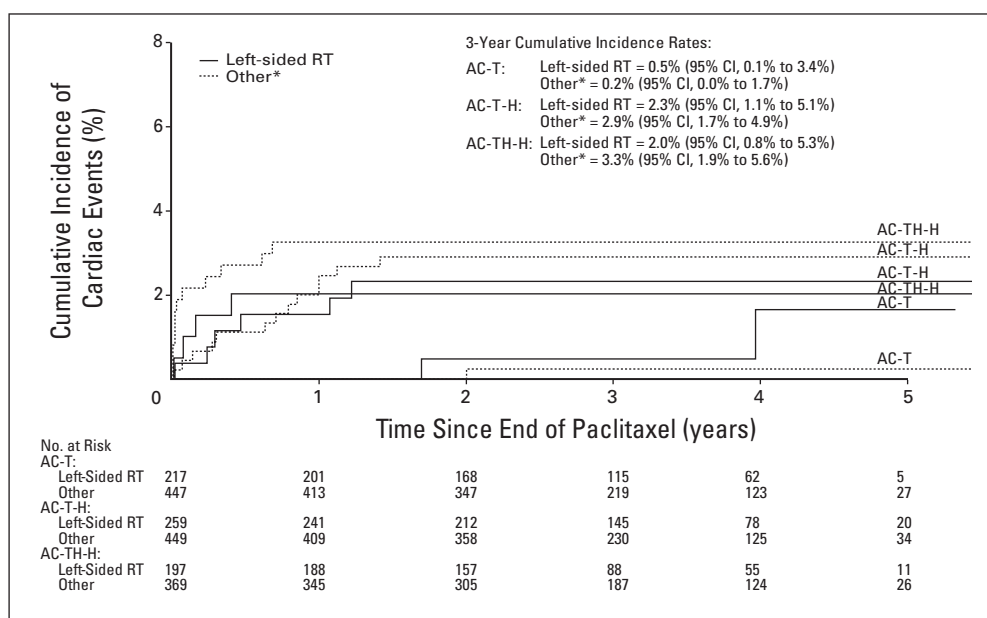

Fig 3. Cumulative incidence of cardiac events after completion of paclitaxel (T) therapy by treatment arm and side treated with radiotherapy (RT). (*) Right-sided RT or no/unknown RT. A, doxorubicin; C, cyclophosphamide; H, trastuzumab.

Table 4. Cardiac Events After Completion of T for Patients Receiving IMN RT

Cardiac Event	AC-T (RT only)		AC-T-H (RT only)		AC-TH-H (RT only)		All RT Patients		All RT Patients
	IMN RT	No IMN RT	IMN RT	No IMN RT	IMN RT	No IMN RT	IMN RT	No IMN RT	
Patients, No.	15	468	14	508	15	398	44	1,374	1,418
Confirmed CHF, No.	0	1	1	13	0	7	1	21	22
Cardiac deaths, No.	1	0	0	0	0	0	1	0	1
Cardiac events, No.	1	1	1	13	0	7	2	21	23

NOTE. Three-year cumulative incidence rates were as follows: AC-T: IMN RT, 0%; no IMN RT, 0.2%; AC-T-H: IMN RT, 7.1%; no IMN RT, 2.6%; and AC-TH-H: IMN RT, 0%; no IMN RT, 1.8%.
Abbreviations: T, paclitaxel; IMN, internal mammary nodes; RT, radiotherapy; AC, doxorubicin and cyclophosphamide; H, trastuzumab; CHF, congestive heart failure.

The incidence of other acute RT AEs did not differ significantly with H compared with chemotherapy alone. No analysis was performed regarding RT field extent and the volume of normal structures irradiated. With larger volumes of normal tissue, AEs with H might have increased. Longer follow-up is needed to identify additional AEs.

Older breast RT techniques with irradiation of a larger portion of the heart resulted in increased cardiac mortality in the older postmastectomy RT series at 10 to 15 years of follow-up.[9,34] Recent data suggest that more modern RT techniques markedly reduce cardiac risks, but long-term follow-up is needed.[10,35,36] We found no apparent increase in CEs associated with concurrent RT with H; the CE rate was lower with RT than without RT or with unknown RT status. These results should be interpreted cautiously because of the brief median follow-up time (3.7 years) and possible underreporting of CHF after on-study cardiac monitoring concluded. We do not infer any protective effect of RT with H that would account for a lower CE rate. Our data provide reassurance that concomitant use of RT and H does not induce unexpected acute toxicities.

This trial prohibited intentional IMN RT but not incidental cardiac irradiation. Not all RT techniques of IMN treatment substantially increase cardiac dose or cause cardiac morbidity. However, because a small portion of the anterior left ventricle is often included in midline tangents, many patients likely received incidental cardiac irradiation while receiving H. Especially notable is the lack of increased acute CEs in patients who received purposeful IMN RT. It is uncertain whether an increased CE incidence would have occurred with a greater volume of the heart. However, reducing incidental cardiac RT whenever possible is prudent.

In-depth analysis of cardiac dose or volume parameters related to RT is not possible because submission of RT materials was not required, including whether patients were treated with three-dimensional or intensity-modulated techniques or whether wedges were used to increase dose homogeneity. The volume of normal structures within the radiation field cannot be commented on in this analysis. It is possible that if larger volumes of normal tissues were included in patients treated with H, then increased toxicities levels could be seen. The short median follow-up time also precluded evaluation of long-term cardiac toxicities.[37-39] As additional follow-up information becomes available, the potential increase in late cardiovascular morbidity can be addressed.

Limitations include nonrandomized RT administration, although random assignment is unlikely given the standard use of adjuvant RT in BC. However, there was a protocol-defined set of recommendations for RT administration. Although data for 140 patients with no RT report forms were analyzed as RT unknown, CEs did not change when data were analyzed with or without these patients. Further detail on the cardiac volume included in the RT fields was also not available. The limited number of CEs limits the statistical power for testing for interaction in a regression model; however, the cumulative CE incidence among RT patients was low in all three arms.

Overall, concurrent treatment with RT and adjuvant H does not seem to increase CEs or acute RT-related AEs except leukopenia. Thus, concurrent RT (with modern techniques involving cardiac sparing) and H may be continued. IMN RT with limited cardiac exposure also seems feasible. Results of the upcoming worldwide Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial (ALTTO; N063D; BIG 2-06; EGF 106708) and other large phase III trials may shed further light on the interaction of RT with H.

AUTHOR CONTRIBUTIONS

Conception and design: Thomas M. Pisansky, Larry Solin, Nancy Davidson, Silvana Martino, Peter Kaufman
Administrative support: Silvana Martino
Provision of study materials or patients: Larry Solin, Nancy Davidson, Silvana Martino, Peter Kaufman, Leila Kutteh, Shaker R. Dakhil

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