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Basic Original Report

Assessing the Need for Adjusted Organ-at-Risk Planning Goals for Patients Undergoing Adjuvant Radiation Therapy for Locally Advanced Breast Cancer with Proton Radiation

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Abstract

Purpose: Locally advanced breast cancer requires surgical management via lumpectomy or mastectomy with or without systemic therapy followed by chest wall or breast (CW) and comprehensive nodal irradiation (CNI). Radiation (RT) dose constraints for the heart and ipsilateral lung have been developed based on photon RT. Proton therapy (PBT) can deliver significantly lower doses of RT to these organs-at-risk (OARs) and may warrant adjustments to OAR planning goals.

Methods and Materials: The RT plans of consecutive patients undergoing adjuvant CW-CNI RT with PBT within a single center were reviewed. A inital treatment volume, comprised of CW/intact breast + CNI (CTV_init) structure, including the CW and CNI but excluding any boost plans was analyzed. Frequency distributions were generated based on doses received by the heart, lungs, and esophagus for validated dosimetric parameters. Frequency distributions were generated and then stratified by laterality and compared using the Kruskal-Wallis H test. The 75th, 85th, and 95th percentiles for each dosimetric parameter were calculated, overall and by laterality. The 75th percentile (Q3), was used as a suggested primary goal, and the 95th percentile was used as a suggested secondary goal.

Results: One hundred and seventy-two plans were analyzed. Forty-nine plans were right-sided, 107 were left-sided, and 16 were bilateral. The overall Q3 of the mean and V25 of the heart were 1.5 Gy and 1.7%, respectively. The mean and V25 to the heart differed significantly by laterality. Pulmonary values were similar to current recommendations. For all lateralites, the median volume of the esophagus receiving 70% prescription dose was $\leq$1 cm^3.

Conclusions: We present the first dosimetric study providing complete OAR dose-volume histograms data for patients undergoing adjuvant pencil-beam scanning-PBT for locally advanced breast cancer, with detailed information on central tendencies, ranges and distributions of data. We have provided suggested planning goals and metrics for the lungs, heart, and esophagus; the latter 2 differing

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significantly from current Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) constraints and classical photon goals.

Introduction

Breast cancer is the most commonly diagnosed non-cutaneous malignancy in women in the United States, with more than 270,000 new cases resulting in more than 65,000 deaths projected to occur in 2020.[1] Surgical resection of the primary tumor with partial or complete dissection of the ipsilateral axilla has remained as a mainstay of treatment in both early and locally advanced disease; with primary tumor resection achieved by either a lumpectomy or mastectomy. In cases of high-risk or locally advanced breast cancer (LABC) systemic therapy is also used either before or after surgical resection based on hormone and human epidermal growth factor receptor 2/neu receptor status. After resection, adjuvant radiation (RT) is recommended to improve local and locoregional control,[2] as well as survival.[3-7]

LABC, in addition to certain scenarios of high-risk early stage breast cancer, necessitates adjuvant RT delivered to the affected chest wall or breast (CW) and regional nodal basins. Comprehensive nodal irradiation (CNI) typically encompasses the ipsilateral axillary, supraclavicular, and internal mammary (IMN) nodal chains.[8,9] Comprehensive nodal irradiation, specifically coverage of the IMNs, often comes at the cost of increased RT exposure to the ipsilateral lung and heart owing to expanded field sizes and the proximity of nodal regions to organs-at-risk (OARs), particularly in the setting of left-sided disease. Radiation-induced esophageal and cardiopulmonary complications have classically been thought of as deterministic effects, with severity of effects increasing with increasing dose. However, in recent years, the thought process has evolved so that for late cardiac complications there is no "safe" threshold of RT exposure below that the risk of complications falls to zero. As such, efforts are made to reduce RT exposures of these critical organs to doses "as low as reasonably achievable." Studies have established thresholds over which the risk of RT pneumonitis and esophagitis becomes clinically significant,[10-12] and additional literature has described direct correlations between increasing RT dose to the heart and significant cardiac events.[13-15] Cardiac damage inflicted by RT can lead to a myriad of long-term complications, including but not limited to coronary artery disease progressing to ischemic events, such as myocardial infarction, and eventual congestive heart failure, as well as arrhythmias and valvular changes.[13,16] The risk of cardiac toxicity can be further heightened by anthracycline-based chemotherapy or human epidermal growth factor receptor 2 directed therapies, which are commonly used in the treatment of LABC.[17]

Throughout the years, task forces have collaborated to establish normal tissue tolerances, or dose constraints, based on available literature and normal tissue complication probability (NTCP) models,[18,19] which in turn have been used as clinical planning goals to ensure an optimized therapeutic ratio for RT delivery. Throughout the past several decades, there have been many advances in RT techniques and modalities, which allow for more conformal RT delivery and lower dose exposures to OARs. In recent years, the utilization of proton therapy (PBT) for breast cancer has increased given its ability to significantly decrease RT dose exposure to the heart and ipsilateral lung compared with photon RT. Although the dosimetric advantages of PBT have been demonstrated in several small studies,[20-24] adjustments to standardized planning goals have not been established to reflect this heightened conformality. As the ability to deliver highly conformal RT increases, planning goals should become more stringent accordingly for quality assessment; however, target ranges for adjuvant RT for LABC remain unclear with variability among proton centers.

