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Clinical Investigation

The impact of chemotherapy on toxicity and cosmetic outcome in patients receiving whole breast irradiation: an analysis within a state-wide quality consortium

Joshua T. Dilworth, MD, PhD[1]; Kent A. Griffith, MS, MPH[2]; Lori J. Pierce, MD[3]; Reshma Jagsi, MD, DPhil[3]; Thomas J. Quinn, MD[1]; Eleanor M. Walker, MD[4]; Jeffrey D. Radawski, MD[5]; Michael M. Dominello, DO[6]; Greg S. Gustafson, MD[7]; Jean M. Moran, PhD[3]; James A. Hayman, MD[3]; Frank A. Vicini, MD[8,*]

Frank.Vicini2@usa.genesiscare.com, on behalf of the Michigan Radiation Oncology Quality Consortium

[1]Beaumont Health System, Royal Oak, Michigan

[2]University of Michigan School of Public Health, Ann Arbor, Michigan

[3] University of Michigan School of Medicine, Ann Arbor, Michigan

[4]Henry Ford Health System, Detroit, Michigan

[5]West Michigan Cancer Center, Kalamazoo, Michigan

[6]Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan

[7]Beaumont Health System, Troy, Michigan

[8]GenesisCare, Farmington Hills, Michigan

*Corresponding author: Frank A Vicini, M.D., F.A.C.R., F.A.S.T.R.O., F.A.B.S., Clinical Professor, GenesisCare U.S.A., 28595, Orchard Lake Road, Farmington Hills, MI, 48334

Abstract

Purpose: We investigated whether the use of chemotherapy prior to whole breast irradiation (WBI) using either conventional fractionation (CWBI) or hypofractionation (HWBI) is associated with increased toxicity or worse cosmetic outcome compared to WBI alone.

Methods and Materials: We identified 6,754 patients who received WBI alone (without a third field covering the superior axillary and supraclavicular nodal regions) with data prospectively collected in a state-wide consortium. We reported rates of four toxicity outcomes: physician-reported acute moist desquamation, patient-reported acute moderate/severe breast pain, a composite acute toxicity measure (including moist desquamation and either patient-reported or physician-reported moderate/significant breast pain), and physician-reported impaired cosmetic outcome at one year following WBI. Successive multivariable models were constructed to estimate the impact of chemotherapy on these outcomes.

Results: Rates of moist desquamation, patient-reported pain, composite acute toxicity, and impaired cosmetic outcome were 23%, 34%, 42%, and 10% for 2,859 patients receiving CWBI and 13%, 28%, 31%, and 11% for 3,895 patients receiving HWBI. Receipt of chemotherapy prior to CWBI was not associated with higher rates of patient-reported pain, composite acute toxicity, or impaired cosmetic outcome compared to CWBI without chemotherapy but was associated with more moist desquamation (OR=1.32 [1.07-1.63], p=0.01). Receipt of chemotherapy prior to HWBI was not associated with higher rates of any of the four toxicity outcomes compared to HWBI alone.

Conclusions: In this cohort, use of chemotherapy prior to WBI was generally well tolerated. CWBI with chemotherapy, but not to HWBI with chemotherapy, was associated with higher rates of moist desquamation. Rates of acute breast pain and impaired cosmetic outcome at one year were comparable in patients receiving chemotherapy prior to either CWBI or HWBI. These data support the use of HWBI following chemotherapy.

Key Words

breast, radiation, hypofractionation, chemotherapy, toxicity

Introduction

Whole breast irradiation (WBI) following breast-conserving surgery decreases the risk of recurrence and improves survival in patients with early stage breast cancer (1). Hypofractionated regimens (HWBI) involve larger radiation doses per fraction and fewer fractions, compared to conventionally fractionated treatment (CWBI). Shortening the treatment course minimizes the burden on patients, treatment facilities, and healthcare resources (2). Randomized clinical trials support the use of HWBI in select women with early-stage breast cancer (3-6). The Ontario Clinical Oncology Group (OCOG) trial allocated patients to receive either 50 Gy/25 fractions over five weeks or 42.5 Gy/16 fractions over three weeks and showed similar rates of local control, excellent/good cosmetic outcomes, and late skin and subcutaneous toxicity between the two arms at ten years (3). The UK START-B trial showed equivalent long-term cancer control in patients receiving either 50 Gy/25 fractions over five weeks or 40 Gy/15 fractions over three weeks and reported less breast shrinkage and edema and fewer telangiectasias in

patients receiving three-week treatment (4). An evidence-based guideline published by the American Society for Radiation Oncology (ASTRO) in 2011 supported appropriateness criteria for the use of HWBI based largely on these trials (7).

The early ASTRO consensus panel did not endorse universal adoption of HWBI, however, as certain patient subsets were underrepresented on prospective trials. For example, only 11% and 25% of patients treated on the OCOG and START trials, respectively, received chemotherapy, and radiation oncologists have been reluctant to offer HWBI to these patients (8,9). A recent National Cancer Database analysis showed that, despite an increase in HWBI utilization from 26% in 2012 to 67% in 2016, only 27% of those receiving chemotherapy also received HWBI (9).

An updated 2018 ASTRO guideline relaxed the restriction on the use of HWBI in patients receiving chemotherapy; however, the panel reported that only "moderate evidence" underpinned this recommendation, which lacked full panel consensus (10). The purpose of this study was to investigate whether the receipt of chemotherapy impacts acute toxicity or long-term cosmetic outcomes in patients who received CWBI or HWBI alone (without a third field covering the superior axillary and supraclavicular nodal regions).

