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Original research article

Acute toxicity outcomes and dosimetric implications from incidental irradiation of adjacent tissues in tangent field hypofractionated breast radiotherapy

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ABSTRACT

Purpose: Adjacent tissues-in-beam (TIB) may receive substantial incidental doses within standard tangent fields during hypofractioned whole breast irradiation (HF-WBI). To characterize the impact of dose to TIB, we analyzed dosimetric parameters of TIB and associated acute toxicity.
Materials and Methods: Plans prescribed to 40.5 Gy/15 fractions from 4/2016-1/2018 were evaluated. Structures of interest were contoured: (1) TIB: all tissues encompassed by plan 30% isodose lines, (2) breast, (3) non-breast TIB (nTIB): TIB minus contoured breast. Volumes of TIB, breast, and nTIB receiving 100%–107% of prescription dose (V100-V107) were calculated. Twelve patient- and physician-reported acute toxicities were prospectively collected weekly. Correlations between volumetric and dosimetric parameters were assessed. Uni- and multivariable logistic regressions evaluated toxicity grade changes as a function of TIB, breast, and nTIB V100-V107 (in cm^3).
Results: We evaluated 137 plans. Breast volume was positively correlated with nTIB and nTIB V100 (rho = 0.52, rho = 0.30, respectively, both $p < 0.001$). V107 > 2 cm^3 were noted in 14% of breast and 21% of nTIB volumes. On multivariable analyses, increasing breast and nTIB V100 significantly raised odds of grade 2+ dermatitis and burning/twinging pain, respectively; increasing nTIB V105 elevated odds of hyperpigmentation and burning pain; and increasing nTIB V107 raised odds of burning pain. Threshold volumes for >6-fold odds of developing burning pain were TIB V105 > 100 cm^3 and V107 > 5 cm^3.
Conclusions: For HF-WBI, doses to nTIB over the prescription predicted acute toxicities independent of breast doses. These data support inclusion of TIB as a region of interest in treatment planning and protocol design

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1. Introduction

Hypofractionated whole breast irradiation (HF-WBI) using tangent fields has become a standard of care for early stage breast cancer. While conventionally-fractionated whole breast irradiation (CF-WBI) is typically delivered to 4500–5000 cGy in 23–25 fractions, HF-WBI utilizes doses of 3900–4250 cGy in 13–16 fractions. An additional tumor bed boost can be delivered with either regimen. The non-inferiority of HF-WBI has been established by at least 4 randomized controlled studies, all showing similar local control and possibly improved toxicity outcomes as compared to more prolonged CF-WBI regimens.[1–3]

HF-WBI trial protocols and current consensus guidelines offer insight to patient selection and treatment planning and delivery. Within each of the 4 key randomized trials for HF-WBI, dose homogeneity goals required that no less than 93–95% but no more than 105–107% of the prescription dose be delivered to tissues within the tangent fields. The American Society for Radiation Oncology (ASTRO) 2018 consensus guidelines specify delivery of 4000–4250 cGy in 15–16 fractions, with or without tumor bed boost. These guidelines recommended coverage of >95% of the breast volume by >95% of the prescription dose while minimizing volumes receiving >105% of prescription dose. There were no limitations specified for chest wall separation or breast size as long as these parameters can be achieved, and three-dimensional conformal radiotherapy (3DCRT) and "field-in-field" techniques were suggested to optimize dose homogeneity.[4]

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Yet within these protocols and guidelines, there exist inconsistencies in the definitions of volumes used to specify dose objectives. The 4 key randomized trials mentioned above evaluated dose homogeneity for tissues for a single breast contour at the central axis plane only. In two of the protocols, the evaluated volume included a 1 cm margin on palpable breast tissue,[2] and each evaluated tissues up to and including the overlying skin. There were no recommendations for dose limitations above or below the central axis plane provided.[1–3] Conversely, the 2018 ASTRO guidelines specified homogeneity goals for the entire clinically defined breast volume.[4] Recent trials with HF-WBI arms, such as the Radiation Therapy Oncology Group (RTOG) 1005 protocol,[5] have defined the whole breast as per an RTOG consensus atlas.[6] When specifying dose objectives for the PTV used for dosimetric evaluation, the volume excluded the first 5 mm of tissue under the skin surface.[5]

Moreover, these HF-WBI protocols and guidelines do not expressly account for dose in the tissues outside of the contoured breast volume that fall within standard tangent fields used for WBI. When atlas-based breast structures are generated, there is inevitably non-contoured soft tissue within the beam path that is not reflected in a dose-volume histogram (DVH) analysis for the breast volume. As such, the acute and late toxicities associated with incidental irradiation of these tissues-in-beam (TIB) are unknown. Because the volume of TIB may be expected to vary by breast size and by prone vs. supine positioning, differences in toxicity outcomes related to TIB may better inform patient selection and treatment planning for patients with HF-WBI.

