

## IMPACT OF HIGH-DOSE CHEMOTHERAPY ON THE ABILITY TO DELIVER SUBSEQUENT LOCAL–REGIONAL RADIOTHERAPY FOR BREAST CANCER: ANALYSIS OF CANCER AND LEUKEMIA GROUP B PROTOCOL 9082

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**Purpose:** To report, from Cancer and Leukemia Group B Protocol 9082, the impact of high-dose cyclophosphamide, cisplatin, and BCNU (HD-CPB) vs. intermediate-dose CPB (ID-CPB) on the ability to start and complete the planned course of local–regional radiotherapy (RT) for women with breast cancer involving  $\geq 10$  axillary nodes. **Methods and Materials:** From 1991 to 1998, 785 patients were randomized. The HD-CPB and ID-CPB arms were balanced regarding patient characteristics. The HD-CPB and ID-CPB arms were compared on the probability of RT initiation, interruption, modification, or incompleteness. The impact of clinical variables and interactions between variables were also assessed.

**Results:** Radiotherapy was initiated in 82% (325 of 394) of HD-CPB vs. 92% (360 of 391) of ID-CPB patients ( $p = 0.001$ ). On multivariate analyses, RT was less likely given to patients who were randomized to HD treatment (odds ratio [OR] = 0.38,  $p < 0.001$ ), older ( $p = 0.005$ ), African American ( $p = 0.003$ ), postmastectomy ( $p = 0.02$ ), or estrogen receptor positive ( $p = 0.03$ ). High-dose treatment had a higher rate of RT interruption (21% vs. 12%,  $p = 0.001$ , OR = 2.05), modification (29% vs. 14%,  $p = 0.001$ , OR = 2.46), and early termination of RT (9% vs. 2%,  $p = 0.0001$ , OR = 5.35), compared with ID.

**Conclusion:** Treatment arm significantly related to initiation, interruption, modification, and early termination of RT. Patients randomized to HD-CPB were less likely to initiate RT, and of those who did, they were more likely to have RT interrupted, modified, and terminated earlier than those randomized to ID-CPB. The observed lower incidence of RT usage in African Americans vs. non–African Americans warrants further study. © 2010 Elsevier Inc.

**Breast cancer, Radiotherapy, High-dose chemotherapy, Toxicity.**

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## INTRODUCTION

Most women with breast cancer present with local–regional disease (breast with or without the regional axillary nodes), without evidence of distant systemic disease. The risk of subsequent systemic relapse is related to the extent of axillary disease (1–4). Among patients with  $\geq 10$  involved axillary nodes at presentation, approximately 50–90% will relapse systemically within 5 years despite conventional adjuvant chemotherapy (5, 6).

Some studies (7–9), albeit not all (10, 11), suggest that chemotherapy intensity might influence its ability to sterilize subclinical distant metastases. Toward this goal, a series of patients with  $\geq 10$  positive axillary nodes were treated on a Phase II study with four cycles of conventional-dose CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) followed by high-dose cyclophosphamide, cisplatin, and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (HD-CPB) with autologous bone marrow support (Cancer and Leukemia Group B [CALGB] Protocol 8782). The 3-year relapse-free survival rate was 72% (12), better than in historical controls.

This observation led to a multi-institution, intergroup, randomized, Phase III study (CALGB 9082, Southwest Oncology Group 9114, National Cancer Institute of Canada MA-13) to test this approach in patients with  $\geq 10$  positive axillary nodes. After surgical removal of all gross disease, patients received initial CAF chemotherapy, followed by randomization to either HD-CPB or intermediate doses of the same drugs (ID-CPB). Preliminary analysis, with a median 3-year follow-up, suggested a reduction in breast cancer relapses but an increase in treatment-related mortality in the HD-CPB arm compared with the ID-CPB arm. Overall survival rates were equivalent in the two arms (13, 14).

All patients in this study were prescribed to receive local–regional radiotherapy (RT) after chemotherapy. We herein report the impact of HD-CPB vs. ID-CPB on the ability to start and complete the planned course of local–regional RT. Other clinical variables that might be associated with omission of the planned RT were also considered. This is an important issue because local–regional RT dramatically reduces the risk of locoregional relapse, reduces the risk of systemic relapse, and improves overall survival (15–25). Therefore, modifications in systemic therapy that reduce one's ability to deliver RT might negatively affect patient outcome.