We present dosimetric data for a large series of consecutive patients treated with adjuvant pencil-beam scanning (PBS) proton radiation (PBT) for LABC within a single institution, including frequency distributions for cardiopulmonary and esophageal tissue exposures, both overall and stratified by laterality. The upper limit of the 75th percentile, or third quartile (Q3), of each parameter may serve as a reasonably achievable primary planning goal, and the 95th percentile as a secondary planning goal for PBT in the treatment of LABC. We hypothesized that the range of cardiac exposures would be significantly lower than currently accepted standardized planning goals and lead to modification of OAR guidelines thereby resulting in improved PBS-PBT plan quality assessment.

Methods

Patient selection

After institutional review board approval, a Health Insurance Portability and Accountability Act-compliant database was created of all patients undergoing CW-CNI for invasive breast cancer at a single proton center between 2015 and 2020; men and women over the age of 18

were included for analysis. Unilateral and bilateral RT plans were included if at least one side of the plan included CNI. All plans included were delivered in 1.8 or 2.0 Gy per fraction to the initial treatment volume; hypo- and hyperfractionated plans were excluded from this analysis.

RT techniques

A inital treatment volume, comprised of CW/intact breast + CNI (CTV_init) structure, including the CW and CNI coverage, but excluding any boost plans was used for analysis. Although some patients received a boost to the surgical scar, lumpectomy cavity, or gross tumoral or nodal disease, these doses varied by clinical scenario and so all values reported on represent the CTV_init structure to provide the highest level of homogeneity and external validity.

Our institutional practice is to routinely treat the ipsilateral axillary, supraclavicular, and internal mammary nodal basins when CNI is recommended. Historically, nodal volumes were delineated based on either the Radiation Therapy Oncology Group[25] or Radiotherapy Comparative Effectiveness Consortium (RADCOMP)[26] contouring atlases, pending individual patient risk factors or trial enrollment. Beginning in late 2018, our institution now predominantly uses the RADCOMP atlas given concerns for undercoverage of nodal basins, particularly in the SCV region, when highly conformal RT techniques are used.[27] For patients with a clinically negative IMN chain, the internal mammary artery is contoured with an anatomic expansion to include the surrounding fat plane from the caudal border of the supraclavicular volume to the cranial edge of the fourth rib. The lung is not included in this volume. In the case of a clinically involved IMN chain, gross disease is contoured separately and expanded 0.3 to 0.5 cm within anatomic boundaries, and the IMN chain is extended inferiorly to the fifth intercostal space.

All plans were delivered with PBS-PBT. In general, when treating CW-CNI fields, PBS-PBT to the CTV_init structure is delivered with 2 anterior beams, one en face and one anterior oblique, and optimized with a single-field optimization technique. Our institution prefers a 2-beam approach to maximize PBS-PBT plan robustness. A notable exception to this occurs when patients present with metal-containing tissue expanders; in these scenarios, plans use 3 to 4 separate beam angles and hybrid optimization techniques are used. Our techniques for delivery of bilateral PBS-PBT have been previously published.[28] All reported proton doses have been adjusted for an estimated radiobiologic effect (RBE) of 1.1 and represent the cobalt Gray-equivalent dose. The majority of plans were created in the Eclipse treatment planning system (TPS; Varian Medical Systems, CA), with the exceptions of cases, including metal-containing tissue expanders being planned in Raystation TPS. Irrespective of the initial TPS used, for study analysis all doses were calculated using the Eclipse TPS.

Table 1 Patient characteristics

Patient characteristic	N (%), n = 172
Age (y)	
Median (range)	54 (18-88)
Sex	
Male	4 (2)
Female	168 (98)
Race	
White	99 (58)
Black	53 (31)
Other	12 (7)
Unknown	8 (5)
ECOG PS	
0	124 (72)
1	39 (23)
2	5 (3)
3	1 (1)
Unknown	3 (2)
Laterality	
Right	49 (29)
Left	107 (62)
Bilateral	16 (9)
Histology	
Invasive ductal carcinoma	150 (87)
Invasive lobular carcinoma	18 (11)
Other	4 (2)
Anatomic stage at presentation	
I*	1 (1)
IIA	26 (15)
IIB	38 (22)
IIIA	41 (24)
IIIB	12 (7)
IIIC	18 (11)
IV†	3 (2)
Recurrent‡	33 (20)
Type of surgery	
Local excision/lumpectomy	54 (31)
Mastectomy	118 (69)
Immediate reconstruction	
Yes	63 (53)
No	55 (47)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

* One clinical T1cN0M0 patient presented with triple negative disease but only received partial neoadjuvant chemotherapy and at the time of surgery there was concern for posttreatment effect in an axillary node previously thought to be negative; thus, she was treated with chest wall and comprehensive nodal irradiation.

