Technical note

Automatic dose verification system for breast radiotherapy: Method validation, contour propagation and DVH parameters evaluation

Jose A. Baeza, Catharina M.L. Zegers, Nienke A. de Groot, Sebastiaan M.J.J.G. Nijsten, Lars H.P. Murrer, Karolien Verhoeven, Liesbeth Boersma, Frank Verhaegen, Wouter van Elmpt *

Department of Radiation Oncology (Maastro), GROW – School for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Breast cancer
Dose guided radiotherapy
Automatic dose verification
Contour propagation

ABSTRACT

Purpose: Image guided radiotherapy (IGRT) strategies allow detecting and monitoring anatomical changes during external beam radiotherapy (EBRT). However, assessing the dosimetric impact of anatomical changes is not straightforward. In current IGRT strategies dose volume histograms (DVH) are not available due to lack of contours and dose recalculations on the cone-beam CT (CBCT) scan. This study investigates the feasibility of using automatically calculated DVH parameters in CBCTs using an independent dose calculation engine and propagated contours.

Method: A prospective study (NCT03385031) of thirty-one breast cancer patients who received additional CBCT imaging (N = 70) was performed. Manual and automatically propagated contours were generated for all CBCTs and an automatic dose recalculation was performed. Differences between planned and CBCT-derived DVH parameters (mean and maximum dose to targets, 95% volume coverage to targets and mean heart dose (MHD)) were calculated using the dose verification system with manual and propagated contours and, in both cases, benchmarked against DVH differences quantified in the TPS using manually contoured CBCTs.

Results: Differences in DVH parameters between the TPS and dose verification system with propagated contours were 1.3% to 0.7% (95% CI) for mean dose to the target volume, 0.3 to 0.2 Gy (95% CI) in MHD and 3.9% to 2.9% (95% CI) in target volume coverage.

Conclusion: The use of an independent fully automatic dose verification system with contour propagation showed to be feasible and sufficiently reliable to recalculate CBCT based DVHs during breast EBRT. Volume coverage parameters, i.e. V95%, proved to be especially sensitive to contouring differences.

Introduction

Radiotherapy effectively decreases tumor recurrence and cancer death in breast cancer patients [1–5]. To reduce long-term toxicities associated to breast radiotherapy the dose to organs at risk (OAR) should be as low as possible [1,6]. Inter-fraction differences, such as set-up errors, changes in anatomy and breathing motion, may occur during external beam radiotherapy (EBRT) of breast cancer. For instance, anatomical variations in breast tissue after breast conserving surgery (BCS) are common [7], especially volume reduction in the postoperative seroma volume [8]. Image guided radiotherapy (IGRT) strategies are used for imaging in the treatment room to: improve patient set-up, monitor anatomical changes and minimize uncertainties [8–10]. The latest development in IGRT technologies and automation of radiotherapy workflow are enabling adaptive radiotherapy [9]. Nevertheless, the lack of a straightforward relationship between anatomical and dosimetric changes could result in suboptimal information when deciding on adaptation [11].

Dose volume histograms (DVH) are commonly used to assess the impact of anatomical changes in treatment outcome and the benefit of adaptation. Still, the re-calculation of DVHs during the course of the treatment is cumbersome, as it entails manual re-delineation of the updated anatomy and dose recalculation. In this regard, automation has been referred as essential for the successful integration of a dose verification system [12].

We hypothesize that an automatic DVH-based dose verification system with automatically propagated contours is feasible, and that the accuracy is sufficient to decide regarding adaptive radiotherapy. The dose verification system aims to assist specialists with updated clinical information at minimal extra workload. The verification system uses an...
independent in-house developed dose calculation engine to calculate the DVHs from cone beam CT (CBCT) imaging acquired during the treatment course and propagated structures, and computes differences between planned and recalculated DVH parameters. The system is evaluated for adaptive radiotherapy of breast cancer patients where we assess the differences in DVH parameters derived from either the dose verification system or the TPS, with both manually and automatically propagated contours.

