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Feasibility of using calibrated cone-beam computed tomography scans to validate the heart dose in left breast post-mastectomy radiotherapy

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Abstract

Objective: In post-mastectomy radiotherapy, high-conformal techniques are a valid method for determining the dose distribution around a target. However, the proximity of critical structures is a reason for concern. This study aims to evaluate the feasibility of using calibrated cone-beam computed tomography (CBCT) scans as a valid tool for a timely heart dose evaluation.

Methods: A retrospective analysis was conducted on 170 retrospective CBCT scans of 17 patients who underwent high-conformal post-mastectomy irradiation. The delivered doses that were calculated using personalized calibrated CBCT were compared with the doses planned, using the dose–volume histogram dosimetric parameters.

Results: The heart volume that was evaluated using CBCT presented a mean increase of 6%; this discrepancy impacted the heart dose in 4 of 17 patients, with an absolute increase of V25 Gy (range, 2.5%–7.6%) and an increase in the mean dose (range, 1.1–3.4 Gy). The dose for the target, ipsilateral lung, and contralateral breast remained unchanged.

Conclusion: Using CBCT to monitor the dose that is delivered to the heart is feasible, allowing for a timely shift to an adaptive plan if clinically necessary.

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Introduction

Breast cancer is among the most commonly diagnosed cancers, accounting for 29% of all new cancers in women.[1] Radiation-associated cardiac disease manifests in its various forms in almost all patients. Acute injury, mainly pericarditis, and late injury, such as heart failure, ischemia, and myocardial infarction, remain a crucial problem for the clinical community. Myocardial infarction is a proven cardiotoxic effect that is caused by incidental irradiation in patients who have breast and lung cancer and are treated with radiotherapy.[2,3] Most early stage patients can be treated with breast conserving surgery, adjuvant radiotherapy, or a systemic treatment combined with neoadjuvant chemotherapy. Patients who have advanced conditions usually receive a mastectomy and postoperative radiotherapy. Adjuvant post-mastectomy radiotherapy was shown to be efficient at reducing the locoregional recurrence rate and improving the overall survival rate for patients with lymph node-positive breast cancer by 10 years.[4–6] However, there is a dosimetric challenge in delivering a uniform target dose to the patient. Comprehensive post-mastectomy radiation is technically difficult given the complexity of the target volume and its close proximity to critical structures, including the contralateral breast, heart, lung, and brachial plexus, and especially because of the involvement of the internal mammary node with left-sided breast cancer.[7]

High-conformal techniques, such as intensity modulated radiation therapy and volumetric modulated arc therapy (VMAT), can serve as valid solutions because of their ability to shape dose distribution around a complex target.[8] VMAT presents the added advantage of a short delivery time. Studies show that high-conformal techniques improve dose homogeneity and significantly spare the heart and left lung.[9] The following dose–effect relationship has been defined: the higher the dose of the incidental radiation to the heart, the higher the likelihood that a cardiovascular complication or generally cardiotoxic effects will occur.[10,11] The overall 5-year survival rate for female breast cancer patients has improved from 75% to 90% over the last four decades.[12] This increase partly results from earlier diagnosis, which is the result of the widespread use of mammography. However, it is mostly a result of the improvements in treatment, with novel surgical techniques, chemotherapy, hormone therapy, and radiotherapy being a part of the standard protocol. Prolonged survival has revealed that, among the side effects of radiotherapy, heart irradiation renders women more susceptible to cardiac death in the 10 to 20 years after treatment.[13] In 2005, a study that was conducted on 300,000 patients with breast cancer, who were undergoing radiotherapy in the United States from 1973 to 2001 noted an excess risk of mortality resulting from heart disease in patients with left breast cancer compared with women who were receiving radiotherapy on their right side. This demonstrated that even lower doses of radiation to the heart may lead to a relevant injury.[14] Increasing irradiation of the heart leads to an increased risk of contracting ischemic heart disease (IHD),[15] and patients with left-sided cancer were shown to have a higher risk of cardiac mortality compared with patients with right-sided cancer.[14]

Thus, it is of great importance to accurately assess the radiation dose that is delivered to the heart.

