Advances in Radiation Oncology (2024) 9, 101651

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Prospective Trial on the Impact of Weekly Cone Beam Computed Tomography-Guided Correction on Mean Heart Dose in Breast Cancer Breath-Hold Radiation Therapy

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Received 21 May 2024; accepted 23 September 2024

Purpose: Surface guided radiation therapy (SGRT) in breast cancer radiation therapy (RT) may decrease the need for image guidance such as cone beam computed tomography (CBCT). The goal of this study was to evaluate the impact of CBCT image guidance on the cumulative and interfractional variation of mean heart dose (MHD) during breath-hold RT in patients with breast cancer. We hypothesized that weekly CBCT is not necessary for SGRT-assisted breath-hold but is still needed in patients treated with voluntary deep inspiration breath-hold (vDIBH) and active breathing control (ABC) to maintain a stable MHD.

Methods and Materials: This was a prospective, single-center trial that sequentially assigned breast cancer patients to adjuvant RT 40 to 50 Gy in 15 to 25 fractions using vDIBH, ABC, or SGRT to reproduce the breath-hold. The MHD was estimated on each of the weekly CBCT images before and after online correction. The cumulative and interfractional variation of MHD, which were represented by the average and SD of MHD in each patient, were compared in the series of CBCT before and after online correction to evaluate whether online CBCT-guided correction could lead to a more reproducible MHD.

Results: Fifty-five patients were included (vDIBH = 16, ABC = 19, and SGRT = 20). The CBCT-guided online correction was associated with a significant decrease in the interfractional variation of MHD in vDIBH (SD difference, 22.6 cGy; $p = .0389$) and ABC (SD difference, 9.9 cGy; $p = .0262$), but not in SGRT ($p = .2272$). The CBCT-guided online correction had no impact on the cumulative MHD in all 3 groups.

Conclusions: This study demonstrated that CBCT-guided online correction could reduce the interfractional variation of MHD in ABC or vDIBH. When SGRT was available, CBCT-guided correction had no impact on the stability of MHD across the treatment fractions. Future studies may explore whether the CBCT frequency could be reduced to less than weekly in SGRT to decrease treatment time and the radiation dose associated with CBCT.

Introduction

Multiple randomized studies have shown that adjuvant radiation therapy (RT) in breast cancer can reduce recurrence and breast cancer mortality.[1,2] Within the context

Sources of support: This work had no specific funding

Research data is not available at this time.

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https://doi.org/10.1016/j.adro.2024.101651

of breath-hold RT for left-sided breast cancer, the European society of radiotherapy and oncology (ESTRO) guidelines recommended that pretreatment imaging such as cone beam computed tomography (CBCT) be used in breath-hold RT to maintain the reproducibility of the breath-hold and reduce systemic errors.[3] Though the National Comprehensive Cancer Network breast cancer guidelines recommended that, at a minimum, weekly imaging should be done to verify treatment setup, this recommendation on the frequency did not take into account the breath-hold technique, which may also influence the setup error.[4] CBCT during breath-holding could increase the total time required at the RT treatment unit, contribute to the radiation dose that could increase the risk of secondary malignancy, particularly in the contralateral breast, and lead to patient fatigue in the form of additional patient breath-hold burden.[5]

There are few studies evaluating the optimal frequency of CBCT specific to each of the commonly used breath-hold techniques, including active breathing control (ABC), voluntary deep inspiration breath-hold (vDIBH), and surface guided RT (SGRT). SGRT, which uses an optical surface scanning system for daily setup and verification of breath-hold, has been shown to reduce the setup error compared with the traditional setup using skin tattoos and room lasers.[6,7] SGRT also has the potential to reduce the need for CBCT while maintaining stable cumulative doses to organs at risk (OARs), including the heart.[8] As the mean heart dose (MHD) is correlated with the risk of future major coronary events,[9] studies evaluating the optimal frequency of CBCT should have the stability of the MHD as one of the endpoints.