Materials and Methods

Data Collection and Sample

We conducted an institutional-review-board-approved query of a state-wide quality consortium database (Figure 1)(11). Eligible patients had invasive, non-metastatic, unilateral breast cancer and received breast-conserving surgery, followed by WBI with boost and without regional nodal irradiation. We identified 6,754 patients

entered between 11/10/2011 and 9/30/2020 with available acute toxicity assessments. We analyzed three sample groups: 6,754 patients treated with either CWBI (n=2,859) or HWBI (3,895); 2,111 patients treated with HWBI with two-week post-radiation assessments; and 2,336 patients treated with CWBI or HWBI with one-year breast cosmetic outcome assessments.

Measures

Acute toxicity included moist desquamation or any patient- or physician-reported moderate/severe breast pain. Patient-reported breast pain was assessed using an approved modification of the Brief Pain Inventory (12) and categorized as moderate/severe if any score was ≥4 on a 10-point scale. Physician-reported breast pain was assessed accordingly to the Common Terminology Criteria for Adverse Events v4.0 and considered moderate/severe if ≥grade 2. Acute toxicity was measured within the time frame spanning seven days prior to the completion of WBI and 42 days after the completion of WBI. To ensure end-of-treatment toxicity was captured, approximately 98% of acute toxicity assessments were made within the time frame spanning seven days prior to the completion of WBI and seven days following WBI. Acute toxicity measurements also comprised those assessments made at two weeks following the completion of radiation therapy for 54.2% (2,111/3,895) of patients who received HWBI. Composite significant acute toxicity was defined as any moist desquamation and patient- or physician-reported moderate/severe breast pain. Rates of impaired cosmetic outcome (“fair” or “poor” per the Harvard scale [13]) at one year were based on physician assessments made within 300 days and 425 days following WBI.

Analyzed sample characteristics included age, BMI, breast volume, separation along the central axis, race, co-morbidities that could impact radiation related breast toxicity or cosmetic outcome (hypertension, diabetes, scleroderma, rheumatoid arthritis, systemic lupus erythematosus, connective tissue disorder and peripheral vascular disease), smoking status, treatment position, use of intensity modulated radiation therapy (IMRT), the maximum dose to 50% of the breast volume, ER/PR/HER-2 negative disease, treatment at an academic facility, receipt of chemotherapy, receipt of neo-adjuvant chemotherapy, receipt of adjuvant chemotherapy, receipt of an anthracycline, and receipt of a taxane. IMRT was defined as volumetric modulated arc therapy, tomotherapy, or static tangent plans with at least one unique gantry angle with ≥5 segments (including the open field).

Analytic Approach

Models were constructed to explain the relationship between the receipt of chemotherapy and the development of moist desquamation, patient-reported breast pain, composite significant acute toxicity, and impaired cosmetic outcome and were constructed separately for patients receiving either CWBI or HWBI. Covariates for the multivariable models were chosen from past modeling experience (14). Successive models were constructed, first adding chemotherapy use, then chemotherapy timing, and finally chemotherapy type. Given our large sample size, estimating the magnitudes of association for the number of covariates included in the models was not problematic; covariate reduction was not necessary, and all covariates were retained to create fully adjusted models. Rates of toxicities for patients who received both neoadjuvant and adjuvant chemotherapy (2% for CWBI and 1.2% for HWBI) were listed in both

chemotherapy groups. To avoid missing possible peak reactions in patients who received HWBI, we conducted an additional sensitivity analysis by limiting the sample size to those patients who had 2-week assessments (defined as those made between seven days after the completion of HWBI and 21 days after the completion of HWBI). This included 2,111 of the 3,895 patients who received HWBI. Similar regression models were run for this limited population to see if associations differed in maximal toxicity for this patient subset during this 2-week period. Strengths of associations, given as an OR [95% CI], were estimated between treatment related factors and clinical outcomes and generated using generalized linear modeling with logistic regression and a series of the binary dependent variables. The SAS v9.4 (Cary, NC, USA) was used to conduct all statistical analyses. P-values below 0.05 were considered significant.

Results

Table 1 lists the characteristics of the study sample of 6,754 patients, which included 2,859 who received CWBI and 3,895 who received HWBI. The most common CWBI doses were 45-46 Gy/23-25 fractions and 50-50.4 Gy/25-28 fractions with boost doses of 10-14 Gy/5-6 fractions and 16 Gy/8 fractions. The most common HWBI doses were 42.6 Gy/16 fractions and 40 Gy/15 fractions with boost doses of 10-12 Gy/4-6 fractions. Chemotherapy was administered in 45% of patients receiving CWBI (34% adjuvant, 9.7% neoadjuvant) and in 25% of patients receiving HWBI (21% adjuvant, 5.2% neoadjuvant). We observed increasing use of HWBI over the period of study, with 19.4% (67/345), 21.2% (141/665), 29.4% (240/815), 46.1% (456/990), 58.8% (623/1060), 66.9% (601/898), 78.4% (519/662), 93.6% (771/824), and 96.4% (477/495) receiving HWBI in the years 2011/2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019,

and 2020, respectively. Of those patients receiving chemotherapy, 14.9% (17/114), 10.7% (24/225), 17.8% (57/320), 27.9% (98/351), 35.4% (120/339), 44.7% (127/284), 65.7% (140/213), 91.1% (225/247), and 95.9% (165/172) received HWBI in the years 2011/2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, and 2020, respectively.

The median [IQR] time intervals between adjuvant chemotherapy and WBI were similar for CWBI (data available for 67% of patients) and HWBI (data available for 31% of patients): 32 [25-42] days and 32 [24-40] days, respectively. The median [IQR] time intervals between neoadjuvant chemotherapy and WBI were similar for CWBI (data available for 63% of patients) and HWBI (data available for 19% of patients): 75 [63-97] days and 87 [67-102] days, respectively. Data regarding the time interval between surgery and WBI were available for 99% of patients. For patients not receiving chemotherapy, median [IQR] time intervals between surgery and CWBI or HWBI were similar: 47 [39-57] days and 48 [39-59] days. For patients receiving neoadjuvant chemotherapy, median [IQR] time intervals between surgery and CWBI or HWBI were similar: 45 [36-62] days and 43 [35-63]. For patients receiving adjuvant chemotherapy, median [IQR] time intervals between surgery and CWBI or HWBI were similar: 166 [133-194] days and 155 [127-188] days.