The risk of cardiac events is associated with dose–volume predictors,[16] and both the dose and irradiated volume are calculated based on planning computed tomography (CT) images. However, the CT images do not reflect the shape of the heart under the influence of breathing and heartbeats. Cone-beam computed tomography (CBCT) encompasses several respiratory heart movements and cardiac cycles, and represents an effective means of graphing the heart-planning-risk volume that is required to plan treatment.[17] We hypothesized that variation in the heart's position during treatment because of normal respiratory and cardiac function impacts the dose delivered to the heart and that the delivered dose is significantly different from the planned dose. Numerous researchers[18,19] take this movement into account by acquiring four-dimensional CT images during the simulation session to outline a realistic planned-organ-at-risk volume for the heart. However, the workload of the radiotherapy routine does not always allow such evaluations, and an alternative solution may be welcome. Other imaging systems, such as cardiac magnetic resonance imaging, may be able to better identify the heart and its actual motions; however, its application to radiotherapy planning remains limited. Previous results showed using CBCT instead of using the planning CT provided better consideration for breathing and heartbeat movements, which are the two main factors that influence the heart location in the thoracic cavity.[20] We used retrospective CBCT data to evaluate the dose that was received by the heart during post-mastectomy irradiation. The consistency of the CBCT data set for each patient, which was acquired along the treatment timeline, was assessed. Planned and delivered doses were compared, focusing on the results on the differences in the dose received by the heart.

Materials and methods

Patients and treatment workflow

Seventeen patients who underwent a mastectomy for left-sided breast cancer and were referred to our hospital between November 2017 and January 2018 for post-operative radiotherapy of the chest wall and regional nodes were enrolled into this retrospective study. At the time of treatment, all the patients presented T3/4 metastatic axillary lymph nodes >4 and had undergone dissection of these lymph nodes; these inclusion criteria select the cases in which a wider region to be treated is susceptible to the influence of the heart. All patients received 50 Gy, delivered as 2 Gy/fraction for 25 fractions over 5 weeks using VMAT. Simulation CT scans were performed while the patient was free-breathing using a high-speed 16-slice helical scanner (Big Bore, Philips Healthcare, Eindhoven, the Netherlands) and 3-mm slices through the region of interest. The patients lay in a supine position with both arms overhead on a wing board and their legs resting on a knee support. A 6-MV photon beam from Elekta Synergy or Axesse Linac (Elekta, Stockholm, Sweden) was used for the treatment. The linac was equipped with an electronic portal imaging device based on the panels of a Si detector (PerkinElmer XRD 1640 AL5, Elekta, Crawley, UK), operating as two-dimensional (2D) photodiode arrays, an xVi CBCT, and a HexaPOD robotic couch. A CBCT was performed during the first therapy session, and thereafter, it was performed twice a week, with a field of view encompassing the external contour of the patient. The CBCT protocol that was used for the acquisition consisted of a 360° gantry rotation, with 120 kVp and a

mean of 0.20 mAs/frame. The couch was moved into the correct position after the CBCT alignment process was completed. The patients' pre-treatment plan verification was performed by irradiating a 2D array (MatriXX Evolution, IBA Dosimetry, Schwarzenbruck, Germany). The measured and calculated planar dose distributions were compared using the gamma analysis, with a distance of 3 mm to agreement and 3% dose-difference end points.

The study was reviewed and approved by the ethics committee of the Sichuan Cancer Hospital (reference number SCCHEC-02-2018-006). Patients participating in the study provided verbal informed consent.