To characterize the impact of incidental irradiation of TIB, we analyzed dosimetric parameters of breast and non-breast TIB (nTIB) volumes for a cohort of patients treated with HF-WBI. We then evaluated twelve prospectively collected, patient- and provider-reported acute toxicity outcomes as a function of TIB, breast, and nTIB volumes.

2. Methods

2.1. Patient population

Patients treated with tangent field HF-WBI using 3DCRT to 4050 cGy in 15 fractions from 4/2016 to 1/2018 across three treatment facilities were included. Initial planning was generally volume-based, with tangent fields placed on the basis of contoured structures. Exclusion criteria were patient age <21 years, concurrent bilateral breast radiation, prior ipsilateral breast irradiation, ipsilateral breast implant, or additional fields used for nodal coverage. Lumpectomy bed boosts were permitted, and prone vs. supine treatment positioning was recorded.

2.2. Target delineation

In order to ensure consistent definitions of volumes used across plans for the purposes of this study, two radiation oncologists retrospectively re-contoured the breast volume for each plan based on the planning CT image set, using the RTOG consensus atlas.[6] The 5 mm of tissue deep to the patient surface was excluded from the breast volume to simulate breast volumes used by recent protocols.[5] Tissues-in-beam (TIB) was defined by the volume encompassing all breast and non-breast tissues within the 30% isodose line. Non-breast TIB (nTIB) volumes were created by subtracting the whole breast volume from the TIB volume. Fig. 1 displays the contoured structures on a patient treated in a prone position. All volumes were reported in cm^3.

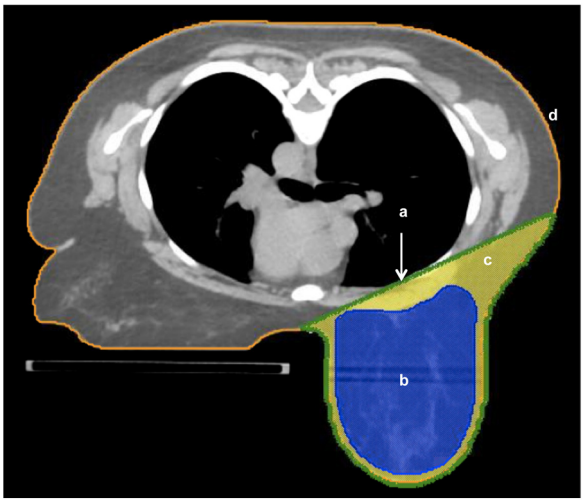

Fig. 1. Example of contoured (a) tissues-in-beam (TIB, in green), (b) breast (in blue), and (c) non-breast tissues-in-beam (nTIB, in yellow) volumes utilized for a patient treated in prone position. The exterior region of interest (d) is in orange. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2.3. Treatment planning and dosimetric parameters

All plans were initially created with 3DCRT using two primary tangential opposed fields. Photon energy from 6 MV through 15 MV, field size, gantry angle, and multileaf collimator blocks were applied according to the treating radiation oncologist's initial plan. The field-in-field technique was utilized to minimize dose heterogeneity, and homogeneity corrections were applied.

Volumes of the breast, TIB, and nTIB receiving at least 100%, 105%, and 107% of the prescription dose were calculated in cm^3 and defined as V100, V105, and V107, respectively.