## METHODS AND MATERIALS

### Patients

The trial was open to accrual between January 1991 and May 1998; details reported elsewhere (14). Eligibility criteria included (1) age  $\geq 18$  years with operable non–locally advanced/inflammatory breast adenocarcinoma involving  $\geq 10$  axillary nodes, but without evidence of distant metastases (negative results on bilateral bone marrow biopsies and aspirates, bone scan, and chest, abdomen, pelvis, and brain CT scans); (2) resection of all gross disease by mastectomy (radical or modified radical) or lumpectomy with Level I to II axillary dissection; (3) negative surgical margins (lymphatic and

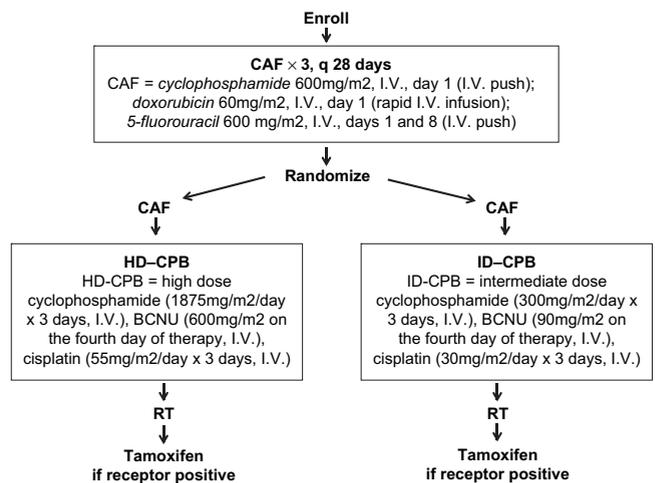


Fig. 1. Scheme of Cancer and Leukemia Group B Protocol 9082. RT = radiotherapy.

vascular involvement was permitted) (pathologic stage T1–3, N1–2; American Joint Committee on Cancer 1988 criteria); (4) Eastern Cooperative Oncology Group performance score of 0–1; (5) no previous chemotherapy or RT; and (6) not pregnant. Patients with prior or concomitant malignancies, other than curatively treated carcinoma *in situ* of the cervix or nonmelanotic skin cancer, were not eligible. Patients with serious comorbid diseases that would have negatively affected their tolerance for therapy were not eligible. Patients with synchronous bilateral breast cancers were eligible. Patients provided written, informed consent to participate in the study.

### Treatment

**Systemic therapy.** Protocol treatment included three cycles of adjuvant CAF chemotherapy followed by randomization to a fourth cycle of CAF plus HD-CPB or a fourth cycle of CAF plus ID-CPB (Fig. 1) (14). Patients were restaged approximately 6 weeks after completion of all chemotherapy. The protocol-prescribed RT was to be delivered in all patients provided there was no evidence of systemic disease at restaging. Patients with positive/unknown hormone receptor status were to receive tamoxifen for 5 years starting 7 weeks after the initiation of CPB. In many patients, tamoxifen was not started until after RT (Fig. 1).

**Radiotherapy.** Sites to be irradiated included the ipsilateral breast/chest wall and supraclavicular lymph nodes. Irradiation of the axilla was not recommended but was permitted at the discretion of the treating radiation oncologist. Treatment of the internal mammary nodes (IMN) was strongly recommended, though not required.

Three treatment techniques were given as options: (1) Technique A: tangent breast/chest wall fields with or without IMN. In some cases, partly wide tangent fields were used that included the superior but not the inferior IMN chain, to reduce incidental irradiation to the heart (26). To consider the possible effect of inclusion of IMN within the RT fields on outcome, patients were further subdivided by IMN dose  $< 30$  Gy (Technique A1) or  $\geq 30$  Gy (Technique A2). The 30-Gy threshold was chosen on the basis of human clinical studies suggesting that doses of  $\geq 25$  Gy can be associated with lung injury. (2) Technique B: anterior or anterior-oblique electron/photon IMN field with tangent photon breast/chest wall fields. (3) Technique C: *en face* chest wall and IMN electron fields (not appropriate for patients undergoing lumpectomy), with bolus as clinically indicated.