The rates of moist desquamation, patient-reported breast pain, and composite significant acute toxicity (which was defined as any moist desquamation and patient- or physician-reported moderate/severe breast pain) were 23%, 34%, 42% for patients receiving CWBI; 12.8%, 28%, 31% for patients receiving HWBI; and 15%, 28%, and 33% for patients who received HWBI and had two-week follow-up assessments (Figure

1). The rates of impaired one-year cosmetic outcome were 9.9% and 10.7% for patients who received CWBI and HWBI, respectively (Figure 1).

Figure 2 presents the multivariable models of the clinical outcomes among patients receiving CWBI. Factors associated with higher rates of moist desquamation included increasing BMI (p=0.01), increasing breast volume (p<0.0001), non-IMRT treatment plans (p=0.002), increasing D50_Breast (p=0.04), and the receipt of chemotherapy (p=0.01), notably if chemotherapy was adjuvant (p=0.02) or if a taxane was administered (p=0.04). The receipt of an anthracycline or neoadjuvant chemotherapy did not predict moist desquamation. Factors associated with more patient-reported breast pain included younger age (p<0.0001), increasing breast volume (p=0.001), race (p<0.0001), smoking (p=0.02), non-IMRT treatment plans (p=0.02). The receipt of chemotherapy did not predict patient-reported breast pain, regardless of the sequencing or type of chemotherapy. Factors associated with more composite significant acute toxicity included younger age (p<0.0001), increasing breast volume (p<0.0001), race (p=0.003), smoking (p=0.009), non-IMRT treatment plans (p=0.003), and increasing D50_Breast (p=0.04). The receipt of chemotherapy did not predict composite significant acute toxicity, regardless of the sequencing or type of chemotherapy. Factors associated with impaired one-year cosmetic outcome included age (p=0.01), smoking (p<0.001), and non-IMRT treatment plans (p=0.03). While neither the receipt of chemotherapy overall, the sequencing of chemotherapy, nor the receipt of a taxane predicted higher rates of impaired cosmetic outcomes, the receipt of an anthracycline was associated with fewer impaired cosmetic outcomes (p=0.02).

Figure 3 presents the multivariable models of the clinical outcomes among patients receiving HWBI. Factors associated with moist desquamation included age ($p=0.01$), increasing BMI ($p<0.0001$), increasing breast volume ($p<0.0001$), race ($p=0.03$), smoking ($p<0.0001$), and treatment at a non-academic facility ($p=0.001$). The receipt of chemotherapy did not predict moist desquamation, regardless of the sequencing or type of chemotherapy. Factors associated with patient-reported breast pain included age ($p<0.0001$), race ($p<0.001$), and smoking ($p<0.001$). The receipt of chemotherapy did not predict patient-reported breast pain, regardless of the sequencing or type of chemotherapy. Factors associated with more composite significant acute toxicity included younger age ($p<0.0001$), increasing BMI ($p=0.001$), increasing breast volume ($p<0.001$), race ($p=0.0001$), smoking ($p<0.001$), non-IMRT treatment plans ($p=0.01$), and treatment at a non-academic facility ($p=0.006$). While neither the receipt of chemotherapy overall, the receipt of neoadjuvant chemotherapy, nor the type of chemotherapy predicted for more composite acute toxicity, the receipt of adjuvant chemotherapy ($p=0.02$) was associated with less composite significant acute toxicity. The receipt of chemotherapy did not predict impaired cosmetic outcome, regardless of the sequencing or type of chemotherapy.

To avoid under-estimating toxicity in patients who received HWBI, we performed a sensitivity analysis of acute toxicity endpoints for patients who received HWBI and had a two-week post-radiation assessment. The receipt of chemotherapy did not predict moist desquamation or composite significant acute toxicity, regardless of the sequencing or type of chemotherapy. While receipt of chemotherapy overall did not predict patient-reported breast pain, regardless of the sequencing of chemotherapy or if

the patient received a taxane, receipt of an anthracycline was associated with more patient-reported breast pain (p=0.03).

Discussion

A large percentage of patients who pursue breast-conserving therapy also receive chemotherapy, which is typically administered prior to whole breast irradiation. Potential sensitization of normal tissues, including the breast, underscored the need to understand the impact that chemotherapy may have on radiation-related toxicities and cosmetic outcome. The utilization of HWBI in the United States has increased over the last decade, yet the majority of patients who receive chemotherapy are treated with CWBI (8,9). The adoption of HWBI within our consortium has also been slower for patients who received chemotherapy. The initial hesitance to offer HWBI to these patients may reflect concern that hypofractionation might worsen late tissue effects (4,15). We thus sought to determine whether the receipt of chemotherapy impacts WBI-related toxicity, independent of fraction size.