Treatment planning

An experienced radiation oncologist defined the target that consisted of a thoracic wall with regional lymph nodes, including the internal mammary, axillary, and supraclavicular regions. The delineations of target and organs at risk (OARs) were determined based on the breast cancer atlas for the radiation therapy planning consensus definitions from the Radiation Therapy Oncology group.[21,22] The whole heart and pericardium were contoured, starting from just below the left pulmonary artery, ending at the diaphragm, and excluding the great vessels for uniformity and simplification.[23] In all the CBCT scans, the entire heart was contoured by the same radiation oncologist using the same window level that was used for the planning CT. VMAT treatment plans, consisting of one or two arcs, were performed using Pinnacle^{TM} Version 9.10 software (Philips Medical Systems, Eindhoven, the Netherlands). Dx% was defined as the dose (in Gy) received by x% of the volume and Vy as the volume (in percentage) that receive y Gy. We aimed to achieve a final goal, delivering at least 95% of the prescribed dose to at least 95% of the planning target volume (PTV; D95% >47.5 Gy), with no more than 5% of the PTV covered by a dose that exceeded 105% (D5% <52.5 Gy). This was completed while ensuring that the OAR doses remained as low as achievable, particularly for the heart (V25Gy <10%) and for the homolateral lung (V20Gy <20%).

Use of CBCTs for dose evaluation

The CBCTs were acquired using a field of view (FOV) that included the external contour of the patient to an accurate CT-CBCT registration and to have a meaningful dataset for a dose calculation. The scan period of 120 s including several respiratory cycles (>15) and cardiac cycles (>100) ensure avoidance of the influence of respiratory and cardiac movements.[24] The first CBCT rigidly registered with the planning CT, considering and taking into account the shift that was applied to the treatment isocenter during online correction, and guided by a bony match that was used for the calibration procedure. For each patient, a personalized CBCT density table was obtained, using the CBCT calibration tool SOFTDISO (SOFTDISO, V1.1, Best Medical Italy, Chianciano, Italy),[25,26] and uploaded into the Pinnacle^{TM} (Philips Medical Systems) treatment planning software to evaluate the delivered dose. The CBCT density assignment was based on the relative electron density that overrides of regions of interest to populate CBCTs with density values.[27] To validate the use of calibrated CBCT for the treatment planning calculation, the CT and CBCT scans of an anthropomorphic phantom were acquired using the same parameters that were set in the clinical routine; the left lung, heart, contralateral breast, and thoracic wall regions of interest (ROI) were contoured in each dataset.

A standard VMAT treatment plan was calculated based on the phantom CT and CBCT images, and the comparison of the ROI dose–volume histogram (DVH) were used to assess the accuracy of the CBCT calculation. The results obtained were within a mean dose difference of 0.3 Gy (range, 0.2–0.7 Gy) and a mean % volume difference of 1.0% (range, 0.5%–1.7%), and were considered to be acceptable for validating the accuracy of the calculation on calibrated CBCT. For each patient, the treatment plan was recalculated based on the CBCTs that were acquired along the treatment to verify the reproducibility of the DVH dosimetric parameters that were obtained. CBCT-based contours that were acquired before each fraction were used for the DVH comparison. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 19.0; IBM, Armonk, NY, USA). A two-sided paired *t*-test was used when the datasets were normally distributed, and otherwise, the datasets were compared using the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered to be statistically significant.

Comparison of planned and delivered doses

The dose planned (calculated based on the planning CT) was compared with the dose delivered (calculated on the first calibrated CBCT). DVH cut-off points were used for the dose comparison, particularly for the heart volume (Vol). The mean dose (Dmean), V25Gy, V10Gy, and V5Gy were evaluated, and Dmean and the maximum dose (Dmax) were used for the contralateral breast. Finally, Dmean and V20Gy were used for the left lung, while D95% was used for the target.

Results

Patients

Seventeen women who underwent a mastectomy for left-sided breast cancer and who underwent post-operative radiotherapy of the chest wall and regional nodes at our hospital between November 2017 and January 2018 were enrolled into this retrospective study. The patients' ages ranged from 32 to 63 years, with a median of 49 years.

Dosimetric parameters from the planning CT

All the plans that were calculated based on the planning CT achieved the target clinical demand, especially D95% >48.7 Gy and D5% <52.3 Gy. Mean and maximum doses for the contralateral breast were 3.6 Gy (range, 2.2–6.8 Gy) and 7.0 Gy (range, 5.1–13.6 Gy), respectively. For the ipsilateral lung, the mean dose was 11.6 Gy (range, 7.8–14.1 Gy), and V20Gy of the ipsilateral lung was at 20.0% (range, 12%–25%). The dosimetric parameters for the heart that were obtained on the planning CT are presented in Table 1.