For all techniques, CT planning was recommended to assess IMN location and for dosimetry. Cobalt-60 and high-energy photons between 4 and 15 MV were used to treat the supraclavicular and axillary nodes, and the chest wall (and IMN) for patients receiving Techniques A and B. Electron energy was selected at the discretion of the treating physician to provide homogeneous coverage to the target volume. Wedges and bolus were used as necessary. A separate anterior medial oblique supraclavicular field (angled approximately 15° to the contralateral side; i.e., medial-anterior oblique) was used. This angulation was recommended to provide adequate coverage of the medially placed nodes without exiting into the spine. Field borders were as follows: inferior—inferior to the clavicular head and matched to the superior border of the breast/chest wall field; medial—medial to the sternocleidomastoid muscle; superior—at the level of the cricoid cartilage; and lateral—at the medial extent the axillary surgery, or at approximately the coracoid process or medial humeral head. Treatment of the full axilla, by extending the lateral border of this supraclavicular field into the axilla, and the use of posterior axillary boost were not recommended but were permitted.

All sites were to be treated to 50.4 Gy at 1.8 cGy per fraction. The prescription point for the supraclavicular field was 3 cm, or at the depth of the supraclavicular vessels as measured on CT imaging. An additional 10 Gy in 5 fractions with electrons was prescribed to the region of the mastectomy scar or tumor bed. This could be omitted at the physician's discretion for patients who had breast reconstruction.

#### *Submission of patient therapy data*

Patient registration and data collection were managed by the CALGB Statistical Center. Demographics and baseline clinicopathologic variables were collected before initiation of protocol treatment. The following data were collected at regular intervals during and after treatment: toxicity, treatment information (dosing, site of delivery, and reason for early termination/noncompliance) for chemotherapy and RT, and disease and survival status. These data were initially reviewed for accuracy and completeness at CALGB Data Operations and subsequently in an independent audit process. Radiotherapy data underwent central review by the Quality Assurance Review Center.

#### *Statistical considerations*

The relationship of demographic and baseline clinicopathologic factors to each of four different outcomes was assessed: (1) initiation, (2) interruption, (3) modification, and (4) completion of protocol-prescribed RT. Because the reason for the occurrence of each outcome was not recorded, each outcome was scored as a dichotomous event, that is, occurred or not, regardless of reason. Outcome 1 was measured for all patients randomized to the Treatment Study 9082, whereas Outcomes 2, 3, and 4 were measured only for those patients who began protocol RT.

Candidate explanatory variables used to model the relationship with Outcome 1 included chemotherapeutic treatment arm (HD/ID), age at enrollment (continuous), race (African American [AA]/non-AA), menopausal status (pre/post), tumor-related variables (estrogen receptor [ER] status [positive/negative]), tumor

Table 1. Patient demographics and baseline disease characteristics by treatment arm

Characteristic	Treatment arm			
	HD-CPB		ID-CPB	
Total randomized	394	(100)	391	(100)
Age at study entry (y)				
<40	115	(29)	114	(29)
40–49	170	(43)	189	(49)
50–59	100	(26)	80	(20)
60+	9	(2)	8	(2)
Race/ethnicity				
Caucasian	315	(80)	317	(81)
Hispanic	6	(2)	5	(1)
African American	28	(7)	22	(6)
Asian	10	(2)	7	(2)
Other	35	(9)	40	(10)
Menopausal status				
Premenopausal	268	(68)	263	(67)
Peri-/postmenopausal	126	(32)	127	(32)
Missing	0	(0)	1	(<1)
Tumor size (cm)				
≤2	103	(26)	96	(24)
>2 and ≤5	193	(49)	206	(53)
>5	90	(23)	75	(19)
Missing	8	(2)	14	(4)
No. of positive nodes				
10–12	162	(41)	160	(41)
13–15	82	(21)	92	(24)
16–20	83	(21)	79	(20)
≥21	67	(17)	60	(15)
Surgery type				
Mastectomy	310	(79)	301	(77)
Lumpectomy	81	(20)	87	(22)
Other*	3	(1)	1	(<1)
Missing	0	(0)	2	(<1)
Initiated RT				
No	69	(18)	31	(8)
Yes	325	(82)	360	(92)
If yes, RT technique				
A	200	(62)	226	(62)
B	83	(25)	85	(24)
C	26	(8)	32	(9)
Other/Unknown	16	(5)	17	(5)

Abbreviations: HD-CPB = high-dose cyclophosphamide, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), and cisplatin; ID-CPB = intermediate-dose CPB; RT = radiotherapy.

Values are number (percentage).

\* Includes biopsy alone, and no breast surgery (*i.e.* only axillary dissection), for patients presenting with axillary disease without a clear primary breast lesion.

however, a suggestion that RT technique as a main effect related to interruption ( $p = 0.064$ ). Technique C was more likely to result in RT interruption than each of the other techniques (OR [95% CI] of C:A1, A2, and B, respectively, were 2.02 [0.96–4.27], 2.31 [1.10–4.85], and 1.36 [0.65–2.80]).