2.4. Acute toxicity measures

Acute toxicities were prospectively assessed and recorded weekly during HF-WBI by the treating radiation oncologist using standardized assessment forms. Assessment forms were identical across all 3 centers and included physician-rated outcomes including dermatitis, hyperpigmentation, Karnofsky Performance Status (KPS), dry desquamation, moist desquamation, and papular rash, as well as patient-reported outcomes including fatigue, pruritus, pain score, burning pain, twinging pain, and tenderness. Radiation dermatitis, pruritus, hyperpigmentation, and fatigue were evaluated as per Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).[7] Presence or absence of dry or moist desquamation, papular rash, burning pain, twinging pain, and tenderness were recorded as binary outcomes. Pain intensity was measured on an increasing scale of 0–10, with 0 representing no pain. KPS was assessed on a scale of 0–100. Baseline and maximum grade, scale score, or side effect status during HF-WBI were recorded for each toxicity. For CTCAE v4.0 and scale outcomes, progression of the toxicity outcome by at least 1 unit from baseline was noted. For binary outcomes, change in side effect status as compared to baseline was reported. For all variables, improvements in grade or resolution of the toxicity outcome over the course of WBI were rare and excluded from analysis. Data points with fewer than 2000 cGy delivered between baseline and final toxicity assessments were also excluded.

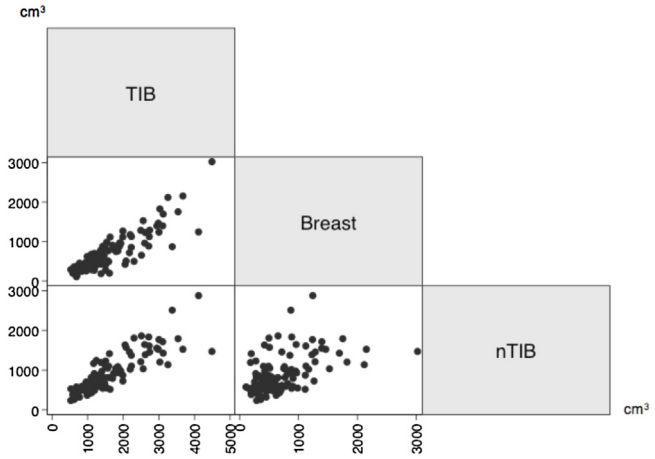

Fig. 2. Matrix displaying correlations between tissues-in-beam (TIB), breast, and non-breast tissues-in-beam (nTIB) volumes in cm^3. Using Spearman's rank order correlation test, there are significant correlations between TIB and breast volumes (rho = 0.849, p < 0.001), TIB and nTIB volumes (rho = 0.868, p < 0.001), and breast and nTIB volumes (rho = 0.523, p < 0.001).

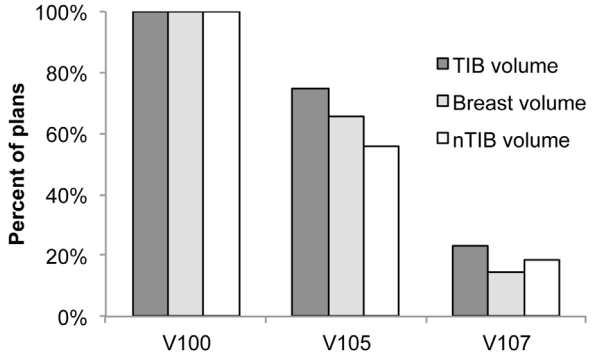

Fig. 3. Percent of plans with V100, V105, and V107 of >2 cm^3 for breast, tissues-in-beam (TIB), and non-breast tissues-in-beam (nTIB) volumes. Volumes receiving >100% and >105% of the prescription dose are common in both breast and non-breast tissues within the treatment beams. Volumes receiving 107% of the prescription are more common in nTIB than in breast volumes.

2.5. Statistical considerations

Chi square tests assessed the relationships between treatment positioning status (prone vs. supine) and both laterality of breast treated and use of breast boost. Mean TIB, breast, and nTIB volumes were compared by treatment positioning status using the Mann–Whitney 2-sample statistic for non-parametric data.

Spearman's rank order correlations for non-parametric data were used to evaluate the relationship between (1) TIB, breast, and nTIB volumes and (2) breast and associated nTIB V100, V105, and V107 volumes, all in cm^3. Percent of cases with V100, V105, and V107 of at least 2 cm^3 for TIB, breast, and nTIB volumes were also calculated.

To assess the relationship between dose and acute toxicities, univariable logistic regressions for change in toxicity grade or side effect status were performed for each toxicity outcome as a function of TIB, breast, and nTIB V100, V105, and V110. To further evaluate maximum grade of dermatitis and pain, each were dichotomized at the median score of 1, corresponding to clinically meaningful respective cutoffs of mild pain and faint erythema or dry desquamation.