To evaluate the necessity of weekly CBCT in breath-hold RT, we designed our study with the primary goal of assessing the impact of weekly CBCT-guided online correction on the interfractional variation of MHD in patients receiving treatment with vDIBH, ABC, and SGRT. The secondary objective was to evaluate the impact of weekly CBCT-guided online correction on the cumulative MHD for each of these 3 breath-hold techniques. We hypothesized that SGRT might reduce the need for CBCT guidance. In our view, the cumulative and interfractional variations of MHD are both clinically relevant. A greater interfractional dose fluctuation, which can occur as a result of setup error, may lead to a higher-than-expected biologically effective dose in some patients. This effect is especially pronounced for normal tissues, such as the heart, which has a lower alpha/beta ratio than most tumors and is more sensitive to the dose per fraction.[10]

Methods and Materials

Study design

This was a single institution, interventional, open-labeled, nonrandomized 3-armed clinical trial (NCT03459898).[11] The inclusion criteria were women who met all of the following criteria: (1) aged 18 or above, (2) required adjuvant left chest wall or breast irradiation after mastectomy or lumpectomy for breast cancer, (3) had Eastern Cooperative Oncology Group performance status <3, and (4) were able to maintain a breath-hold of 15 seconds or longer. The choice of the dose-fractionation schedule was at the treating physician's discretion, per our institutional guidelines. Exclusion criteria included partial breast irradiation and the need for bolus, which makes surface tracking difficult.

The targeted sample size was 60, with sequential allocation to the 3 breath-hold technique groups. No additional screening was done prior to the group allocation to assess whether patients would be good candidates for a particular breath-hold technique. The first 20 patients were recruited to the vDIBH group. Once the accrual goal was reached, the next 20 patients were assigned to the ABC group and the last 20 patients to the SGRT group. The study was approved by the Research Ethics Board. All patients gave informed consent to this study.

RT setup and delivery

Patients were positioned using a breast board in a supine position. Simulation computed tomography (CT) was done during breath-hold with a slice thickness of 3 mm. In each group, the breath-hold technique at simulation CT was identical to that during treatment. Pinnacle was used for the treatment planning and dose calculations. Radiation was delivered using tangential fields, using a photon energy of 6 to 18 MV. The target coverage was 95% of the prescribed dose to cover the entire breast or chest wall. The field-in-field technique was used to improve the dose homogeneity, with the goal of keeping any dose variation between 95% and 107%. Weekly CBCT imaging verification scans were acquired for all patients. On other treatment days, patients were set up using skin tattoos. Orthogonal radiograph imaging was not used on any of the treatment days.

Breath-hold techniques

In the vDIBH group, a high-resolution camera in the treatment bunker was used to visualize the marks on the patient's skin (left side) in order to reproduce the breath hold. Breath-holding with ABC was performed with the Elekta apparatus, which included a spirometer to monitor and assist with each breath-hold for a given length of time. In the SGRT group, the AlignRT (Vision RT) system, which is a surface imaging system, was used to monitor and reproduce the breath-hold. When using the AlignRT system, the region of interest (ROI) included the breast or chest wall, mid-sternum and ribs, and the lower portion of the supraclavicular fossa if 4-field RT was given. These ROI delineations were consistent with the recommendations of the manufacturer. If the breasts were pendulous, the ROI would include only the chest wall surrounding the breast tissue.

CBCT technique and matching

The Elekta X-ray Volumetric Imaging (XVI) system was used to acquire weekly CBCT half scans. A low-dose S20 collimator and turbo CBCT preset were used. The exact number of CBCTs performed for each patient would depend on the total number of fractions. The CBCT scans were automatically registered to the planning CT using 3 degrees of freedom and a gray value algorithm, followed by a manual adjustment using the chest wall as a reference if necessary (see Fig. 1). Any translation error of 1 mm or more was corrected. The CBCT-guided correction was done online, and the translation in each dimension was recorded.

MHD analysis

The MHD was determined for each weekly CBCT. The CBCT images were imported into the Pinnacle planning system, and the MHD based on the anatomy visualized on CBCT was calculated. In order to calculate the MHD, the beam settings from the original treatment plan, including the number of monitor units and field segments, were locked. Appropriate density overrides were applied to the planning CT according to the position of the heart in the CBCT, such that the recalculated MHD would take into account the new heart position.

Within each patient, the interfractional variation of MHD was measured by the SD of MHD across the weekly CBCTs. The cumulative MHD was the average of the MHD in each weekly CBCT.

Effect of online CBCT correction analysis

For each patient, a simulated scenario was created where no CBCT-guided online corrections were applied. The MHD was recalculated based on the position of the heart in each CBCT without any translations accounting for online correction. This reflects the MHD where the patient is aligned using skin tattoos only, without any online CBCT correction. We referred to this as the simulated scenario. We calculated the cumulative MHD and the interfractional variation of MHD in this scenario, which were represented by the average and SD of the MHD across the weekly CBCTs.