† Indicates patients presenting with American Joint Committee on Cancer stage IV chest wall and comprehensive nodal irradiation disease, who were managed definitively after an excellent response to neoadjuvant chemotherapy.

‡ Indicates local or locoregional recurrence of prior disease.

Statistical analysis

Frequency distributions were generated based on doses received by the heart, esophagus, and lungs for previously validated dosimetric parameters. Frequency distributions were generated for all patients, then stratified by laterality and compared using the Kruskal-Wallis H test. Dosimetric data was represented on dotplots superimposed on box-and-whiskers plots, with each box representing the 25th to 75th percentiles; whiskers represent minimum and maximum data points not considered outliers, and data points outside of whiskers represent outliers (more than 3/2× upper quartile). To further assess the overall distributions of RT doses received by the relevant OARs, complete dose-volume histograms (DVHs) were exported and combined to create one composite DVH for each structure. All DVH information was exported directly from the Eclipse TPS, and composite graphs were generated using MATLAB (MathWorks),

The median and range for each parameter were calculated and reported, first for the overall data and then stratified by laterality. As some data sets were positively skewed and reporting standard-deviation based recommendations would have been less applicable, the upper 75th, 85th, and 95th percentiles for each parameter were reported to describe reasonably achievable planning goals, with the 75th percentile representing a suggested primary planning goal and the 95th percentile representing a suggested secondary planning goal.

Selection of RT parameters

Cardiopulmonary and esophageal parameters were selected based on endpoints which have been clinically validated as predictors of toxicity and are relevant during adjuvant LABC planning. The exception to this is the endpoint of cubic centimeters (cm^3) of the esophagus receiving 70% or more of the CTV_init prescription dose; this is an endpoint that has been used by our institution as a surrogate measure for esophageal exposure. The relative volume of the esophagus receiving 35 Gy (V35) has been listed as a predictive measure by historical QUANTEC literature; however, as it is predominantly the mid and upper esophagus exposed to RT during treatment for LABC, our institution preferentially uses an absolute volume. As the majority of our cases are planned to a CTV_init dose of 50 or 50.4 Gy, the volume receiving 70% of the prescription dose would correspond to the volume receiving ~35 Gy. The maximum grade of acute esophagitis experienced by each patient was reported from prospectively recorded physician assessments, according to CTCAE v.5.0 criteria. Pearson's correlation was used to demonstrate the relationship between esophageal dose and clinical esophagitis.

Table 2 Treatment characteristics

Treatment characteristic	N (%), n = 172
Total RT dose	
(median, range)	50.4 (45.0-72.0)
CTV_init dose (Gy)	
Median (range)	50.4 (45.0-51.0)
CTV_init fraction size (Gy)	
Median (range)	1.8 (1.8-2.0)
SFB	
Yes	83 (48)
Scar	25 (30)
Lumpectomy	30 (36)
Gross residual disease	3 (4)
Nodal disease	18 (22)
Multisite	7 (8)
No	89 (52)
SFB dose	
Median (range)	10 (5.4-21.6)
Prior in-field RT	
Yes	16 (9)
No	156 (91)
Neoadjuvant chemotherapy	
Yes	97 (56)
No	75 (44)
Adjuvant chemotherapy	
Yes	57 (33)
No	115 (67)

Abbreviations: CTV_init = inital treatment volume, comprised of CW/intact breast + CNI; RT = radiation therapy; SFB = small-field boost.

Results

One hundred and seventy-two plans were analyzed. One hundred and seven (62%) plans were left-sided, 49 (20%) were right-sided, and 16 (9%) were bilateral. The median age at treatment start was 54 years (range, 18-88), and 168 (98%) of patients were women (Table 1). Nearly half of all patients presented with American Joint Committee on Cancer Eighth edition[29] anatomic stage III disease; 20% of patients were treated for recurrent disease. Sixty-nine percent of patients underwent a mastectomy of which 63 women (53%) underwent immediate reconstruction; reconstruction options included a deep inferior epigastric perforator flap, immediate permanent implant, or temporary tissue expanders. Ninety-seven (56%) of patients underwent neoadjuvant chemotherapy, and 57 (33%) were treated adjuvantly. Sixty-nine (40%) of patients were treated with anthracycline-based chemotherapy as part of neoadjuvant or adjuvant therapy.

Sixteen (9%) of our population had prior in-field RT; initial RT course was for prior breast cancer (15 of 16, 94%), or lymphoma (1 of 16, 6%). It is our general institutional practice to deliver chest wall reirradiation with standard, 1.8 Gy fractions based on available literature describing safety and efficacy.[30-32] Occasionally, a