To partition the effects of dose contained within the contoured breast volume versus the nTIB volume on toxicity outcomes, multivariable logistic regressions were then performed for each toxicity as a function of breast V100, V105, and V107 and corresponding nTIB V100, V105, and V110. Further adjustment for prone vs. supine positioning and delivery of a surgical bed boost (yes or no) were also performed.

To establish threshold volumes of TIB associated with toxicity outcomes, logistic regressions for the odds of change in toxicity grade or side effect status were assessed for binary candidate cutpoints for all toxicity outcomes with a significant multivariable association with breast or nTIB V105 or V107. Threshold calculations were performed for the TIB structure instead of the nTIB structure because the former can be more directly assessed in standard practice by evaluating doses contained with a commonly used external region of interest (See Fig. 1). Moreover, when controlling for breast volumes, TIB and nTIB would be expected to be collinear. Candidate threshold cutpoints were selected due to commonality of their use in current and past protocols as follows: at 10 cm^3, 50 cm^3, 100 cm^3 for TIB V105 and 0.03 cm^3, 2 cm^3, and 5 cm^3 for TIB V107. The final cutpoint for each toxicity was selected according to the scoring method of Miller and Siegmund.[8] Bonferroni correction for level of significance of 0.017 was used to account for 3 candidate cutpoints and type I error of 0.05.

All statistics were performed using STATA, version 14.0 (College Station, TX).

3. Results

3.1. Patient and treatment characteristics

In total 137 plans met the study inclusion criteria, and 118 plans (86%) contained complete toxicity data for analysis. Table 1 shows patient and treatment characteristics, stratified by treatment in prone vs. supine positioning. All participants were female. A slight majority of patients (53%) was treated in a prone positioning, and patients treated in a supine position were significantly more likely to have right-sided tumors. Most plans (78%) included a surgical bed boost, ranging in dose from 700 cGy to 1000 cGy.

3.2. Dosimetric outcomes

After application of the original beam arrangements and planning specifications to the breast volumes recontoured as per RTOG definitions, mean D95 (the percentage of prescription dose covering 95% of the newly-defined breast volume) was 95.4% [standard deviation (10%)].

Mean breast, TIB, and nTIB volumes by treatment position are listed in Table 1. Breast volume 25-, 50-, 75-, and 100-percentile values were 388.7, 600.7, 880.1, and 3023.0 cm^3, respectively. For a prone position, 8.5, 20.0, 38.6, and 32.9% of patients fell into these quartiles, respectively, and for a supine position, 40.4, 33.3, 10.5, and 15.8% of patients fell into these quartiles, respectively, p < 0.001.

While mean breast volume was significantly higher among patients treated in a prone as compared to supine position (866.8 vs. 498.5 cm^3, respectively, p < 0.001), there was no significant difference in TIB by positioning, and nTIB volume was lower among patients treated in a prone vs. supine position (792.3 vs. 980.5 cm^3, respectively, p = 0.027).

There were significant correlations between TIB, breast, and nTIB volumes, as demonstrated in Fig. 2. Notably, breast volume was positively correlated with nTIB volume (rho = 0.523, p < 0.001).

Fig. 3 shows the percent of plans with V100, V105, and V107 of at least 2 cm^3 for TIB, breast, and nTIB volumes. V105 and V107 of >2 cm^3 were noted in 65% and 15% of breast volumes but also in 56% and 19% of nTIB volumes, respectively. Increasing breast volume was significantly correlated with increasing breast V100 (rho = 0.981, p < 0.001), V105 (rho = 0.269, p = 0.002),

Table 1
Patient and treatment characteristics by treatment position.

	Overall n = 137	Prone n = 73	Supine n = 64	p-Value
Side treated—N (%)				
Right	79 (58%)	36 (49%)	43 (67%)	**0.035**
Left	58 (42%)	37 (51%)	21 (33%)	
Surgical bed boost— N (%)				
Yes	107 (78%)	57 (79%)	49 (77%)	0.715
No	30 (22%)	15 (21%)	15 (23%)	
Volumes—mean (SD) in cm^3				
Breast volume	696.8 (453.1)	866.8 (496.4)	498.5 (294.2)	**<0.001**
TIB volume	1558.6 (788.9)	1637.1(816.7)	1465.9 (751.0)	0.147
nTIB volume	879.8 (455.8)	792.3 (380.3)	980.5 (514.5)	**0.027**

SD, standard deviation; TIB, tissues-in-beam; nTIB, non-breast tissues-in-beam.

and V107 (0.269, p = 0.039). Although increasing breast volume was significantly associated with increasing nTIB V100 (rho = 0.30, p < 0.001), it was not correlated with nTIB V105 or V107.