Statistical analysis

To evaluate whether online CBCT correction had any impact on the cumulative and interfractional variation of MHD, we compared these 2 parameters in the scenario with CBCT-guided translation and without CBCT-guided translation. The 2-sample *t* test was used to look for any significant difference. The mean value and 95% CI were estimated for each of the comparisons in the 3 breath-hold techniques.

If a significant difference was detected in the cumulative MHD or the interfractional variation of MHD with and without online CBCT correction, linear regression analysis was performed to look for any differences between the 3 breath-hold technique groups.

A p value of <.05 was considered significant.

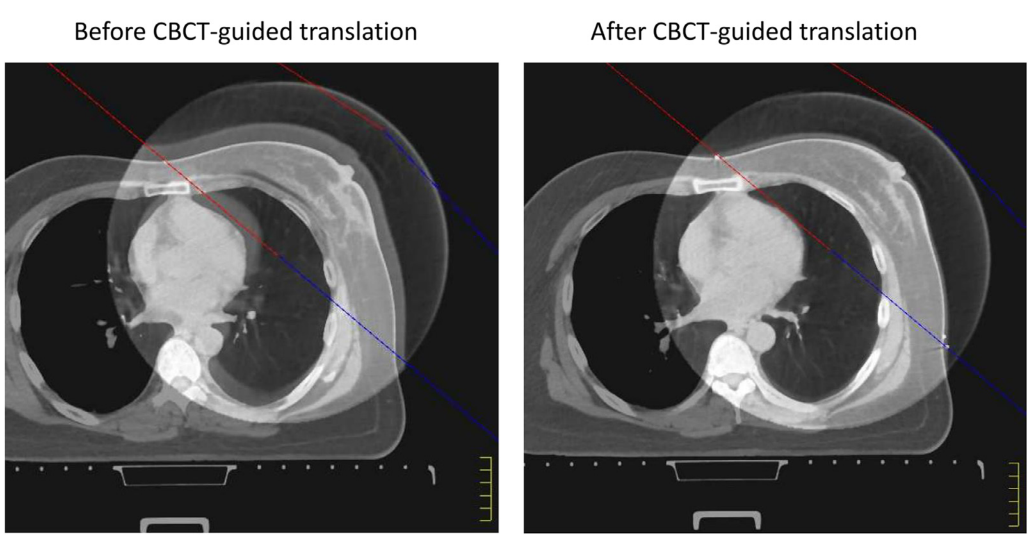

Figure 1 An example showing the overlay of planning computed tomography and cone beam computed tomography (CBCT) images before and after online CBCT-guided translation.

Results

A total of 60 patients were recruited, and 5 withdrew from the study, leaving 55 patients for analysis (vDIBH: n = 16; ABC: n = 19; SGRT: n = 20). The mean (IQR) age was 55 (46-64) years. Forty-four patients (80%) had breast-conserving surgery, and 11 patients (20%) had mastectomy. The most commonly used dose-fractionation was 42.56 Gy/16 fractions (81.8%), followed by 50 Gy/25 fractions (12.7%) and 40.05 Gy/15 fractions (5.5%). The details are given in Table 1. The average (IQR) of MHD based on the CBCT in the vDIBH, ABC, and SGRT groups were 1.85 Gy (1.45-1.92), 1.88 Gy (1.50-2.07), and 2.09 Gy (1.59-2.39), respectively.

Impact of online CBCT corrections on the interfractional variation of MHD

The SD of the simulated MHD without CBCT-guided translations was significantly higher than the SD of MHD with CBCT translations applied in patients treated with vDIBH (mean difference, 22.6 cGy; 95% CI, 1.3-43.8; p = .0389) and ABC (mean difference, 9.9 cGy; 95% CI, 1.3-18.4; p = .0262). Such difference was not observed in patients treated with SGRT (mean difference, 5.4 cGy; 95% CI, −3.7 to 14.7; p = .2272). The details are given in Table 2.