Methods

Patient data and treatment strategies

31 Breast cancer patients were recruited in a clinical prospective trial (NCT03385031) and included in this study. Treatments included adjuvant breast and thoracic wall RT without regional nodal irradiation. Nineteen patients were prescribed 15 fractions of 2.67 Gy to the clinical target volume (CTV-1). The remaining twelve patients were prescribed a simultaneous integrated boost (SIB) of either 20x2.67 Gy or 22x2.67 Gy to the tumor bed (CTV-2) while maintaining a constant biologically effective dose to the CTV-1 (i.e. 20x2.18 Gy and 22x2.03 Gy). Voluntary (v)mDIBH was prescribed to left-sided breast cancer patients in order to decrease the radiation dose to the heart [13].

Ten out-of-31 patients presented with seroma of at least 3 cm in diameter on the pCT, and all but one followed the non-SIB strategy. Treatment plans consisted of tangential modulated beams, complemented by an arc segment in the SIB cases.

In total Seventy CBCT scans were included in this work. Sixty-two of these CBCTs were acquired as part of this prospective study, which required their acquisition at the first and last treatment fraction, in order to monitor anatomical variations during the course of the treatment and investigate the need of decision-making systems and suitable thresholds for adaptation. Besides the mandatory CBCTs for the prospective trial, 8 additional CBCTs were acquired during standard clinical practice for various reasons mainly due to difficulties in patient positioning.

CBCT scans were stitched to their corresponding pCTs in the cranio-caudal direction, i.e. pCT slides were used to compensate for the limited CBCT field of view (FOV) information. A dedicated Hounsfield unit to electron density curve for CBCT was used to minimize the impact of the intrinsic differences between CBCT and CT in dose calculation [14].

All pCT and CBCT scans were manually contoured by clinical experts following ESTRO guidelines [15]. In addition, manual contours on pCTs, including targets and OAR, were automatically propagated to the 70 available CBCTs using a deformable registration software package (Mirada Workflow Box version 2.0, Mirada Medical Ltd, Oxford, UK).

System evaluation, dose comparison metrics and quantification of uncertainties

The clinically approved treatment plans were used to recalculate the

![Diagram](image-url)
dose on every pCT and CBCT scan in the TPS (Acuros XB, ECLIPSE, Varian Medical System, Palo Alto, CA, USA). Manual contours were used to recalculate DVHs on the planning CT and follow-up CBCT, resulting in planning DVH and follow-up DVH respectively. The differences between planning and follow-up DVH parameters calculated in the TPS (ΔTPS) were used as reference (Fig. 1).

Similarly, dose distributions were also recalculated on every pCT and CBCT scan using an in-house independent Monte Carlo based dose calculation system (called dose-guided radiotherapy (DGRT)), which was previously validated [16–18]. Differences in DVH parameters between pCT and CBCT were calculated using manual contours with the independent dose calculation algorithm and referred to as ΔDGRTmanual. Also, differences in DVH parameters using automatically propagated contours, from the pCT to the CBCT scans were computed and referred to as ΔDGRTprop (Fig. 1).

ΔTPS values were compared with ΔDGRTmanual to evaluate the consistency between both dose calculation algorithms. Furthermore, ΔTPS was compared with ΔDGRTprop to analyze the impact of propagated contours in DVH parameter. For simplicity, ΔDGRTmanual and ΔDGRTprop are commonly referred to as ΔDGRT.

The DVH parameters evaluated were the mean dose to the primary target lesion (CTV-1: Dmean), and to the boost volume when present (CTV-2: Dmean), the volume covered by 95% of the dose prescribed to the target (CTV-1: V95%) and boost (CTV-2: V95%), the mean heart dose (HEART: Dmean) and the maximum dose to the patient (PATIENT: Dmax). Clinical target volumes (CTV) were chosen for treatment verification for being purely anatomical volumes that need to be ultimately irradiated.

Contour comparison metrics

Dice similarity coefficient (DSC) [19], and Hausdorff distances (HD) [20,21] were used to compute volume similarities between manual and automatic contours. Specifically, in this study distances between contours were computed using the mean slice-wise HD.

Furthermore, the relationship between contour dissimilarity and differences in DVH parameters was investigated: Contour comparison metrics between manual and propagated follow-up contours were correlated with differences in DVH parameters (ΔDGRTmanual minus ΔDGRTprop).

Statistical analysis of DVH parameters

To quantify differences between TPS and the dose verification system, the mean and standard deviation of the differences in DVH parameters were calculated, and the 95% confidence interval presented. Where appropriate Pearson’s correlation coefficients are calculated [22].