Our study shows higher crude rates of moist desquamation and acute moderate/severe patient-reported breast pain in the CWBI group, compared to the HWBI group (23% versus 13% and 34% versus 28%, respectively), even when including only HWBI patients with a two-week post-radiation assessment (15% and 28%, respectively) at which time detection of acute toxicities was maximized. While we did not perform a direct, adjusted comparison between CWBI and HWBI, results from a randomized clinical trial comparing patients receiving CWBI plus boost versus HWBI

plus boost also showed fewer acute side effects, including fatigue, dermatitis, and breast pain in patients receiving HWBI (5). Rates of grade 2 dermatitis (moderate-brisk erythema, moderate edema, or patchy moist desquamation) were 36% in the HWBI arm and 69% in the CWBI arm. Rates of moist desquamation vary in the literature. De Langhe *et al.* reported an overall incidence of 15% for moist desquamation and identified CWBI (compared to HWBI), large BMI, large bra size, and smoking as predictors (17). Parekh *et al.* similarly showed higher rates of moist desquamation with CWBI (compared to HWBI) and higher BMI (18). This latter study also showed higher rates of moist desquamation in patients receiving chemotherapy, yet two other series showed no correlation between chemotherapy and moist desquamation (19,20). In our study, the receipt of any chemotherapy was associated with a small absolute increase in the rate of moist desquamation for patients receiving CWBI (compared to patients receiving CWBI without chemotherapy) but no difference for patients receiving HBWI, regardless of the sequencing or type of chemotherapy, even when only considering those patients who had two-week post-radiation assessments.

Our study identified increasing BMI and breast volume as predictors of moist desquamation, which underscores the importance of optimizing dose homogeneity during radiation treatment planning. A randomized clinical trial compared toxicity in patients treated with either standard wedge compensated tangent plans or IMRT (21,22). IMRT plans had significantly lower maximum point doses and lower volumes of the breast receiving 105%, 107%, 110%, and 115% of the prescription dose. The improved dose homogeneity conferred by multileaf collimator segmentation in IMRT plans translated into a decrease in moist desquamation, which was 31%, compared to

48% in those receiving non-segmented plans. Our study also showed that the use of IMRT was associated with less acute toxicity. Approximately 49% of CWBI plans and 39% of HWBI plans were coded as IMRT, yet for our analysis, only volumetric modulated arc therapy, tomotherapy, or static tangent plans with at least one unique gantry angle with ≥5 segments (including the open field) were designated as IMRT. The vast majority (94% of CWBI cases and 95% of HWBI) of treatment planning involved some degree of segmentation; however, if acceptable homogeneity was achieved with a higher number of gantry angles or a higher cumulative number of segmented fields that were distributed more evenly among the gantry angles, the plan was not classified as IMRT.

Rates of patient-reported moderate/severe breast pain were 34% for patients receiving CWBI and 28% for patients receiving HWBI in our study. This is consistent with an earlier study by Jagsi *et al.*, which reported 41% and 24% of patients receiving CWBI and HWBI, respectively, self-reporting moderate or severe breast pain near the end of treatment (16). The randomized clinical trial from the MD Anderson Cancer Center also showed lower rates of physician-rated ≥grade 1 (“mild”) breast pain in the HWBI arm (55%), compared to the CWBI arm (74%) (5). In addition to fractionation, race was associated with patient-reported breast pain in our cohort, with patients self-reporting as Black noted as having increased rates of patient-reported breast pain, regardless of fractionation. This finding is consistent with other reports that describe more radiation-related toxicity, including breast pain (14,23) and moist desquamation (24) among Black patients and highlights the broader need to identify and reconcile disparities among different populations in cancer treatment-related outcomes (24).

Chemotherapy did not impact overall rates of patient-reported breast pain for all patients receiving chemotherapy, regardless of fractionation. Analyses investigating potential interactions between specific interactions between specific chemotherapeutic agents and radiation-related toxicity are limited by smaller numbers of patients in these subsets.

Compared to published prospective trials, the rates of impaired cosmetic outcomes in patients treated within our consortium were low, approximately 10% for both CWBI and HWBI. Approximately 30% of patients on the MD Anderson and OCOG randomized studies reported impaired cosmetic outcome at three years and 10 years, respectively (3,5), and 18% of patients treated with IMRT in the randomized trial published by Pignol *et al*. had impaired cosmetic outcome at 10 years (21,22). IMRT was associated with improved cosmetic outcomes in patients receiving CWBI in our study. Receipt of chemotherapy did not impact cosmetic outcome, regardless of type and regardless of fractionation schedule. Assigning a cosmetic outcome score can be subjective, and implementing more objective measures of the shape, color, and size of the treated breast, relative to baseline and to the contralateral breast are warranted to mitigate inter-observer variability. For example, quantitative measurements from 2- and 3-dimensional breast photographs have been utilized to help assign objective cosmetic outcome scores (26,27).

The American Society of Radiation Oncology has shifted toward promoting HWBI more strongly over the last decade, from its initial consensus statement in 2011 (7), to its participation in the Choosing Wisely campaign in 2014 (28), to its updated consensus statement in 2018 (10). With respect to those patients receiving chemotherapy, our

study offers evidence to bolster the panel's statement that the decision to offer HWBI should be independent of chemotherapy received prior to radiation.

There are strengths of this analysis. First, our study includes a large cohort of patients treated across multiple centers and with prospectively collected data, which makes our data generalizable. Second, we chose clinical endpoints that reflect significant toxicity that often correlates with the need for medical intervention and predicts late treatment-related sequelae. Moist desquamation in the acute setting, for example, predicts chronic breast pain, chronic breast induration, telangiectasia, and poor cosmetic outcome (21,29). Further, moist desquamation is a relatively objective finding and clinically relevant as it typically requires medical intervention. Third, clinical assessments were made within 7 days prior to the completion of WBI and 42 days following the completion of WBI, and a majority of patients receiving HWBI had two-week post-radiation assessments; this helps avoid missing the peak of skin and breast toxicity. Weaknesses of our study include the inability to account for all confounding variables, including the potential bias that some physicians may tend to avoid HWBI in patients receiving chemotherapy. Although we applied rigorous multivariable models to explain associations between patient- and treatment-related factors and clinical outcomes, association does not imply causation. For example, usage and sequencing of anti-estrogen therapy, HER-2-directed therapies, and other targeted immunotherapies with radiation therapy may impact acute toxicity and long-term cosmetic outcomes, especially when administered concurrently with radiation therapy. For example, while systemic chemotherapy and WBI are routinely given sequentially, anti-HER-2 directed therapies may be given concurrently with WBI. Furthermore,

patients receiving longer courses of breast irradiation may also receive more doses of concurrent anti-HER-2-directed agents. Additional investigation into potential sensitization of these agents to CWBI and HWBI is warranted. the number of doses of various anti-HER-2-directed agents may be higher Further, longer follow-up is needed to assess cosmetic outcomes, since global changes in the breast appearance may occur beyond one year following the completion of whole breast irradiation.