3.3. Toxicity outcomes

Table 2 shows the maximum grade or side effect status for each acute toxicity outcome by the end of HF-WBI as well as the change in grade or side effect status over baseline during HF-WBI. Toxicities noted to be present at baseline evaluation were fatigue in 19%, tenderness in 16%, twinging pain in 10%, and pruritus in 3% of patients. The majority developed worsening fatigue (54%) and radiation dermatitis (87%) by the end of HF-WBI, whereas dry or moist desquamation rates were low (<10% of cases).

Univariable logistic regression for the change in toxicity grade or side effect status as a function of TIB, breast, and nTIB volume is summarized in Table 3, with full output available in Supplementary Tables 1–3. On multivariable analysis, increasing breast V100 was independently associated with higher odds of developing grade 2+ radiation dermatitis, and nTIB V100 was independently associated with development of burning pain and twinging pain. Moreover, after controlling for corresponding breast doses, increasing nTIB V105 was significantly associated with higher odds of developing hyperpigmentation and burning pain, and increasing nTIB V107 was associated with higher odds of developing burning pain. After further adjustment for prone vs. supine position and delivery of surgical bed boost, each of these p-values remained significant with the exception of burning pain in association with nTIB V107. Multivariable outcomes are summarized in Table 4, with full output available in Supplementary Table 4.

A threshold volume of TIB V105 > 100 cm^3 was significantly associated with development of burning pain (OR 6.333, 95% CI 1.885–21.275, p = 0.003), and there was no statistically significant threshold for development of hyperpigmentation. For TIB V107, the threshold volume of >5 cm^3 was associated with development of burning pain (OR 6.818 95% CI 2.123–21.892 p = 0.001).

Table 2
Maximum grade or side effect status of each acute toxicity outcome and change in grade or side effect status over baseline by the end of hypofractionated whole breast irradiation (HF-WBI).

CTCAE v4.0 grades	Maximum grade by end of HF-WBI—N (%)	Increase in grade over baseline by ≥1 unit—N (%)
Radiation Dermatitis		
0	7 (6%)	101 (87%)
1	90 (78%)	
2	19 (16%)	
3+	0 (0%)	
Fatigue		
0	29 (25%)	63 (54%)
1	85 (73%)	
2	2 (2%)	
3+	0 (0%)	
Hyperpigmentation		
0	81 (70%)	35 (30%)
1	35 (30%)	
2	0 (0%)	
Pruritus		
0	76 (66%)	37 (32%)
1	40 (34%)	
2+	0 (0%)	
[10pt] Scales	Score at end of HF-WBI—N (%)	Progression of score over baseline[a]—N (%)
KPS, minimum score		
100	51 (44%)	30 (26%)
<100	65 (56%)	
Pain intensity scale		
≤1	76 (66%)	45 (39%)
2+	40 (34%)	
[10pt] Binary outcomes[b]	Presence of side effect by end of HF-WBI—N (%)	Change in side effect status over baseline—N (%)
Dry desquamation	8 (7%)	8 (7%)
Moist desquamation	1 (1%)	1 (1%)
Papular rash	45 (39%)	45 (39%)
Burning pain	19 (17%)	19 (17%)
Twinging pain	50 (43%)	37 (32%)
Tenderness	61 (53%)	44 (38%)

CTCAE v4.0, Common Terminology Criteria for Adverse Events Version 4.0; HF-WBI, hypofractionated whole breast irradiation; KPS, Karnofsky performance status.
[a] Refers to decrease in KPS value and increase in pain scale value as compared to baseline.
[b] Presence of side effects at end of HF-WBI and change in side effect status over baseline are equal in value if the side effect was not present at the baseline assessment.

4. Discussion

Our study demonstrates that doses to TIB in excess of the prescription were common both in- and outside of the contoured breast volume and were significantly associated with acute toxicity outcomes including burning pain and hyperpigmentation. Such associations persisted after accounting for corresponding within-breast V100-V107, suggesting that nTIB doses are independently associated with toxicity outcomes. To our knowledge, this is the first report to evaluate the impact of incidental irradiation of TIB on toxicity outcomes in HF-WBI and supports the inclusion of TIB as a region of interest in treatment planning and protocol design.