Graphically, the relationship between differences in DVH parameters was represented via scatter plots with identity lines, and bar plots with probability distribution estimations.

Results

Fig. 2 shows the correlation between differences in DVH parameters calculated with the TPS (ΔTPS) and with the independent dose verification methods (ΔDGRT) for every available CBCT.

Pearson’s correlation of DVH differences calculated using both

Fig. 2. Overall correlation between ΔTPS and ΔDGRT for all DVH parameters. Above, DVH differences calculated using manual contours for the follow-up DVHs (i.e. ΔTPS versus ΔDGRTmanual). Below, DVH differences calculated using propagated contours for the follow-up DVHs (i.e. ΔTPS versus ΔDGRTprop). Differences are given in percentage to the TPS values and zoomed insets are shown on the right.
manual and propagated contours for the follow-up DVHs was high (0.987, \(p < 0.00001\) and 0.947, \(p < 0.00001\), respectively).

Using the same contours for both calculation methods represents the differences between dose calculation algorithm (upper Fig. 2), which showed a maximum standard deviation of 1.5%, with the exception of mean heart dose (3.4%). Differences between ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) increased compared to the manual contours. These differences are most pronounced for the V95% of the targets (CTV-1 and CTV-2) with standard deviations of 1.7% and 3.6% respectively. Differences in maximum dose between ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) (lower Fig. 2), and ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) manual (upper Fig. 2) are identical, as the maximum dose location was inside both contours.

The comparison between propagated and manually delineated contours, resulted in Dice similarity coefficients of 0.92 ± 0.027 for CTV-1, 0.77 ± 0.056 for CTV-2 and 0.92 ± 0.017 for heart; and mean slice-wise HD of 0.96 ± 0.29 for CTV-1, 1.10 ± 0.26 for CTV-2 and 1.36 ± 0.28 for heart. Scatter plots relating contour dissimilarities to DVH parameter differences showed no strong correlations and are provided in the supplementary material.

Fig. 3 and Fig. 4 show the distribution of differences between ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) for CTV-1 mean dose, and V95%. Differences in mean dose to CTV-1 are −0.9% to 0.7% (95% CI) for manual contours and −1.3% to 0.7% (95% CI) for propagated contours. Differences in 95% volume coverage of CTV-1 are −2.1% to 1.9% (95% CI) for manual contours and −3.9% to 2.9% (95% CI) for propagated contours.

The distribution plots for the other DVH parameters (i.e. CTV-2: Dmean, CTV-2: V95%, HEART: Dmean and PATIENT: Dmax) are provided in the supplementary material.

Table 1 presents the mean and standard deviations for the DVH parameters of CTV-1: Dmean, CTV-2: Dmean, CTV-1: V95%, CTV-2: V95%, HEART: Dmean, PATIENT: Dmax, in relative values, showing consistency between dose calculation methods with standard deviations of a maximum of 1% for mean dose to the targets.

Table 1 shows that the introduction of propagated contours to calculate the follow-up DVH, ∆\(\text{DGRT}\), increased the differences with the ∆\(\text{TPS}\), with respect to ∆\(\text{DGRT}\) manual, for all DVH parameters. Nevertheless, the accuracy (95% CI) for the mean dose values remained high, −1.3% to 0.7% for CTV-1: Dmean, −2.3% to 1.7% for CTV-2: Dmean and −0.28 Gy to 0.2 Gy for HEART: Dmean. Volume coverage parameters (V95%) showed a lower accuracy (95% CI) when using propagated contours, i.e. −3.9% to 2.9% for CTV-1 and −7.9% to 6.5% for CTV-2.

While relative differences in mean heart dose are high (−4% to 9.6% for the 95% CI for ∆\(\text{DGRT}\) manual) and sensitive to the usage of propagated contours (−20.9% to 15.5% for the 95% CI for ∆\(\text{DGRT}\) prop). Absolute differences in mean heart dose showed less variation for both ∆\(\text{DGRT}\) manual (−0.05 Gy to 0.11 Gy for the 95% CI) and ∆\(\text{DGRT}\) prop (−0.28 Gy to 0.2 Gy for the 95% CI).

**Discussion**

We developed a fully automatic dose verification system based on the recalibration of DVH parameters for breast EBRT and presented the analysis of uncertainties of DVH parameters derived from dose verification with manual and automatically propagated contours.