A comparison was made among the vDIBH, ABC, and SGRT groups to see which of the 3 breath-hold techniques was associated with a larger difference in the interfractional variation of MHD with and without CBCT-guided online correction. Compared with vDIBH, SGRT was associated with a trend toward a smaller difference in the interfractional variation of MHD with and without CBCT, but the difference did not reach statistical significance (Least squares means (LSM): 5.5cGy in SGRT vs 22.6cGy in vDIBH; p = .0611).

Table 2 Comparison of the interfractional dose variation of mean heart dose with and without online cone beam computed tomography-guided corrections applied

Breath-hold technique	Mean	95% CI of mean		*P* value
SD of simulated MHD minus SD of MHD on CBCTs, cGy				
ABC (n = 19)	9.85	1.30	18.4	.0262
SGRT (n = 20)	5.47	−3.71	14.7	.2272
vDIBH (n = 16)	22.6	1.31	43.8	.0389

Abbreviations: ABC = active breathing control; CBCT = cone beam computed tomography; MHD = mean heart dose; SGRT = surface guided radiation therapy; vDIBH = voluntary deep inspiration breath-hold.

Impact of online CBCT corrections on cumulative MHD

Online CBCT corrections did not influence the cumulative MHD in patients treated with ABC (mean

Table 1 Baseline characteristics

Characteristics	Category	vDIBH (n = 16), %	ABC (n = 19), %	SGRT (n = 20), %
Age, y	Mean (IQR)	54.6 (47-65)	56.6 (47.5-62.5)	53.7 (44.3-64.2)
Dose fractionation	50 Gy/25 fr	6.3	15.8	15
	42.56 Gy/16 fr	75	84.2	85
	40.05 Gy/15 fr	18.8	0	0
Sequential tumor bed boost	Included	56.3	52.6	40
Field arrangement	2 field	68.8	47.3	35
	3 or 4 field	31.2	52.6	65
T stage	is	25	5.3	5
	1	43.8	47.4	55
	2	25	42.1	35
	3	6.3	5.3	5
	4	0	0	0
N stage	0	68.8	42.1	40
	1	25	52.6	50
	2	6.3	0	10
	3	0	5.3	0

Abbreviations: ABC = active breathing control; fr = fraction; SGRT = surface guided radiation therapy; vDIBH = voluntary deep inspiration breath-hold.

Table 3 Comparison of the cumulative mean heart dose with and without online cone beam computed tomography corrections applied

Heart dose and position parameters	Mean	95% CI of mean		*P* value
Cumulative MHD with CBCT minus cumulative MHD without CBCT, cGy				
In ABC (n = 19)	−4.5	−16.5	7.4	.4341
In SGRT (n = 20)	−0.6	−13.1	11.9	.9198
In vDIBH (n = 16)	20.2	−4.1	44.5	.0961

Abbreviations: ABC = active breathing control; CBCT = cone beam computed tomography; MHD = mean heart dose; SGRT = surface guided radiation therapy; vDIBH = voluntary deep inspiration breath-hold.

difference, −4.5 cGy; p = .4341) and SGRT (mean difference, −0.6 cGy; p = .9198). In patients treated with vDIBH, there seemed to be a trend toward a higher cumulative MHD without CBCT-guided online corrections (mean difference, 20.2 cGy; p = .0961), but it did not meet statistical significance. The details are given in Table 3.

Discussion

Our results showed that there was a statistically significant difference between the SD of MHD with and without online CBCT-guided setup corrections in patients who had vDIBH and ABC. This implies that online CBCT could potentially reduce the interfractional variation of MHD in these patients and validates the recommendation that online image verification should be used to verify the depth of breath-hold in breast cancer RT.[3] No such difference was observed in patients treated with SGRT. We hypothesize that the observed reduced benefit of CBCT-based patient setup correction could be related to the more reproducible patient setup by SGRT compared with the use of skin tattoos and room-based lasers. This is consistent with prior studies showing that SGRT has the potential to reduce the frequency of routine image guidance.[12] Alternatively, it is also possible that our sample size was too small to capture any differences, which could be a limitation of our study.