Table 3 Frequency distributions

Dosimetric parameter	Overall (n = 176)	Right (n = 49)	Left (n = 107)	Bilateral (n = 16)	Kruskal-Wallis H *P* value
Mean heart (Gy)					
Median (range)	0.9 (<0.1-3.9)	0.7 (<0.1-2.8)	1.1 (<0.1-3.7)	1.3 (<0.1-3.9)	<.01
95th percentile	2.4	2.5	2.4	3.3	
85th percentile	1.8	1.8	1.9	1.9	
75th percentile	1.5	1.2	1.7	1.8	
V25 heart (%)					
Median (range)	0.8 (0.0-6.6)	0.3 (0-3.9)	0.9 (0-6.6)	1.5 (0-5.3)	<.01
95th percentile	3.4	3.4	3.2	4.3	
85th percentile	2.3	2.2	2.3	2.3	
75th percentile	1.7	1.0	1.7	2.2	
V20 lung (%)					
Median (range)	15.0 (2.4-33.9)	16.0 (4.6-33.9)*	15.0 (2.4-29.2)*	14.7 (6.6-23.5)†	N/A
95th percentile	26.9	25.0	27.4	21.2	
85th percentile	20.0	20.0	20.0	20	
75th percentile	18.5	19.0	18.2	18.1	
V5 lung (%)					
Median (range)	41.0 (10.6-62.2)	42.7 (17.5-62.2)*	41.0 (11.0-59.8)*	37.8 (10.6-53.1)†	N/A
95th percentile	55.0	56.1	55.3	47.0	
85th percentile	51.0	50.2	51.8	42.9	
75th percentile	47.6	47.6	47.9	42.6	
Volume of esophagus receiving 70% Rx dose (cm^3)					
Median (range)	0.1 (0.0-8.4)	0 (0-3.2)	0.2 (0-8.4)	0 (0-5.4)	.2
95th percentile	4.3	2.4	5.1	3.9	
85th percentile	1.6	1.0	2.0	1.6	
75th percentile	0.8	0.3	1.0	1.5	

Abbreviation: Rx = prescription.
* Indicates V5 and V20 to ipsilateral lung.
† Indicates V5 and V20 to bilateral lungs.

twice-daily (BID)b.i.d. schedule will be used, particularly if the interval between treatment courses is <6 months; however, patients with nonstandard fractionation schemes were excluded from analysis. When delivering reirradiation for recurrent breast cancer, it is also our institutional practice to proceed with whole breast or CW and CNI given the aggressive nature of locoregionally recidivistic disease.

The median dose to CTV_init was 50.4 Gy (45.0-51.0), median total RT dose was also 50.4 Gy, but ranged from 45 to 72.0 Gy. Our institutional planning goals for target coverage include 95% of the CTV_init structure receiving ≥100% of prescription dose, including elective IMN volumes. All patients were treated to the CTV_init in 1.8 or 2.0 Gy fractions. Forty-eight percent of patients underwent a small-field boost to an additional 5.4 to 21.6 Gy (Table 2).

The median, 75th, 85th, and 95th percentiles of values for the mean and V25 heart, V20, and V5 lung, and cm^3 of the esophagus receiving 70% prescription dose are summarized in Table 3. The Q3 for the heart mean and V25 were markedly lower than current QUANTEC dose constraints, both overall and for each individual laterality. The overall median for mean heart doses was 0.9 Gy (ranging from <0.1-3.9 Gy), and the overall median V25 was 0.8% (0.0-6.6; Table 3, Fig 1a). For overall mean heart dose, data outliers were seen in cases of bilateral treatment (n = 2), gross IMN disease (n = 1) and unfavorable chest wall anatomy (n = 1). There were significant differences in the mean and V25 heart doses by laterality, with doses for bilateral plans < left sided plans < right sided plans; however, despite left-sided and bilateral plans having significantly higher dose exposures, these values still fell far below current standards (Table 3, Fig 1).

The observed values for lung V20 and V5 were congruous to slightly lower than historical planning goals (overall median 15% [2.4-34] and 42% [11-62], respectively; Table 3, Fig 2a-b). Data sets for pulmonary endpoints were not compared statistically, as bilateral plans evaluated total long volume rather than ipsilateral lung volume. No patients experienced acute RT-related pneumonitis. All pulmonary outliers as delineated in Figure 2a-b, including for V5 and V20, occurred in the presence of either a metal-containing tissue expander, or gross IMN disease.