Dosimetric parameters from the CBCTs

The DVH dosimetric parameters of the heart V5Gy, V10Gy, V25Gy, and Dmean and the heart volume, which were obtained per patient over the different CBCTs that were acquired throughout treatment, showed no statistical differences. Figure 1 summarizes the results that were obtained per patient regarding the reproducibility of the DVH heart dosimetric parameters that were obtained from the planning calculation on the CBCT scans that were acquired throughout treatment. There were no significant differences for V5Gy, V10Gy, V25Gy, and the Dmean. Moreover, heart volumes for each patient were similar among the

Table 1. Dose volume histogram mean dosimetric parameters for the heart, which were calculated using planning computed tomography scans for 17 patients.

	Volume (cm^3)	V5Gy (%)	V10Gy (%)	V25Gy (%)	Dmean (Gy)
Mean	543 ± 70	70.2 ± 17.3	26.2 ± 17.8	4.6 ± 3.3	9.1 ± 2.6
Median	539	73.5	22.1	3.7	8.5
Range	426–662	40.3–97.8	3.3–67.5	0.7–11.7	5.4–14.9

VxGy, volume receiving x Gy; Dmean, mean dose

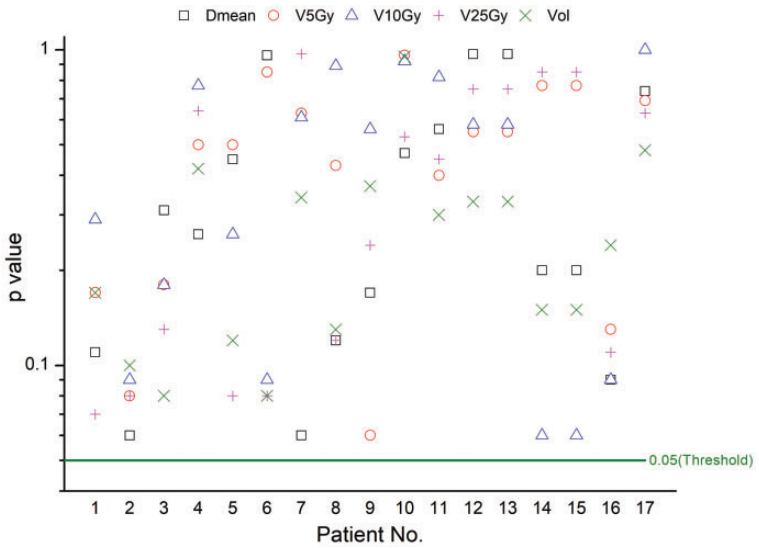

Figure 1. P-values obtained for the DVH parameters (Volume, V5Gy, V10Gy, V25Gy, Dmean) calculated using the repeated CBCTs that were acquired throughout the treatment in each patient. The continuous line represents the threshold for a significant difference ($p < 0.05$).
CBCT, cone-beam computed tomography; DVH, dose volume histogram; Dmean, mean dose; VxGy, volume receiving x Gy.

CBCT images, and there were no significant differences.

DVH comparison of the planning CT and CBCT

The mean absolute difference that was obtained per patient between the heart DVH dosimetric parameters that were calculated based on the CBCT and the corresponding parameters that were calculated based on the planning CT are presented in Table 2. The absolute difference was obtained by subtracting the dosimetric parameter that was obtained from the CBCT calculations from the corresponding calculated parameter from the planning CT.

For each patient, the volumes of the heart that were identified on the first CBCT were significantly larger compared with the planning CT scans (576 ± 79 cm^3 vs. 543 ± 74 cm^3; $t = -6.71$, $p = 0.001$), with a mean increase of 6%. This discrepancy impacted the dosimetry of the heart for 4 of 17 patients. In particular, V25Gy (%) and Dmean that were calculated based on the CBCT were higher compared with those calculated based on the CT, with an

Table 2. Mean absolute difference between the heart DVH dosimetric parameters calculated based on the CBCT and those calculated based on the planning CT.