Table 4 shows the percentage of patients whose RT was interrupted according to RT technique and surgery type. Among nonmastectomy patients, there was no difference among Techniques A1, A2, and B; however, among mastectomized patients, Technique C (26%) had a slightly higher incidence of interruption than Techniques A1, A2, or B (17%, 13%, and 20%, respectively).

### Modifications to protocol RT

One hundred forty-five (145, 21%) of the patients who initiated RT underwent modifications to the planned RT regimen. Incidence of modification on the HD arm (29%) was more than twice that of the ID arm (14%;  $p = 0.001$ , OR = 2.46, 95% CI = 1.68–3.61; Table 2). In multivariate analysis, treatment arm was the only significant predictor of modification. The most frequent reason for RT modification was RT-related toxicity for the ID arm (33%) and chemotherapy-related toxicity for the HD arm (39%) (Table 5).

### Completion of protocol RT

The noncompletion incidence on the ID arm was only 2%, compared with 9% on HD ( $p = 0.0001$ , unadjusted OR = 5.35; Table 2). In multivariate analyses, treatment arm ( $p = 0.0002$ ) and RT technique ( $p = 0.023$ ) significantly predicted RT noncompletion. The OR of HD:ID on noncompletion was 5.68 (95% CI = 2.29–14.1). Technique C was more likely to result in noncompletion than each of the other techniques (OR [95% CI] for C:A1, A2, and B, respectively, was 2.89 [0.98–8.55], 2.50 [0.89–7.04], and 6.62 [1.80–24.2]).

Table 6 shows the incidence of noncompletion according to RT technique and surgery type. Failure to complete RT was greatest for mastectomized patients irradiated with Technique C (14%) compared with any of the other subgroups defined by technique and surgery (ranging from 0 to 8%).

### Reported RT-associated toxicities

The precise reason for an interruption, modification, or cessation of RT was not always clear (Table 5). Data forms on RT-related toxicity were submitted for 681 patients (Table 7). The most frequently reported side effect was skin related (ID: 34% vs. HD: 24%). The HD vs. ID arms differed most in incidence of Grade ≥2 RT-associated events in the lung (7% vs. <1%), anemia (8% vs. <1%), and thrombocytopenia (9% vs. <1%). Other events were infrequent. Although these events were scored as RT-associated, they likely were also related to the prior chemotherapy.

## DISCUSSION

Initial data from CALGB 9082, with modest follow-up, suggests that HD-CPB does not provide an advantage with regard to overall survival compared with ID-CPB (13, 14). Interestingly, there seems to be a small improvement in breast cancer-specific survival in the high-dose arm that was offset by treatment-related mortality. High-dose chemotherapy can be toxic (12, 14, 27–30). With improvements in our ability to prevent and manage these morbidities, high dose may provide some therapeutic advantage. At present the majority of available data do not support the routine use of high-dose chemotherapy for patients with breast cancer (31–33).

The present analysis suggests that HD-CPB hinders the ability to deliver RT, compared with ID-CPB. This difference is not related to any pretreatment factors, and it persists in subgroups defined by race, age, and RT technique. This observation is noteworthy because RT plays an important role

Table 2. Incidence of RT initiation, interruption, modification, and early termination by treatment arm

Parameter	Treatment arm		<i>p</i> *	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	HD-CPB	ID			
Randomized, <i>n</i> (%)	394 (100)	391 (100)			
Began RT, <i>n</i> (% of randomized)	325 (82)	360 (92)	0.001	0.41 (0.26–0.64)	0.38 (0.23–0.61)
Began RT, <i>n</i> (%)	325 (100)	360 (100)			
RT interrupted	69 (21)	43 (12)	0.001	2.05 (1.34–3.14)	N/A
RT modified	94 (29)	51 (14)	0.001	2.46 (1.68–3.61)	N/A
RT not completed <sup>†</sup>	29 (9)	8 (2)	0.0001	5.35 (2.17–13.16)	5.68 (2.29–14.1)

*Abbreviations:* OR = odds ratio of HD:ID related to each endpoint; 95% CI = 95% confidence interval around the OR; N/A = treatment arm was the only significant variable, therefore the univariate OR is used. Other abbreviations as in Table 1.

Unadjusted OR is from univariate analysis; adjusted OR is from multivariate logistic regression controlling for other covariates.

\* *p* value from comparison of two proportions.