Our data highlights a number of interesting findings. First, we demonstrated a significant positive correlation between breast and nTIB volumes. Prone positioning was associated with larger breast volumes but smaller nTIB volumes; however, significant increases in toxicity outcomes persisted with increasing TIB volume even

Table 3
Significant univariable logistic regressions for change in toxicity grade or side effect status as a function of V100, V105, and V107 in cm^3 for tissues-in-beam (TIB), breast, and non-breast tissues-in-beam (nTIB).

	TIB			Breast			nTIB		
	Odds ratio	95% CI	p-Value	Odds ratio	95% CI	p-Value	Odds ratio	95% CI	p-Value
V100									
Hyperpigmentation	1.001	1.000–1.002	0.013	1.001	1.000–1.002	0.029	1.002	1.000–1.005	0.039
Pain intensity scale >2	1.001	1.000–1.002	0.006	1.001	1.000–1.002	0.017	1.003	1.001–1.006	0.015
Dermatitis grade >2	–	–	–	1.001	1.000–1.002	0.032	–	–	–
Burning pain	–	–	–	–	–	–	1.003	1.000–1.006	0.021
KPS level change	–	–	–	–	–	–	0.995	0.990–1.000	0.045
Twinging pain	–	–	–	–	–	–	1.004	1.000–1.007	0.012
V105									
Hyperpigmentation	1.009	1.003–1.016	0.005	1.009	1.000–1.017	0.039	1.020	1.003–1.037	0.016
Pain intensity scale >2	1.007	1.001–1.013	0.020	1.008	1.000–1.017	0.048	1.016	1.001–1.031	0.034
Burning pain	1.007	1.001–1.012	0.018	–	–	–	1.025	1.008–1.043	0.005
V107									
Hyperpigmentation	1.054	1.004–1.107	0.036	–	–	–	–	–	–
Pain intensity scale >2	1.053	1.001–1.108	0.045	–	–	–	–	–	–
Burning pain	1.073	1.015–1.135	0.012	1.117	1.007-–1.238	0.036	1.130	1.013–1.202	0.024

TIB, tissues-in-beam; nTIB, non-breast tissues-in-beam; CI, confidence interval; KPS, Karnofsky performance status.

Table 4
Significant multivariable logistic regressions for change in toxicity grade or side effect status as a function of V100, V105, and V107 in cm^3 for breast and non-breast tissues-in-beam (nTIB)[a].

	Breast			nTIB		
	Odds ratio	95% CI	p-Value	Odds ratio	95% CI	p-Value
V100						
Radiation Dermatitis >2	1.001	1.000–1.003	0.029	–	–	–
Burning pain	–	–	–	1.003	1.001–1.007	0.017
Twinging pain	–	–	–	1.004	1.001–1.007	0.015
V105						
Hyperpigmentation	–	–	–	1.017	1.001–1.033	0.039
Burning pain	–	–	–	1.025	1.007–1.043	0.006
V107						
Burning pain	–	–	–	1.098	1.000–1.204	0.049

nTIB, non-breast tissues-in-beam.

[a] After adjusting for prone vs. supine treatment position and delivery of surgical bed boost, all significant p-values remained <0.05 except for development of burning pain with nTIB V107.

after adjusting for positioning. Thus, our findings support a continued use of prone positioning to minimize TIB in large-volume breast plans but stress the need for attention to TIB doses even with this approach.

Moreover, while increasing breast volumes were associated with higher nTIB V100, larger breast size was not significantly correlated with higher nTIB V105-V107. This suggests that inattention to dose heterogeneity may lead to nTIB receiving doses in excess of the prescription even among plans with smaller breast volumes. Such areas of high dose in the nTIB may not be readily apparent using a DVH analysis of the contoured breast volume.

Further, we found that incidence of V107 > 2cm^3 was higher in nTIB as compared to within-breast volumes. Plan review demonstrated that these nTIB V107 were found in tissues medial, lateral, and posterior to the breast as well in the first 5 mm of the skin excluded from breast contours. The first 5 mm deep to the patient surface is often excluded from clinical target volume (CTV) and PTV structures used for evaluation in protocols due to the concern for inaccuracies of dosimetry in the build-up region. To ascertain if such dosimetric inaccuracies could be dictating associations between toxicity outcomes and TIB volumes, we additionally considered a "skin-in-beam" volume comprised of a 5 mm rind just deep to the patient surface and contained with TIB. Secondary multivariable logistic regression for nTIB V100-107 controlling both breast and skin-in-beam V100-107 did not affect the significant independent association of nTIB with development of burning pain, twinging pain, and hyperpigmentation. This suggests that doses in excess to the prescription to nTIB medial, lateral, and posterior to the breast may be particularly important to consider during treatment planning.