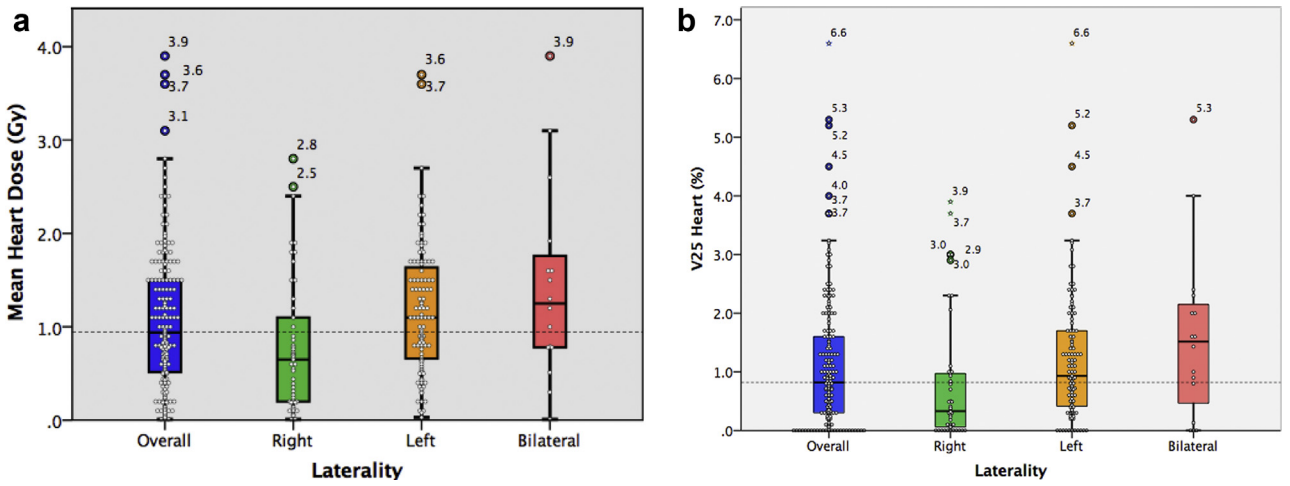

Figure 1 Box Plot overlaid with dot plot demonstrating frequency distributions for mean heart dose (a) and V25 heart (b), stratified by laterality. Box represents 25th to 75th percentiles; whiskers represent minimum and maximum data points not considered outliers. Data points outside of whiskers represent outliers (more than 3/2× upper quartile). Hashed lines represent overall median mean heart of 0.9 Gy (a) and overall median V25 of 0.8%

The volume of the esophagus receiving 70% prescription dose was remarkably low in the majority of plans, ranging from 0 to 8.4 cm^3 overall; with an overall median, 75th and 95th percentile of 0.1, 0.8, and 4.3 cm^3, respectively. There was no statistical difference in the amount of esophageal exposure by laterality (Table 3, Fig 2c); however, when examining the "overall" esophageal exposures, the majority of data outliers occurred in cases of left sided or bilateral disease. Overall, 45 (26%) and 13 (8%) of patients experienced acute grade 1 or 2 esophagitis, respectively; no patients experienced ≥grade 3 esophagitis. Pearson's correlation demonstrated a statistically significant ($P < .01$) correlation between increasing volume of the esophagus within the 70% isodose line and severity of esophagitis ($r = 0.31$).

Complete DVH information was available to be exported for 168 (98%) of patients; partial information was available for export for 170 (99%). Median, upper and lower quartiles, and fifth through 95th percentiles have been delineated on each composite DVH as a comprehensive reference from which other discreet parameters can be extrapolated (Fig 3).

Discussion

We have presented data for a large cohort of patients being treated with adjuvant PBT for LABC. We demonstrate that, in accordance with published literature and regardless of laterality, our observed cardiac doses are remarkably low and fall far below typical photon planning goals, thus warranting adjustment for better assessment of plan quality. We have demonstrated that the ranges of our pulmonary values are similar to historical pulmonary constraints, and although planning goals may not need adjustment, they should be adhered to strictly. We have also demonstrated the ability to reliably minimize esophageal exposure through the use of a novel metric, using the absolute rather than relative volume of exposure. Through the demonstration of full frequency distributions of observed cardiopulmonary and esophageal doses, we are able to provide not only measures of central tendency, but ranges of data as examples of pragmatically achievable primary and secondary planning goals represented by the 75th and 95th percentiles of each data set.

There now exists a significant body of in silico and in vivo literature describing the potential to decrease integral RT dose exposure to normal tissues when PBT is used across several body sites.[33-41] For breast cancer specifically, small series have described significantly reduced cardiac and pulmonary exposures when RT is delivered with photons compared with protons, with particular emphasis on cardiac structures.[20-22,42] However, clinicians and national clinical trial protocols[43] continue to base RT planning goals (and, by extrapolation, plan quality) on historical photon constraints. Although it is widely accepted that PBT plans should meet, if not significantly improve, on classical photon dose constraints, new target ranges have not been established.

Inherent to the safe delivery of radiation therapy is detailed knowledge of the effects of RT on normal tissues throughout the human body. In the first major attempt to quantify the effects of therapeutic RT on normal tissues, an National Cancer Institute-supported task force published seminal work summarizing all available clinical evidence as well as expert opinions on and institutional experiences with normal tissue tolerances to RT. Subsequently, detailed dose constraints for several tissues or organs were suggested; these were colloquially known as the "Emami guidelines."[18]