<sup>†</sup> Excludes 27 patients with unknown completion status.

in the care of patients with breast cancer. Postlumpectomy RT reduces the risk of in-breast recurrences by approximately 80% (34–36). Postmastectomy RT reduces the risk of local–regional recurrence by approximately 67% and improves overall survival by 5–12% (15–25, 37). Therefore, alterations in the chemotherapy regimen that hinder the ability to deliver radiation might negatively impact on disease-free and overall survival. However, in CALGB 9082 the relapse-free survival in the HD group was higher than in the ID group (14), suggesting that possible detrimental effects on disease control resulting from the limitations on the RT delivery were offset by the possible additional anticancer effects afforded by the HD therapy.

The relevance of the current data set can be questioned, given that high-dose chemotherapy and bone marrow rescue is not typically performed for patients with multi-node-positive breast cancer at present. Nevertheless, this approach may

have some utility in certain subsets of patients (*e.g.*, young patients), and the findings from the present project might be applicable if this therapy were to make a resurgence. Furthermore, there is continued interest in intensifying chemotherapy regimens for some subsets of patients, as evidenced by the use of dose-dense chemotherapy regimens (38), and the use of combined anthracycline/taxane regimens (39). Therefore, the potential impact of these more-intensive chemotherapy regimens on the ability to deliver subsequent postchemotherapy radiation may be relevant as well.

#### Radiation technique

It is not clear why Technique C was associated with a higher rate of treatment interruption and failure to complete treatment (Tables 4 and 6). The use of *en face* chest wall electrons is a well-accepted technique and was used in the Danish trials demonstrating an improved survival with postmastectomy RT (18, 40–41). Fewer patients were treated with Technique C than the other techniques; additionally, the technique was not used on lumpectomy patients. This made robust comparisons difficult. This finding may reflect physician practice

Table 3. Initiation of RT: Results from multivariate logistic regression (*n* = 774)

Effect	More:Less likely to begin RT	OR (95% CI)	<i>p</i>
Treatment arm	ID:HD	2.66 (1.65–4.27)	<0.0001
Age (y)	40:60	2.22 (1.27–3.92)	0.005
Race*	Non-AA:AA	2.99 (1.45–6.17)	0.003
Surgery	Nonmastectomy:mastectomy	2.10 (1.12–3.94)	0.02
Tumor ER status	Negative:positive	1.72 (1.06–2.78)	0.03
Race × age interaction			0.07
Age <50 y	Non-AA:AA	1.83 (0.76–4.41)	
Age ≥50 y	Non-AA:AA	9.43 (2.08–43.48)	

*Abbreviations:* AA = African American; ER = estrogen receptor. Other abbreviations as in Table 1.

\* Main effects of race and age tested in the absence of the interaction term.

Table 4. Incidence of RT interruption by RT technique and type of surgery

RT technique	Mastectomy		Nonmastectomy <sup>†</sup>	
	<i>n</i>	% with interruption	<i>n</i>	% with interruption
Total patients who began RT*	525	17	158	15
A: Tangents				
A1: IMN <30 Gy	145	17	40	13
A2: IMN ≥30 Gy	160	13	79	15
B: Separate IMN field	137	20	31	23
C: Chest wall electrons	58	26	0	—
Other/unknown	25	0	8	0

*Abbreviation:* IMN = internal mammary nodes. Other abbreviations as in Table 1.

\* Excludes patients with missing data on type of surgery.

<sup>†</sup> Lumpectomy, *n* = 155; axillary dissection, *n* = 3.

Table 5. Reasons for RT modification by treatment arm

Reason	Treatment arm		Total
	HD	ID	
RT modified	94 (100)	51 (100)	145 (100)
Reason for modification*			
Toxicity from RT	15 (16)	17 (33)	32 (22)
Toxicity from chemotherapy	37 (40)	3 (6)	40 (28)
Patient noncompliance	2 (2)	0	2 (1)
Scheduling difficulties/ mechanical problems	6 (6)	7 (14)	13 (9)
Complicating medical conditions	20 (21)	8 (16)	28 (19)
Other	14 (15)	16 (31)	30 (21)

Abbreviations as in Table 1.

Values are number (percentage).

\* Taken from data sheets submitted, usually not containing detailed information; thus the categorization may not be specific.

patterns regarding the use of different RT techniques and their tendency to alter an initiated course of RT. A review of RT techniques among participating institutions did not reveal any obvious systematic differences. Nevertheless, this observation may be due to the preferential use of Technique C in patients with a lot of chemotherapy-associated toxicity. The exact cause of an interruption or failure to complete therapy was not systematically recorded and often is multifactorial. Therefore, the degree to which, for example, increased skin toxicity may have been seen in the electron patients is not known.