Conclusions

In this large, multi-center cohort, rates of composite acute toxicity and impaired cosmetic outcome at 1 year were not higher in patients receiving chemotherapy prior to either CWBI or HWBI, compared to those not receiving chemotherapy. There was a very small absolute increase in the rate of moist desquamation in patients receiving CWBI and chemotherapy. There was a detectable increase in patient-reported moderate/severe breast pain in patients receiving HWBI and an anthracycline, but this observation was only true for the small sub-set of patients who had valid 2-week acute toxicity acute toxicity assessments. These data support the use of HWBI in patients following chemotherapy.

Data sharing statement

Data are owned by the local collaborating sites, and therefore the Michigan Radiation Oncology Quality Consortium is not permitted to share the data used for this study.

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Conflicts of Interest

Lori J. Pierce is a co-founder of PFS Genomics; Jean M. Moran has received a grant from Varian Medical Systems

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Table 1. Baseline patient characteristics for entire cohort analyzed and stratified by radiation fractionation

Characteristic	All Patients (N = 6754)	CWBI (N=2859)	HWBI (N=3895)	P-value†
Age at Diagnosis (years)	61 (10.6) [20-93.9]	62.5 (10.2) [26.6-93.9]	59.1 (10.8) [20-90.3]	<0.0001
Race				0.066
White	5268 (78%)	3081 (79.1%)	2187 (76.5%)	
Black	1142 (16.9%)	619 (15.9%)	523 (18.3%)	
Asian	121 (1.8%)	69 (1.8%)	52 (1.8%)	
Other	223 (3.3%)	126 (3.2%)	97 (3.4%)	
BMI	30.5 (7.1) [15.3-68.2]	31.3 (7.7) [15.5-68.2]	29.9 (6.6) [15.3-59.8]	<0.0001

Smoking Status				0.816
Never Smoker	3854 (57%)	1625 (56.8%)	2229 (57.2%)	
Former Smoker	2121 (31.4%)	896 (31.3%)	1225 (31.5%)	
Current Smoker	779 (11.5%)	338 (11.8%)	441 (11.3%)	
Laterality				0.005
Left	3387 (50.2%)	1491 (52.2%)	1896 (48.7%)	
Right	3367 (49.9%)	1368 (47.9%)	1999 (51.3%)	
Group Stage				<0.0001
I	4938 (73.1%)	1974 (69.1%)	2964 (76.1%)	
II	1788 (26.5%)	866 (30.3%)	922 (23.7%)	
III	28 (0.4%)	19 (0.7%)	9 (0.2%)	
T-Stage				0.002
0	77 (1.1%)	37 (1.3%)	40 (1.0%)	
1	5185 (76.8%)	2128 (74.4%)	3057 (78.5%)	
2	1422 (21.1%)	654 (22.9%)	768 (19.7%)	
3	49 (0.7%)	28 (1.0%)	21 (0.5%)	
4	10 (0.1%)	5 (0.2%)	5 (0.1%)	
X/Missing	11 (0.2%)	7 (0.2%)	4 (0.1%)	
ER Status				<0.0001
Negative	1175 (17.4%)	609 (21.3%)	566 (14.5%)	
Positive	5568 (82.4%)	2245 (78.5%)	3323 (85.3%)	
Missing/Unknown	11 (0.2%)	5 (0.2%)	6 (0.2%)	
PR Status				<0.0001
Negative	1693 (25.1%)	818 (28.6%)	875 (22.5%)	
Positive	5038 (74.6%)	2031 (71%)	3007 (77.2%)	
Missing/Unknown	22 (0.3%)	10 (0.3%)	13 (0.3%)	
HER2 Status				<0.0001
Negative	5762 (85.3%)	2363 (82.7%)	3399 (87.3%)	
Positive	858 (12.7%)	440 (15.4%)	418 (10.7%)	
Missing/Unknown	134 (2%)	56 (2%)	78 (2%)	
Triple Negative				<0.0001
No	5919 (87.6%)	2421 (84.7%)	3498 (89.8%)	
Yes	835 (12.4%)	438 (15.3%)	397 (10.2%)	
Surgical Margin Status				0.771
Close	877 (13%)	360 (12.6%)	517 (13.3%)	
Negative	5605 (83%)	2370 (82.9%)	3235 (83.1%)	
Positive	210 (3.1%)	90 (3.2%)	120 (3.1%)	
Unknown	62 (0.9%)	39 (1.4%)	23 (0.6%)	
Chemotherapy Status				<0.0001
No	4489 (66.5%)	1567 (54.8%)	2922 (75%)	
Yes	2265 (33.5%)	1292 (45.2%)	973 (25%)	

†P-value from the 2 sample *t* test for continuous covariates and from the chi-square test statistic for categorical covariates comparing HWBI to CWBI. Missing/unknown categories were ignored for comparison when present.