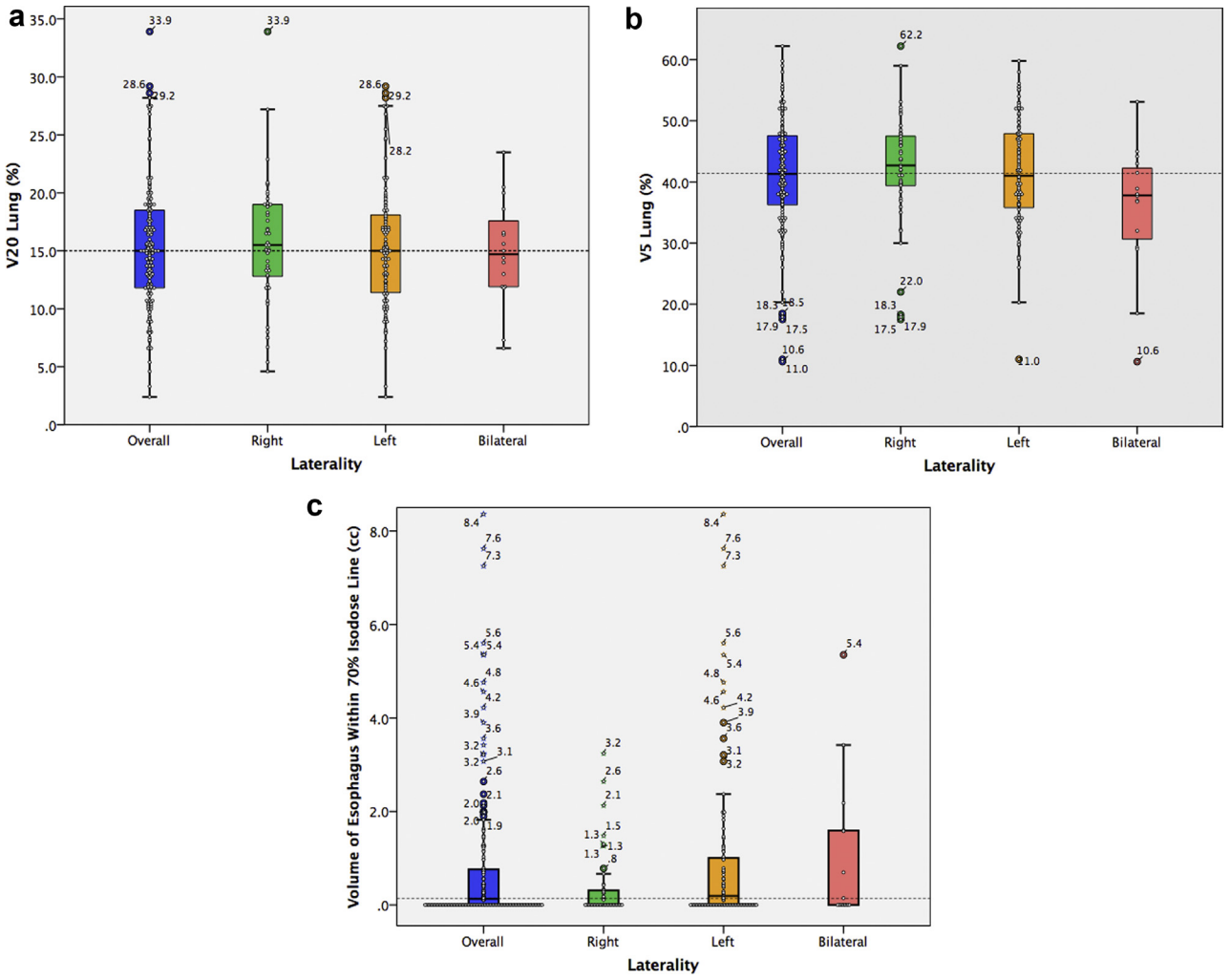

Figure 2 Box plot overlaid with dot plot demonstrating frequency distributions for V20 lung (a) and V5 lung (b) and volume of esophagus within 70% IDL (c), stratified by laterality. Box represents 25th to 75th percentiles; whiskers represent minimum and maximum data points not considered outliers. Data points outside of whiskers represent outliers (more than 3/2x upper quartile). Hashed lines represent overall medians of 15.0%, 41.0%, and 0.1 cm^3, respectively. *Abbreviation*: IDL = Isodose line.

Additional work led to the development of the Lyman-Kutcher-Burman model for NTCP.[44-46]

To reflect the publication of new clinical toxicity and dosimetric data and to reflect evolving RT techniques and multimodality treatment paradigms, a new task force was formed nearly a decade later in 2010 with the goal to develop and describe organ site-specific overviews of quantitative dose-volume relationships, and to provide updates to the Emami guidelines.[19,47] This group of publications, collectively known as the Quantitative Analysis of Normal Tissue Effects in the Clinic, or "QUANTEC" data, provided detailed dose constraint recommendations for several parameters for a number of normal tissues and has guided clinical radiation oncologists for the last decade, including those treating LABC.

Notably, all previous guidelines were developed from photon-based NTCP models, given the eras in which they were created. Although a RBE of 1.1 is commonly accepted for proton therapy, this is thought to overgeneralize the biologic effects of PBT in both normal and malignant tissues, thus bringing into question the applicability of previously established NTCP models. The clinical implication of nearing a classical dose constraint with a proton plan is not as well understood, and therefore extreme caution must be exhibited when doing so.[48-50] The hypothesis of a variable RBE model makes the implementation of stringent PBT planning goals all the more critical.