Patient	Vol (cm^3)	Dmean (Gy)	V5Gy (%)	V10Gy (%)	V25Gy (%)
1	+4.5% (625.0)	+0.3 (12.2)	+1.6 (91.6)	−0.1 (53.8)	+1.4 (6.5)
2	+9.8% (506.0)	+0.3 (5.4)	+0.4 (40.3)	+0.9 (6.9)	+0.3 (0.7)
3	+4.5% (499.6)	+0.1 (5.7)	−0.1 (45.0)	+0.4 (11.7)	+0.3 (0.9)
4	+5.1% (633.0)	**+1.1 (14.9)**	−1.4 (97.8)	−0.7 (67.5)	**+3.3 (10.8)**
5	+5.7% (627.2)	**+2.2 (11.9)**	−0.1 (75.5)	+0.4 (39.2)	**+2.5 (10.7)**
6	+2.3% (580.4)	0.0 (6.6)	0.0 (51.7)	0.0 (17.6)	0.0 (1.7)
7	+6.1% (469.0)	**+3.1 (10.3)**	−0.8 (79.6)	−0.6 (33.4)	**+7.6 (6.8)**
8	+1.7% (614.0)	+0.2 (8.7)	−1.1 (70.4)	+0.7 (22.9)	+0.9 (4.3)
9	+4.7% (488.9)	0.0 (11.1)	−0.7 (82.7)	+1.1 (40.2)	+1.9 (5.5)
10	+3.0% (556.5)	+0.2 (9.8)	−1.3 (74.5)	−0.5 (34.6)	+0.5 (5.8)
11	+9.6% (460.2)	+0.5 (8.5)	−0.7 (73.5)	+2.0 (24.7)	+1.8 (2.6)
12	+5.7% (514.7)	+0.6 (6.8)	+1.1 (51.3)	+2.0 (15.2)	+1.4 (3.0)
13	+10.5% (426.7)	**+3.4 (12.1)**	−1.9 (94.1)	−0.1 (45.3)	**+4.1 (8.3)**
14	+8.8% (490.7)	+0.3 (7.5)	−0.6 (83.8)	+1.7 (11.9)	+0.7 (0.8)
15	+6.5% (548.9)	+0.3 (7.7)	+0.3 (62.8)	+1.2 (17.7)	+0.9 (2.8)
16	+6.0% (538.8)	+0.3 (6.8)	+1.1 (55.5)	+1.2 (11.1)	+0.9 (2.5)
17	+13.0% (661.7)	+1.6 (8.3)	+3.9 (64.1)	+6.5 (22.1)	+3.8 (3.7)
Mean	6.3%	+0.9	0.0	+0.9	+1.9
Median	5.7%	+0.3	−0.1	+0.7	+1.4
Range	1.7%–13.0%	0–3.4	−1.9–3.9	−0.7–6.5	0–7.6

Note: Dosimetric reference values that were calculated based on the planning CT are in parentheses. The values that are close to the clinical threshold are in bold, and these were set by the radiation oncologist.
CT, computed tomography; CBCT, cone-beam computed tomography; DVH, dose volume histogram; VxGy, volume receiving x Gy; Dmean, mean dose.

absolute increase in the V25Gy (range, 2.5%–7.6%) and the Dmean (range, 1.1–3.4 Gy). These parameters were close to the acceptability threshold that was defined by the radiation oncologist. No significant difference was found for the PTV dose coverage (D95%, Dmean, Dmax), for the ipsilateral lung (Dmean and V20Gy), and for the contralateral breast (Dmean and Dmax), which were evaluated on the calibrated CBCT and on the planning CT.