Table 2: Sample Distribution stratified by fractionation and receipt of chemotherapy:

Characteristic†	HWBI Without Chemotherapy (N = 2,922)	HWBI With Chemotherapy (N=973)	CWBI Without Chemotherapy (N = 1,567)	CWBI With Chemotherapy (N = 1,292)
Age at Diagnosis (years)	63.07 (10.06) [29.70 - 93.70]	60.67 (10.28) [26.60 - 93.90]	60.27 (10.71) [30.80 - 90.30]	57.64 (10.68) [20.00 - 84.90]
Race				
White	2363 (80.9%)	718 (73.8%)	1263 (80.6%)	924 (71.5%)
Black	421 (14.4%)	198 (20.4%)	227 (14.5%)	296 (22.9%)
Asian	45 (1.5%)	24 (2.5%)	25 (1.6%)	27 (2.1%)
Other	93 (3.2%)	33 (3.4%)	52 (3.3%)	45 (3.5%)
BMI	30.0 (6.7) [15.3 - 59.8]	29.5 (6.2) [16.6 - 54.1]	31.7 (7.9) [15.5 - 68.2]	30.8 (7.4) [16.6 - 64.7]
Smoking Status				
Never Smoker	1666 (57.0%)	563 (57.9%)	917 (58.5%)	708 (54.8%)
Former Smoker	924 (31.6%)	301 (30.9%)	463 (29.6%)	433 (33.5%)
Current Smoker	332 (11.4%)	109 (11.2%)	187 (11.9%)	151 (11.7%)
Laterality				
Left	1409 (48.2%)	487 (50.1%)	808 (51.6%)	683 (52.9%)
Right	1513 (51.8%)	486 (49.9%)	759 (48.4%)	609 (47.1%)
Stage				
I	2333 (79.8%)	631 (64.9%)	1258 (80.3%)	716 (55.4%)
II	583 (20.0%)	339 (34.8%)	305 (19.5%)	561 (43.4%)
III	6 (0.2%)	3 (0.3%)	4 (0.3%)	15 (1.2%)
T-Stage				
0	3 (0.1%)	37 (3.8%)	4 (0.3%)	33 (2.6%)
1	2425 (83.0%)	632 (65.0%)	1319 (84.2%)	809 (62.6%)
2	480 (16.4%)	288 (29.6%)	233 (14.9%)	421 (32.6%)
3	5 (0.2%)	16 (1.6%)	2 (0.1%)	26 (2.0%)
4	5 (0.2%)	0	2 (0.1%)	3 (0.2%)
X/Missing	4 (0.1%)	0	7 (0.4%)	0
ER Status				
Negative	155 (5.3%)	411 (42.2%)	88 (5.6%)	521 (40.3%)
Positive	2762 (94.5%)	561 (57.7%)	1474 (94.1%)	771 (59.7%)
Missing/Unknown	5 (0.2%)	1 (0.1%)	5 (0.3%)	0
PR Status				

Negative	378 (12.9%)	497 (51.1%)	162 (10.3%)	656 (50.8%)
Positive	2534 (86.7%)	473 (48.6%)	1397 (89.2%)	634 (49.1%)
Missing/Unknown	10 (0.3%)	3 (0.3%)	8 (0.5%)	2 (0.2%)
HER2 Status				
Negative	2749 (94.1%)	650 (66.8%)	1461 (93.2%)	902 (69.8%)
Positive	100 (3.4%)	318 (32.7%)	59 (3.8%)	381 (29.5%)
Missing/Unknown	73 (2.5%)	5 (0.5%)	47 (3.0%)	9 (0.7%)
Triple Negative				
No	2806 (96.0%)	692 (71.1%)	1498 (95.6%)	923 (71.4%)
Yes	116 (4.0%)	281 (28.9%)	69 (4.4%)	369 (28.6%)
Surgical Margin Status				
Close	400 (13.7%)	117 (12.0%)	201 (12.8%)	159 (12.3%)
Negative	2410 (82.5%)	825 (84.8%)	1297 (82.8%)	1073 (83.1%)
Positive	95 (3.3%)	25 (2.6%)	51 (3.3%)	39 (3.0%)
Unknown	17 (0.6%)	6 (0.6%)	18 (1.1%)	21 (1.6%)
Chemotherapy type and timing				
Adjuvant Chemotherapy				
Yes	0	803 (82.5%)		1063 (82.3%)
No	2922 (100%)	170 (17.5%)	1567 (100%)	229 (17.7%)
Timing‡	N/A	32 [24 – 40]		32 [25 – 42]
Neoadjuvant Chemotherapy				
Yes	0	201 (20.7%)	0	278 (21.5%)
No	2922 (100%)	772 (79.3%)	1567 (100%)	1014 (78.5%)
Timing	N/A	87 [67 – 102]		75 [63 – 97]

†Statistics are N (%) or Mean (SD) [Minimum – Maximum] unless otherwise specified

‡Days from end of chemotherapy to start of radiotherapy for cases with dates reported. Reported as Median [25th, 75th percentiles].