Minimizing integral RT dose to cardiac structures continues to be a top priority when planning RT for breast cancer. In a pivotal study examining cardiac complications in breast cancer patients, late RT-induced cardiac complications have been shown to increase linearly with increasing RT dose, at a rate as high as 7.4% per Gy of mean heart dose,[13] and several large trials have repeatedly demonstrated that there is no "safe" threshold below

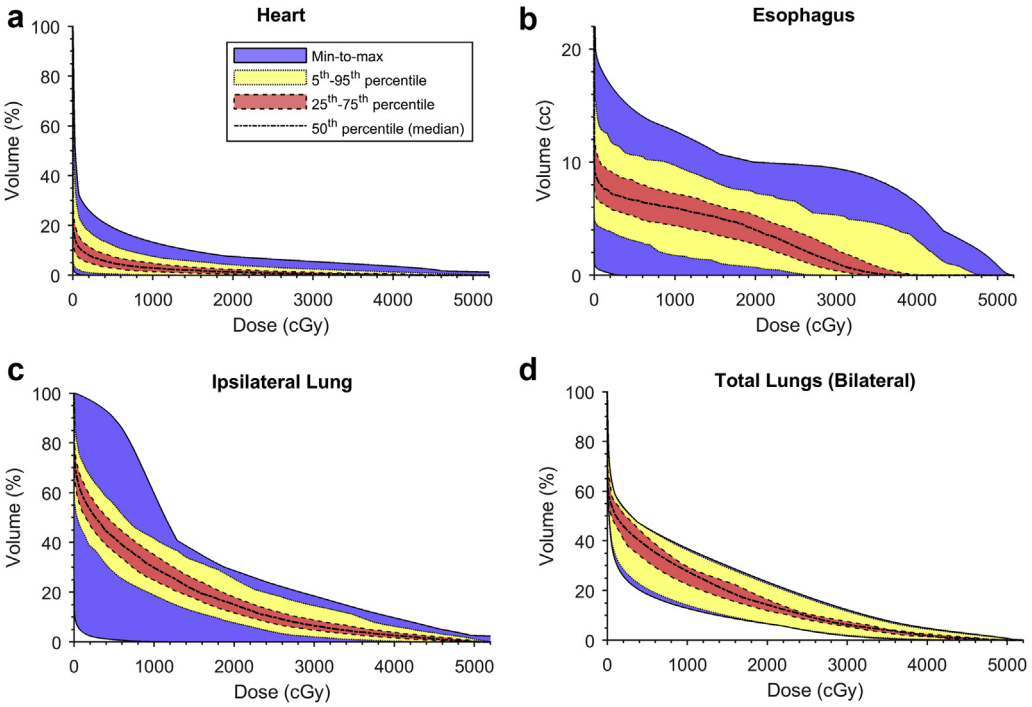

Figure 3 Composite graphical representations of complete dose-volume histogram curves for OARs of interest. (a) Composite dose-volume histograms (DVH) for "heart" contours of 170 patients. (b) Composite DVH for "thoracic esophagus" contours of 170 patients. (c) Composite DVH for "ipsilateral lung" contours for 153 patients, all treated for ispsilateral disease. (d) Composite DVH for "total lung" contours for 15 patients, all treated for bilateral disease.

which cardiac risks do not increase.[51,52] Patients with breast cancer, even locally advanced disease, frequently have good prognoses and long life expectancies, and for these reasons it is imperative to understand what is truly achievable with PBT, and to avoid acceptance of suboptimal plans, despite cardiac values which may look favorable compared with what is expected from photon RT.

Several small series investigating the use of PBT for the adjuvant treatment of LABC have reported median mean heart doses <1 Gy.[53,54] In contrast, for patients warranting CNI inclusive of the IMN chain, contemporary photon literature has described mean heart doses above 3 Gy and 10 Gy, with and without respiratory gating, respectively.[20,22,54,55] This frequently came at the cost of compromised coverage of the IMN chain. Although it is widely accepted that proton plans should meet, if not significantly improve, on classical photon dose constraints, dosimetric studies with sufficiently large patient data sets have not yet been published to establish new planning goals. This presents a dilemma at the time of plan evaluation, as PBT plans may be seen as "acceptable" per classical photon constraints, although further optimization may have actually been achievable. For example, although smaller, single-institution protocols have adjusted cardiac planning goals,[53] larger, national randomized trials have not, and either continue to use photon standards (such as the RADCOMP protocol, which specifies a target mean heart dose ≤15 Gy), or rely on the "as low as reasonably achievable" principle.[43,56] In the absence of more stringent planning goals, less experienced clinicians may accept nonoptimal proton plans that still meet protocol photon-based constraints. This is particularly relevant with the increasing frequency of proton centers, both across the United States and worldwide, which are often initially staffed with personnel, including clinicians, physicists, and dosimetrists with minimal or no proton therapy experience.

Our median pulmonary doses are concordant with previously published PBT literature,[20-22,53] and our institutional 75th percentile falls below classical QUANTEC photon constraints (V20 to <30-35[57]) and what has been demonstrated as achievable with conformal photon RT (mean V20 16%-33%[58-60]). When treating with protons or photons, it is our institutional practice to use a more conservative pulmonary goal of V20 <20%. Similar to the additive risk of cardiotoxicity seen when anthracycline-based chemotherapy is used, taxane-based chemotherapy (also commonly used in the management of breast cancer) can lead to acute or subacute interstitial pneumonitis, and thus it is also critical to minimize pulmonary exposures. We recommend continued strict adherence to current dose constraints.