As previously noted, current 2018 ASTRO HF-WBI guidelines recommended minimizing doses to the breast >105% of the prescription dose. Our data augments these guidelines by providing clinically useful threshold volumes that can guide decision-making for radiation planning. By minimizing TIB V105 to <100 cm^3 and TIB V107 to <2 cm^3, odds of developing burning pain may be reduced by >6-fold. While specific techniques for decreasing these dosimetric parameters may vary by plan, additional field-in-field segmentation or alteration of prescription isodose lines may serve as useful methods to reduce excess dose to nTIB. As with other dosimetric objectives, this must be balanced against decrements to coverage of target structures on an individual, personalized basis per plan.

Although our toxicity rates fall within in the ranges previously reported, it is noted that incidences do vary substantially between studies. For 578 patients receiving HF-WBI, Jagsi et al. reported 27.4% grade >2 dermatitis, 15.7% burning/stinging bother, and 18.9% fatigue rates.[9] For 138 patients randomized to HF-WBI, Shaitelman et al. reported 36% dermatitis, 54% pruritus, 55% breast pain, 9% hyperpigmentation, and 9% fatigue rates.[10] Differences likely reflect varied definitions of toxicity outcomes per study. However, toxicity rates have also been shown to increase by race/ethnicity category, younger age, higher body mass index, and presence of comorbidities.[11,12] Thus, for patients with these risk factors, the role of nTIB may be particularly important to consider in an effort to reduce acute toxicities.

Our analysis is limited to acute toxicity outcomes in tangent field HF-WBI. Thus, associations with and appropriate threshold

doses for late toxicity outcomes or for CF-WBI may differ. Of note, previous studies do describe incidental axillary coverage during standard supine tangent-field CF-WBI,[13–16] with 10–66% of the level I-II axillary volumes inadvertently covered by 95%–100% of the prescription dose. Although late toxicity outcomes for such incidental nodal irradiation have not been well described, both the current and previous data emphasize growing attention to the importance of doses to nTIB and toxicity outcomes. Moreover, given that rates of specific toxicities from HF-WBI may be lower than those associated with CF-WBI,[17,18] the findings of this study may suggest an even greater impact of doses to nTIB in the use of CF-WBI.

While initial planning was generally volume-based, it should be noted that beam arrangements and prescription specifications from the original plans were applied to breast volumes that were recontoured as per RTOG definitions. Although this procedure was performed in order to ensure consistency across plans, we cannot entirely exclude that beam arrangements based on the RTOG definitions may have varied from those used on the original plans. Yet the mean D95 for the RTOG-based breast volumes was calculated at 95.4%, suggesting that the plan coverage for the recontoured volumes was likely similar to the intended coverage of the original plans. Notably, findings would be expected to differ should alternative contouring strategies or consensus contouring guidelines be applied.

Additionally, our analysis cannot provide explanation for the biological mechanisms underlying acute toxicity arising from doses to the nTIB. Moreover, we cannot comment on the role of an individual's inherent radiation sensitivity and its association with breast size and other unmeasured factors such as race/ethnicity and concurrent medications. As such, our data should serve as a nidus for future research aimed at isolating patient-specific biological and demographic features associated with acute toxicity for HF-WBI.

In conclusion, this study supports the use of dosimetric parameters for non-breast tissues falling within standard tangent fields in an effort to reduce acute toxicities. Caution should be applied when relying on DVH-based analysis of breast plans that do not reflect doses to nTIB. Because creation of an nTIB volume is non-standard and requires additional steps in the planning workflow, we would recommend that the TIB volume should be used instead for planning purposes. The TIB structure can be approximated by the volume contained within the exterior region of interest (see Fig. 1), which can be routinely auto-generated on radiation planning systems. Inclusion of threshold doses to TIB in excess of the prescription should be considered in future trial design as well. Our future work will characterize late toxicities associated with incidental irradiation of nTIB volumes, with implications for both treatment planning and protocol design.

Conflict of interest

Each co-author listed is an employee of the Johns Hopkins University School of Medicine. Otherwise, there are no other conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rpor.2020.02.009.

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