The results of this study show that differences in DVH values between the TPS and our dose verification system are consistent when using the same manual contours in both systems. These differences increased moderately when introducing automatically propagated contours to our dose verification system. Depending on the specific organ at risk or target volume, different uncertainties are to be expected. This should be known before implementing alternative or automatic dose recalculation algorithms in clinical routine.

Despite the fact that several commercial solutions for automatic (re-)contouring have become available in the last years, the validity of propagated contours still needs to be investigated on a case-by-case basis [23]. Automatic contour propagation may be hampered when adjacent tissues have similar densities and borders are not clearly visible, which is often the case for soft tissues and targets.

In our study we observed a high DSC (−0.9) and low mean slice-wise HD (around 1 mm), which suggest an agreement between manual and automatically propagated contours for the target volume, i.e. CTV-1, and the heart. However, for the tumor bed (CTV-2) a lower DSC was observed, probably as a result of its smaller mean size (63 cm³) compared to CTV-1 (688.5 cm³) and heart (746.5 cm³). Also, the lack of clear visual boundaries has been reported as challenging in manual delineation [24] even in the use of delineation guidelines [25] or by visual guidance of surgical clips [26]. In our study the uncertainty of CTV-2 Dmean increased only slightly from a standard deviation of 0.8% to 1%. The limited effect on dose parameters is partially due to adequate PTV margins and lack of substantial anatomical changes.

During the design and execution of the study, the maximum dose value was used for reporting. The current agreement in maximum dose differences suggests that this metric could be included in decision-making under the presented methodology. However, the maximum dose is influenced by the dose engine and image artifacts. Monte Carlo dose engines are known to be affected by statistical noise, which may artificially increase the maximum dose to a single pixel. The use of doses to small volumes, e.g. a D0.03 cc or a D1cc, is recommended instead of single pixel values for future works.

Volume coverage parameters, i.e. V95%, showed a relatively lower consistency between ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) prop. Volumes receiving a certain dose are highly sensitive to variations in dose distributions, which makes them attractive for decision-making but sensitive to noise.

![Fig. 3. Correlation between ∆\(\text{TPS}\) and ∆\(\text{DGRT}\) values for the mean dose to the CTV-1 (left) and the CTV-1 vol covered by 95% of its prescription dose (right). Extracted from Fig. 2.](image-url)
Unfortunately, our data suggests that their accuracy may not be sufficient for some decision-making applications, resulting in 95% CI of 3.9% to 2.9% for CTV-1: V95% and 7.9% to 6.5% for CTV-2: V95%.

Limitations of this study are that 1) none of the patients included in the prospective study were adapted due to anatomical variations, which may be due to the relative low incidence of adaptions in breast cancer (3% in 2016 at our clinic [27]) compared to our sample size of 31 patients. A wider cohort including patients with more obvious anatomical differences would increase the reliability of these results as the contour propagation system would have been exposed to more significant anatomical changes and the differences between dose distributions could have arisen higher deviations. 2) The intrinsic differences between CT and CBCT images and their impact in the dose calculation. These differences, which are outside the scope of this work, can vary notably between vendors [14], but had limited impact in our previous work comparing CBCT versus re-CT imaging in breast cancer patients [27]. 3) The craniocaudally stitching of the CBCT in the CT may influence the dose calculation, affecting especially OAR that may not be contained to the CBCT FOV.

To conclude, a fully automatic dose verification system based on differences in DVH parameters has been presented. The verification system, which does not require extra clinical workload, aims to assist clinical specialists in decision-making for breast cancer treatment adaptation. Careful manual review of dose distributions and propagated contours on CBCT scans is recommended when significant DVH changes are reported.

Disclosure statement
MAASTRO has research agreements with Varian Medical Systems.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2022.03.017.

References
[1] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Early Breast Cancer Trials Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–106.
[2] Early Breast Cancer Trials Collaborative Group E. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death:
meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet. 2011;378(9797):1707–16.

[3] McGale P, Taylor C, Coorey C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Elsevier; 2014.

[4] Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001;345(19):1378–87.

[5] Smith BD, Bellon JR, Blitzblau R, Freedman G, Halasy M, Hahn C, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Practical Radiat Oncol 2018;8(3):145–52.