Although acknowledged as a potential acute toxicity of adjuvant RT for LABC due to the treatment of the IMN and supraclavicular regions, rates of RT-induced acute esophagitis and the parameters used for dose constraints or planning goals are not well reported in historical

photon cohorts. Although nondisease site-specific dose constraints for the esophagus were suggested by the QUANTEC group, they too acknowledged difficulty in identifying dosimetric parameters truly predictive of severe esophagitis.[61]

Using the method of minimizing overlap of the 70% isodose line of the CTV-init structure kept our overall rate of esophagitis to 34%, which is similar to other early PBT studies,[22,62] and potentially improved given that the majority (76%) of our events were grade 1. As increasing volumetric exposure was correlated with increasing severity of esophagitis, the 75th and 95th percentiles given in Table 3 can provide reasonable primary and secondary planning goals. Owing to the short segment of esophagus that is typically exposed to RT in breast cancer in the cervical region, the volumetric dose as opposed to the mean dose is a more relevant parameter to evaluate. For example, commonly used esophageal constraints of mean dose <34 are heavily extrapolated from thoracic literature, and are unlikely to be truly applicable to breast plans given the inherent difference in high dose distributions and the inherent variability in how esophageal contours are delineated. Estimating the mean dose to an organ depends on the reliable contouring of the entire length of the organ. In the case of the esophagus, this can be both observer-dependent and dependent on the inferior extent of a CT planning scan; thus, the use of an absolute rather than volumetric parameter is a more reliable metric.

Although there was not a statistical difference in the amount of esophageal exposure by laterality, when looking at the overall distribution of esophageal exposures, high-volume outliers occurred almost exclusively within left-sided or bilateral plans. This is understandable given the location of the esophagus within the lower neck and upper thorax, and it was likely that a statistical difference was not observed because overall, all volumetric exposures were quite low (0-8.4 cm^3).

The strengths of our study lie in the large number of patients included, which were all treated with CNI including IMN coverage. Notably, although many studies have reported median or average mean heart doses for adjuvant PBT for LABC, none have reported more detailed frequency distributions, demonstrating a range into which the majority of their plans fell. Although we too present medians and ranges to allow for direct comparisons with related literature, data on both mean and median doses alone are not sufficient for establishing new planning goals, as not enough information is provided about the overall distribution of observed values. Measures of central tendency, such as mean or median values may not be appropriate targets, particularly if data do not follow a "normal" Gaussian distribution. We have also provided data stratified by laterality to illustrate differences in expectations in left versus right-sided disease, and to highlight the feasibility of safe delivery of bilateral PBS-PBT, on which little has been published. Additionally, the creation of composite OAR DVHs provides a reference from which to extrapolate reasonably achievable ranges for other discreet planning parameters. As a result of this analysis, we have revised our institutional practice guidelines and use these values to analyze the quality of all PBS-PBT plans. Supplementary A provides a reference table describing how our results for all OARs compare against classical photon dose constraints and our previous institutional dose constraints.

Our data has limitations, including its retrospective nature and the exclusive use of PBS-PBT. To date, there is little literature directly comparing the dosimetry of PBS-PBT with other proton delivery techniques, such as passive scattering (PS-PBT). Although several studies demonstrating improved cardiopulmonary dosimetry with PBT compared with photon RT used PS-PBT, our data should be extrapolated with caution as it remains unclear whether the same cardiac dose ranges would have been achievable with PS-PBT.

Recently, a group from Massachusetts General Hospital published a thought-provoking article describing an increased incidence of radiation-induced rib fractures in patients undergoing proton RT for breast cancer compared with photon RT.[63] The increase was thought to be related to end-of-range uncertainty in RBE, with concerns that this could translate to a similar risk of cardiac damage. Our study is limited by a relatively short follow-up, with many patients having less than 6 months of post-RT follow-up at the time of analysis, and rib fractures as well as cardiac toxicities typically develop on a longer timeline. Prior reports have documented the median time to radiation induced rib fractures as 15 to 22 months,[64,65] and cardiac toxicities may become apparent years after treatment. For this reason, until a longer median follow can be obtained, the authors have chosen to report cardiac dosimetric data alone in lieu of correlating to toxicity endpoints at this point in follow-up. As esophagitis is considered an acute toxicity, the authors felt comfortable reporting it as a clinical correlate. Future directions include reporting on oncologic and late toxicity outcomes after further data maturation.

Conclusions

We present the first dosimetric study providing complete OAR DVH data for a large series of patients undergoing adjuvant PBS-PBT for LABC, with detailed information on central tendencies, ranges and distributions of data. Our intent is to provide updated, proton-specific planning goals to ensure optimal quality of PBT plans. We have provided suggested planning goals and metrics for the lungs, heart, and esophagus; the latter 2 differing significantly from classical photon goals. Future directions include further validation through the analysis of multi-institutional and collaborative group data, and

incorporation of new constraints into prospective protocols.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2020.09.003.

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