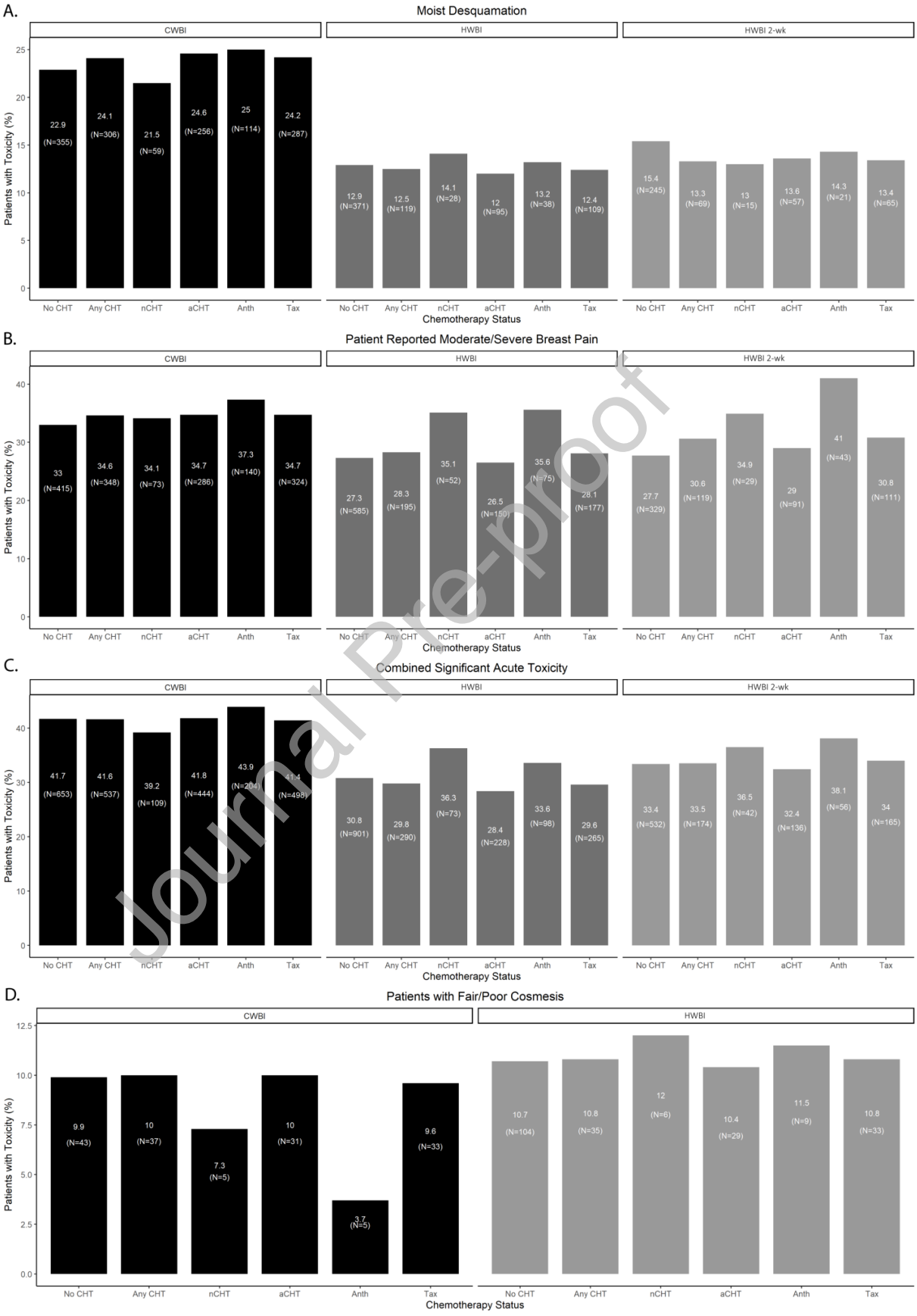

Figure 1. Rates of moist desquamation, patient-reported moderate/severe breast pain, composite acute toxicity, and impaired (“fair” or “poor”) cosmetic outcome, stratified by radiation fractionation and type/sequencing of chemotherapy.