Among patients treated with Technique A, there were no statistically significant differences in the rates of interruption or completion between those in whom the IMN dose was estimated to be <30 Gy vs. ≥30 Gy. Treatment of the IMN tends to increase irradiated lung volumes, suggesting that lung irradiation was not the major cause for treatment modifications. However, because IMN treatment was not assigned randomly, this may not be a valid conclusion. Furthermore, given interpatient anatomic variability, inclusion of the

Table 6. Incidence of noncompletion of RT by RT technique and type of surgery

RT technique	Mastectomy		Nonmastectomy	
	n	% terminated early	n	% terminated early
Total patients who began RT*	505	6	151	5
A: Tangents				
A1: IMN <30 Gy	140	5	36	8
A2: IMN ≥30 Gy	152	6	79	5
B: Separate IMN field	132	3	29	0
C: Chest wall electrons	56	14	0	—
Other/unknown	25	8	7	0

Abbreviations as in Tables 1 and 4.

\* Excludes patients with missing data on type of surgery and RT completion status.

Table 7. Incidence of radiation-associated toxicity rates by treatment arm\*

Toxicity and grade	Treatment arm	
	HD-CPB (n = 322)	ID-CPB (n = 359)
Skin		
Grade 2	72 (22)	98 (27)
Grade 3	8 (2)	22 (6)
Grade 4	0	2 (<1)
Lung		
Grade 2	8 (2)	1 (<1)
Grade 3	13 (4)	1 (<1)
Grade 4	2 (<1)	0
Leukopenia		
Grade 2	17 (5)	17 (5)
Grade 3	6 (2)	6 (2)
Grade 4	0	0
Anemia		
Grade 2	19 (6)	1 (<1)
Grade 3	7 (2)	0
Grade 4	1 (<1)	0
Thrombocytopenia		
Grade 2	15 (5)	1 (<1)
Grade 3	11 (3)	0
Grade 4	2 (<1)	1 (<1)
Upper gastrointestinal		
Grade 2	2 (1)	0
Grade 3	1 (<1)	0
Grade 4	0	0

Abbreviations as in Table 1.

Values are number (rate [%]).

\* Grade ≥2 only. Data available in 681 patients. Some patients with more than one toxicity scored. Events scored as “radiation-related,” but certainly may be related to chemotherapy. Other minor toxicities with <1% incidence are not shown (e.g., breast edema).

IMN within the tangent fields does not always translate into a larger volume of incidentally irradiated lung (42).

In this analysis, patients treated with mastectomy and lumpectomy were combined. This is reasonable given that the RT fields in the postlumpectomy and postmastectomy settings are essentially equivalent. One would not therefore expect the rates of, for example, treatment modification and interruption, to be related to the presence/absence of an intact breast. It is nevertheless possible that physicians use a different threshold for interruption/modification/suspension of RT in postlumpectomy vs. postmastectomy settings. Similarly, some of the observed results (HD vs. ID) may be due to the application of more conservative thresholds (e.g., more likely to use a treatment interruption) in patients that have received more aggressive chemotherapy (i.e., with a more troubling toxicity profile).

Postmastectomy and postlumpectomy RT are generally well tolerated. Acute RT-associated morbidity requiring treatment interruption or modification in the planned RT is unusual. Therefore the 12% rate of treatment interruption in the ID-CPB cohort might be higher than would be expected. It is possible that the chemotherapy regimen in the control arm of this study was more aggressive than conventional chemotherapy. The majority of modifications seem to have been

treatment related. However, treatment interruptions were liberally scored to include events such as machine breakdown and the development of systemic disease, suggesting that the reported rate may be artificially high.

Prior Phase I–II studies suggest that it is more difficult for patients to complete local–regional RT after high-dose chemotherapy than after conventional-dose chemotherapy. In the Phase I–II pilot study of the HD-CPB regimen (CALGB 8782), radiotherapy was interrupted or discontinued in 9 of 40 irradiated patients (22%) (43)—a rate similar to the 21% interruption rate observed in the HD-CPB arm of the present study. Several other reports of non-randomized patients receiving HD-chemotherapy along with RT do not note similar RT-compliance issues (44–46). However, inter-study differences make comparisons difficult.

#### *Influence of other clinical factors*

Radiotherapy was more likely to be initiated in patients who

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