[6] Taylor C, Coorey C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017;35(15):1641–9.

[7] Alderliesten T, Heemskerken WD, Betgen A, Topolejuk R, Elkhuizen PHM, van Vliet-Vroegindeweij C, et al. Breast-shape changes during radiation therapy after breast-conserving surgery. Phys Imag Radiat Oncol 2018;6:71–6.

[8] Yang T-I J, Elkhuizen PHM, Minkema D, Heemskerken W, van Mourik AM, Cancer J, et al. Clinical factors associated with seroma volume reduction in breast-conserving therapy for early-stage breast cancer: a multi-institutional analysis. Int J Radiat Oncol Biol Phys 2010;76(5):1325–32.

[9] Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nat Rev Clin Oncol 2012;9(12):688–99.

[10] Betgen A, Alderliesten T, Sonke J-J, van Vliet-Vroegindeweij C, Bartelink H, Remeijer P. Assessment of set-up variability during deep inspiration breath hold radiotherapy for breast cancer patients by 3D-surface imaging. Radiother Oncol 2013;106(2):225–30.

[11] Moller DS, Khalil AA, Knapp MM, Hofmann L. Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. Radiother Oncol 2014;110(3):517–22.

[12] Olairegui-Ruiz I, Beddar S, Greer P, Jornet N, McCurdy B, Paiva-Fonseca G, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Elsevier; 2014.

[13] Brouwers PJAM, Lustberg T, Borger JH, van Baardwijk AAW, Jager JJ, Alderliesten T, Heemsbergen WD, Betgen A, Topolnjak R, Elkhuizen PHM, van Vliet-Vroegindeweij C, Bartelink H, Horiot J-C, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, McGale P, Taylor C, Correa C, Cutter D, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017;35(15):1641–9.

[14] de Smet M, Schuring D, Nijsten S, Verhaegen F. Accuracy of dose calculations on kV cone beam CT images of lung cancer patients. Med Phys 2016;43(11):5934–41.

[15] Offersen BV, Boerma LJ, Kirkove C, Hoë S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiotherapy of early stage breast cancer. Radiother Oncol 2015;114(1):3–10.

[16] Fippel M. Fast Monte Carlo dose calculation for photon beams based on the VMC electron algorithm. Med Phys 1999;26(3):1466–75.

[17] Baeza JA, Wolfs CJA, Nijsten SMJG, Verhaegen F. Validation and uncertainty analysis of a pre-treatment 2D dose prediction model. Phys Med Biol 2018;63(3):035033.

[18] van Elmp JWC, Nijsten SMJG, Schiffeleers RFH, Dekker ALAJ, Mijnheer BJ, Lambin P, et al. A Monte Carlo based three-dimensional dose reconstruction method derived from portal dose images. Med Phys 2006;33(7Part1):2426–34.

[19] Dice LR. Measures of the amount of ecologic association between species. Ecology 1945;26:297–302.

[20] Atallah MJ. A linear time algorithm for the Hausdorff distance between convex polygons. Inform Process Lett 1983;17(4):207–9.

[21] Grünbaum B, Klee V, Perles MA, Shephard GC. Convex polytopes; 1967.

[22] Martin Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;2(8476):307–10.

[23] Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: report of the AAPM Radiation Therapy Committee Task Group No. 132. Med Phys 2017;44(7):e43–76.

[24] Li XA, Tai A, Arthur DW, Buchholz TA, Macdonald S, Marks LB, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG Multi-institutional and Multiobserver Study. Int J Radiat Oncol Biol Phys 2009;73(3):944–51.

[25] van Mourik AM, Elkhuizen PHM, Minkema D, Duppen JC, van Vliet-Vroegindeweij C. Multinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. Radiother Oncol 2010;94(3):286–91.

[26] Coles CE, Harris EJ, Donovan EM, Bliss P, Evans PM, Fairfoul J, et al. Evaluation of implanted gold seeds for breast radiotherapy planning and on treatment verification: a feasibility study on behalf of the IMPORT trials. Radiother Oncol 2011;100(2):276–81.

[27] Zegers CML, Baeza JA, van Elmp W, Murrer LHP, Verhoeven K, Boersma L, et al. Three-dimensional dose evaluation in breast cancer patients to define decision criteria for adaptive radiotherapy. Acta Oncol 2017;56(11):1487–94.