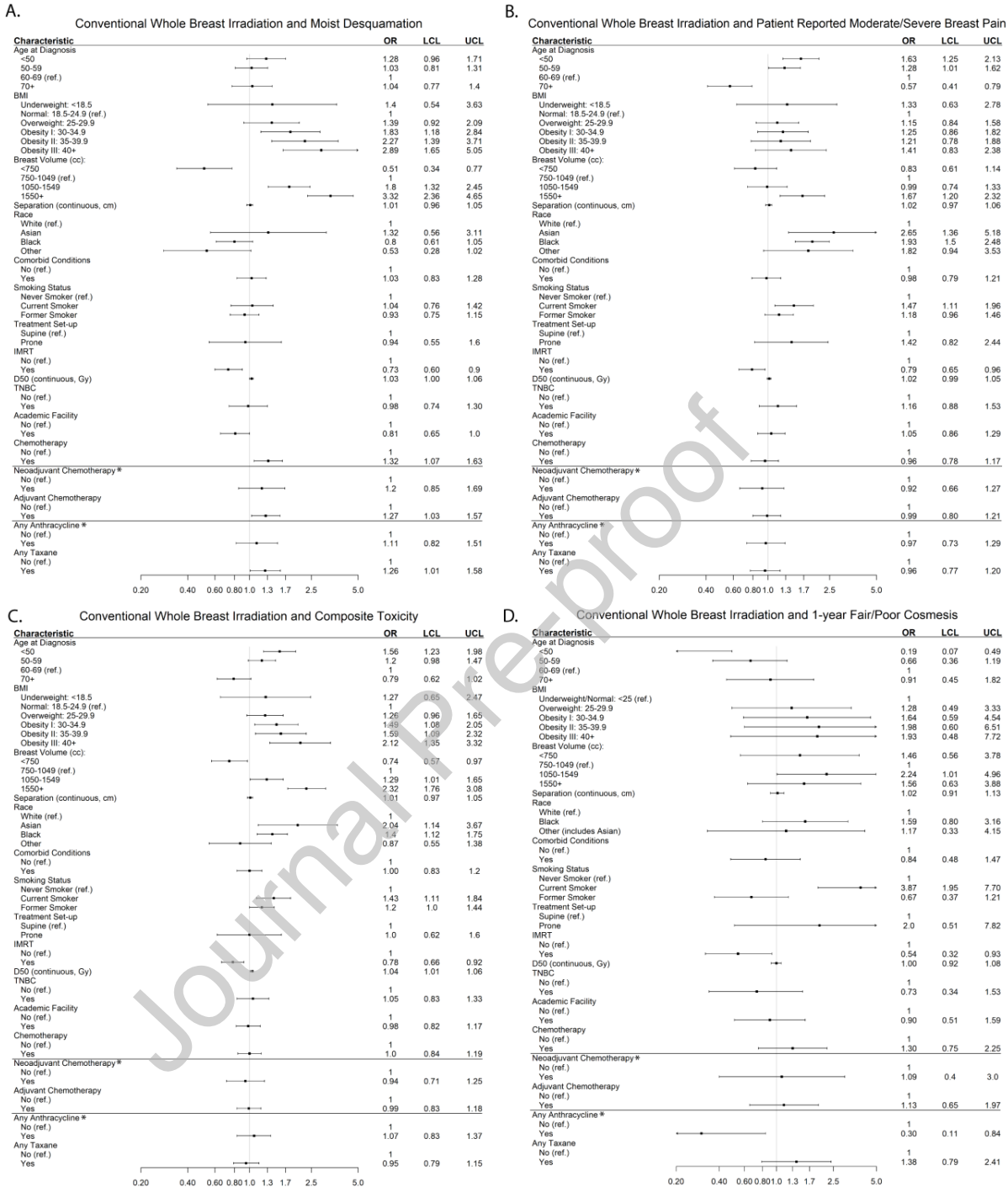

Figure 2. Forest plot representing variables correlated with toxicity endpoints in patients receiving CWBI. Successive multivariable models were constructed, first adding

chemotherapy use, then chemotherapy timing (neoadjuvant and adjuvant), and finally chemotherapy type (any anthracycline or any taxane administered). The associations estimated for the other covariates were similar between these successive models and reported here for only the models including chemotherapy use (yes/no).

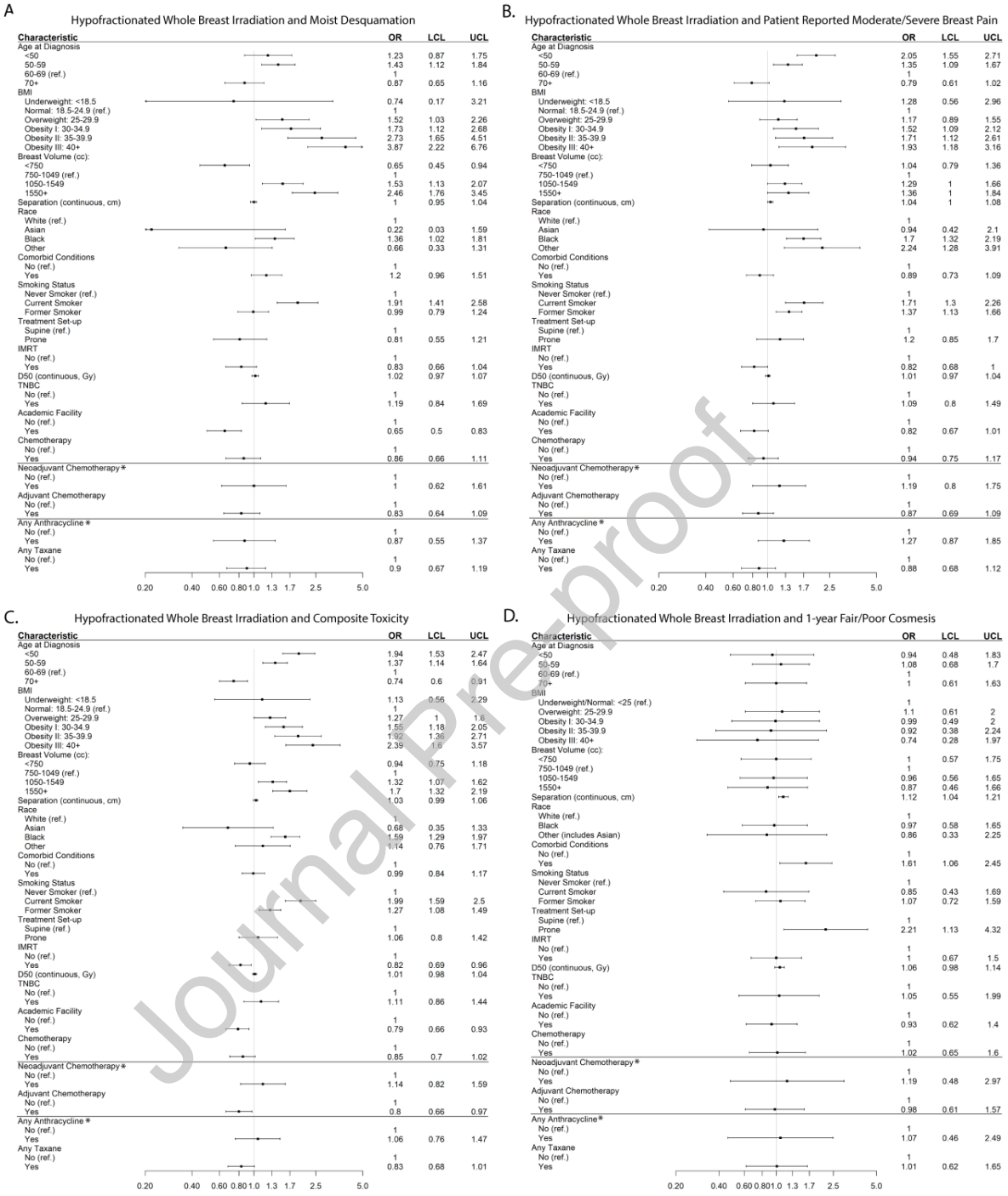

Figure 3. Forest plot representing variables correlated with toxicity endpoints in patients receiving HWBI. Successive multivariable models were constructed, first adding chemotherapy use, then chemotherapy timing (neoadjuvant and adjuvant), and finally

chemotherapy type (any anthracycline or any taxane administered). The associations estimated for the other covariates were similar between these successive models and reported here for only the models including chemotherapy use (yes/no).