Discussion

In our study, the recalculation of the treatment plan using CBCTs that were acquired throughout the treatment yielded reproducible DVH dosimetric parameters, and this was verified for each patient. Moreover, for every patient, the delivered dose that was calculated on the first calibrated CBCT was compared with the planned dose that was calculated using the CT. We found that the heart volume on the CBCT set was higher compared with the volume that was identified on the planning CT, confirming the findings of previous researchers.[20] However, we highlighted that this discrepancy in the heart volume impacted the heart dosimetry of almost 25% of the cases studied, giving values of Dmean and V25Gy for the heart that were close to the threshold that was identified by the radiation oncologist. It has been demonstrated that the mean dose of radiation to the heart was a predictor of the rate of major coronary events.[2] Radiation-induced cardiac toxicity can have a wide spectrum of manifestations. IHD has been studied the most because it is a leading cause of non-cancer mortality in breast cancer patients. Acute pericarditis is associated with mean doses

above 30 Gy because lower doses have a longer latency period and manifest in a broad spectrum of cardiac disorders, including IHD, which often occur 10 to 20 years post-irradiation. An increasing amount of evidence suggests that no dose is completely safe, with even 5 cGy resulting in cardiac disease.[28,29] Additionally, previous studies have demonstrated a linear relationship between the mean heart dose and the risk of IHD, which is consistently seen at a range of doses with no indication of a safe lower threshold.[2,30] Taking into account the above considerations, it is extremely important to accurately assess the dose that is administered to the heart. The use of dosimetric parameters as clinical endpoints is the gold standard in the radiotherapy routine, and therefore, any deviations that are between planned and the delivered heart dose should be subject to a radiation oncologist evaluation.

The Danish Breast Cancer Cooperative Group[31] recommends that the volume of heart that receives more than 40 Gy should be kept below 5% and the volume that is receiving more than 20 Gy should be kept under 10%. For a clinically relevant example, it has been suggested that if 5% of the heart receives 40 Gy, the risk of cardiac mortality exceeds 2%. Therefore, using calibrated CBCT images in the treatment planning evaluation can offer objective information to the radiation oncologist regarding the delivered heart dose, which will help with developing a timely adaptive plan if it is clinically required. Although the use of dosimetric parameters as a clinical endpoint is questionable, they are currently the gold standard in the clinical practice.

The results of our research should be interpreted within the insightful limitations of our study. The study involved several patients from a single institution, and the contouring on CT and CBCT scans was performed by a single radiation oncologist. Therefore, the study was not validated using a multi-institutional quality assurance program. Other uncertainties arise from the reliability of the contouring procedure that is related for single day-to-day variations in patient positioning, immobilization, organ movement,[32] and for inter-observer variation in the delineation of the heart. Because this approach is based on DVHs, which are calculated by treatment planning systems from three-dimensional (3D) imaging data of individual anatomy, the accuracy of the density table for the CBCT scans that are acquired for each patient is crucial. However, the results of our study show that discrepancies between the delivered and planned heart dose can arise for some patients and that these deviations can be highlighted in a timely manner if the CBCTs that are acquired in the clinical routine are used to evaluate the doses that are delivered to the patient. In this context, our study shows that it is necessary to ensure that the radiotherapy treatment that is outlined to minimize the dose to the heart while ensuring that good coverage of the target is maintained throughout the course of radiotherapy. Heart contouring, based on kilovoltage (kV)-CBCT, is feasible with good reproducibility. Accurate and objective dose–volume indices may be obtained for the left-side breast post-mastectomy patients using kV-CBCT to plan the VMAT radiotherapy. In our experience, CBCTs that are performed throughout the duration of the treatment are reproducible for the indicated volumes and the dose received by the OARs and targets. The heart volume and the dose that is delivered to the heart could be higher compared with the planned dose, while offering the same dose to the contralateral breast, ipsilateral lung, and the target. These results suggest that the use of CBCT imaging may be a good option to validate the heart dose in VMAT post-mastectomy irradiation.

Conclusion

The use of calibrated CBCTs that were acquired clinically can be a valid support method to evaluate the dose that is delivered to the heart in a timely manner. Objective information can support the radiation oncologist in deciding upon the possible adaptive procedures.

Declaration of conflicting interest

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