We found that CBCT-guided online corrections did not influence the cumulative MHD in patients treated with vDIBH (p = .0961), ABC (p = .4341), and SGRT (p = .9198). It is known that cumulative MHD correlates well with the risk of long-term heart disease.[13] Our findings suggest that the omission of CBCT would not alter the cumulative MHD. However, this must be interpreted alongside our finding that the interfractional variation of MHD could be greater without online CBCT in patients treated with vDIBH and ABC. Hypofractionated RT is increasingly being used in breast cancer to deliver the entire course of RT over 1 week or 3 weeks.[14,15] Compared with the tumor, the cardiomyocyte has an alpha/beta ratio of 2 and is more sensitive to the effect of dose per fraction.[16] Even for a similar cumulative MHD, a larger interfractional variation might mean that the dose per fraction on some treatment days is much larger than the planned dose. This is still undesirable from a dosimetric point of view, though the clinical impact remains uncertain. In our view, the goals of CBCT should include achieving a stable cumulative heart dose and minimal interfractional dose variation.

The impact of interfractional dose variation may be more significant in ultrahypofractionated RT delivered in 5 fractions, which has been increasingly used in recent years.[17] Random errors in patient setup are more likely to average out as the number of fractions in the course of RT increases.[18] Conversely, when the entire course of RT is delivered in 5 fractions, interfractional dose variation is more likely to result in a residual error that may increase the cumulative MHD. In our study, there was a trend toward an increase in the cumulative MHD among patients treated with vDIBH in the absence of online CBCT-guided corrections (p = .0961), though we could not be certain whether this difference would become significant with a larger sample size.

Based on our results, CBCT should be done at least weekly in patients treated with breath-hold RT using ABC and vDIBH to ensure the interfractional stability of MHD. In SGRT, further studies should evaluate whether the frequency of CBCT could be reduced without compromising target volume or adequate sparing of OARs. Although our study focused on the MHD, it should be borne in mind that keeping the OAR dose low and reproducible is not the only goal of CBCT. Other aims of CBCT included the detection of anatomic changes and ensuring adequate coverage of the target volume.[19,20] A lower cumulative MHD might not always be desirable if it is caused by a random error that moves the entire patient, including the breast and heart, away from the treatment beam, because it would result in compromised target volume coverage and possibly tumor control. Our study did not evaluate the impact of CBCT-guided online corrections on target volume coverage. Nevertheless, it should be noted that our CBCT matching was based on the left chest wall and/or breast, which at least partially includes the entire target volume; therefore, a geographic miss of the target volume should be less likely. Future studies evaluating the utility of CBCT should take into account its impact on the target volume coverage, anatomic changes, and dose to the OARs. Other factors to consider include the cost or reimbursement issue, as 65% of the 200 institutions that participated in an international survey ranked cost as the most important barrier to SGRT implementation.[18]

An important limitation of our study is that only weekly CBCT was performed. The cumulative MHD calculated in our study was under the assumption that the patient anatomy during the 3 to 5 weekly CBCTs was representative of the anatomy during the entire course of RT. Also, most models that estimate the risk of cardiac mortality are based on the MHD at planning CT.[21-23] While, in theory, a larger interfractional dose variation may result in a higher dose per fraction on some days and increase the cumulative biologically effective dose received by the heart, there is no model to estimate the magnitude of the increased risk of heart disease in this context. As a result, the clinical significance of this interfractional dose variation needs to be examined in future studies. It is also not known whether orthogonal radiograph image matching alone may be adequate to correct setup errors for each of the 3 breath hold techniques we examined, because we did not use or evaluate the performance of orthogonal radiograph imaging in our study. Another limitation is the nonrandomized allocation of patients to the 3 breath-hold technique groups. In addition, we did not collect any data regarding the skin tone, radiation dermatitis, and body mass index of patients, all of which may influence the accuracy of SGRT.[12,24] The breath hold might be less reproducible in patients with very high body mass index.[25]

Conclusions

Our study showed that CBCT-guided online correction could reduce the interfractional variation of MHD in ABC or vDIBH but not in SGRT. The cumulative MHD was not affected by CBCT-guided online correction. Based on our results, in patients who undergo breath-hold RT using vDIBH or ABC, CBCT, which is performed at least weekly, is recommended. In patients who undergo breath-hold RT using SGRT, future studies may explore whether the CBCT frequency could be reduced to less than weekly to achieve a good balance between the benefit of ensuring consistent setup and the detriment of increased treatment time, breath-hold burden, and radiation exposure associated with CBCT.

Disclosures

Hanbo Chen received an honorarium from Novartis. Irene Karam received an honorarium for the EMD Serono advisory board on locally advanced head and neck cancers in November 2023. There are no other conflicts of interest.

Acknowledgments

Liying Zhang was responsible for statistical analysis.

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