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Original Article

Reducing the dose of gadolinium-based contrast agents for DCE-MRI guided SBRT: The effects on inter and intra observer variability for preoperative target volume delineation in early stage breast cancer patients

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ABSTRACT

Background and purpose: This study aimed to determine the effects of reducing the dose of contrast agent (CA) in a DCE-MRI scan on inter- and intra-observer variability in the context of MRI-guided target volume delineation for stereotactic body radiation therapy of early stage breast cancer patients. This is in hopes of reducing risks to patients due to findings of residual CA in brain and bone.

Materials and methods: Twenty-three patients receiving neoadjuvant radiation therapy were enrolled. Five observers delineated the gross target volume (GTV) using DCE-MRI for guidance. 14/23 patients received the full clinical dose of CA and 9/23 received half. Clinical target volumes (CTV) were created through a 0.5 cm uniform expansion. Several metrics were used to quantify the inter and intra-observer reliability including differences in delineation volume and the reliability coefficient.

Results: There were no significant differences in the volume, though half contrast patients had a lower median for both the GTV and CTV (difference of 0.26 cm^3 and 1.27 cm^3, respectively). All indicated a high degree of agreement between and within observers for both dose groups. However, the full dose group had a greater inter-observer variability, most likely due to the full CA causing more pronounced enhancement in the periphery.

Conclusions: Reducing the dose of contrast agent did not significantly alter inter- or intra-observer variability. These results have prompted our centre to reduce the dose of gadolinium in all patients enrolled in the SIGNAL trial.

The current standard of treatment for early stage breast cancer patients opting for breast conserving therapies (BCT) is lumpectomy followed by whole breast radiotherapy delivered over several weeks [1]. This treatment time can be prohibitively long for many patients. Accelerated partial breast irradiation (APBI) techniques can reduce treatment time by treating a smaller volume and increasing the dose per fraction (hypofractionate). Long-term studies [2–4] have found equivalent tumour control and recurrence compared to whole breast radiotherapy. Further studies have shown that performing neoadjuvant to lumpectomy can reduce treatment volumes, allowing further dose escalation [5,6].

An important aspect of APBI is target volume delineation [7,8] which relies heavily on image quality. Previous investigations [6] have focused on adjuvant external beam APBI, which use the lumpectomy cavity as the target volume and can be visualized without contrast. Our centre is currently enrolling early-stage breast cancer patients in a neoadjuvant stereotactic radiation therapy trial [9] which requires use of a contrast agent as there is no endogenous contrast at the tumour site. Patients are receiving a dynamic contrast enhanced MRI using a gadolinium-based contrast agent (GBCA). This image sequence is being used for tumour

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guided delineation as well as to assess patient response to radiotherapy.

Contrast enhanced (CE) techniques involve injecting a contrast agent which causes the tumour to appear hyperintense. This technique can be performed with CT or MRI. Previous studies have shown CE-MRI to be superior to standard CT imaging in the context of breast cancer [7]. For example, in one study [10] comparing contouring the gross target volume (GTV) on CE-CT versus CE-MRI in neoadjuvant BCT, observers missed the tumour in 2/14 patients. They also found a significant reduction in GTV definition variability across observers.

While the use of CE-MRI has increased, recent research has provided evidence for longer term retention of gadolinium in body tissues [11,12]. This depends on the specific class of GBCA, with higher levels of retention for those GBCAs having ligands with a linear configuration, compared to those where the ligand surrounds the gadolinium (macrocyclic). It also appears to depend on the dose a patient has received. It is not known what effect the retention causes and no pathological risks have been identified from these recent findings. However, the association between nephrogenic systemic fibrosis and GBCAs was not discovered for decades in renally impaired patients [12] and so more time is needed to comprehensively evaluate what this retention may cause, though there are known pathological issues associated with heavy metal toxicities including free gadolinium [12]. It has yet to be established in what form the retained gadolinium exists in the body. In response to these findings, the European Medicines Agency and Health Canada have indicated that the agents found to be more stable (macrocyclic) can still be used but with the lowest possible doses [13,14], while the FDA is requiring that patients be informed of the currently unknown risk [15]. As such, it is important to investigate methods of minimizing exposure and, hence, any potential health risk to patients. One way would be to reduce the dose of GBCA given to patients per scan [12]. However, in the context of radiotherapy delivery (particularly in stereotactic body radiation therapy (SBRT) techniques), we must ensure visibility of the tumour is not compromised by reducing the contrast dose.

We hypothesize that reducing the concentration of gadolinium to half of the standard clinical dose will not significantly affect gross target volume as delineated by expert observers. The objective of this study was to quantitatively assess the efficacy of target volume delineation on CE-MR images obtained with half the standard dose of GBCA compared to full dose GBCA for early stage breast cancer patients. Specifically, the quantitative measures of efficacy were based on the inter- and intra- observer variability, volume of delineation, and centre of mass of the delineation.

Methods

Patients

Data were collected from a phase I/II clinical trial conducted at the London Regional Cancer Program [9]. Inclusion and exclusion criteria are included in the clinical trial document [9]. Patients enrolled in the study had a surgical clip placed adjacent to the tumour at the time of the initial biopsy. A subset of the latest 23 patients within the SIGNAL trial at the time of the experiment were included in this study.

Image acquisition

Patients were imaged prone with their ipsilateral arm raised above their head to mimic the radiotherapy treatment positioning. For radiotherapy, this was done to minimize the impact of respiratory motion and reduce inclusion of normal tissue. The contralateral breast was compressed so only the ipsilateral breast was in the coil and the prone breast board. Patients received a planning CT scan (Brilliance Big Bore, Philips Medical Systems, Best, The Netherlands) with a prone board (Aktina Medical, New York, USA) and a DCE-MRI scan on a Siemens Biograph mMR 3T-PET/MRI system (Siemens Medical, Munich, Germany) with a four channel prone breast coil [16].

Three-dimensional fat suppressed fast flow angle shot (FLASH) images were acquired with the following parameters: TR = 4.1 ms, TE = 1.5 ms, flip angle = 15°, spatial resolution = 1.0 × 2.1 × 2.1 mm interpolated to 1.0 × 1.0 × 1.2 mm, field of view = 38 × 38 cm, slab thickness = 13.4 cm. The DCE series contained a pre-contrast image and 28 post-contrast images as the clinical trial protocol also includes kinetic analysis to assess tumour response using non-invasive perfusion biomarkers [9]. The GBCA used was gadobutrol (Gadavist®). Of the 23 patients, 14 received a clinical dose of 0.1 mmol/kg with an injection rate of 2 ml/s. Following the findings of gadolinium retention, we decided to reduce the dose to half the standard dose, so patients imaged before and after radiotherapy would only receive a standard dose in total and not increasing their risk for a research only scan (the post-radiation treatment). Thus far, 9 patients have received half the clinical dose (0.05 mMol/kg) with an injection rate of 0.75 ml/s. This was chosen to match the injection protocol to a population derived arterial input function for DCE-MRI kinetic analysis (outside objective of this study) [17]. A late post-contrast MRI that visually had the highest signal in the tumour was chosen by an expert external to the study to aid the observers in contouring the tumour.

Target volume delineation

The patient data from both groups were pooled and randomly ordered for contouring. The CT and late post-contrast CE-MRI scan (that visually showed peak intensity) were fused and manually aligned by a single expert external to this study in MIM (v6.8.0, Mim Software, Cleveland, USA) such that the tumour was in the same location. Five radiation oncologists (ROs), all of whom had enrolled patients on APBI trials, including the SIGNAL trial and RTOG 0413, were asked to delineate the GTV on the CT image with the aid of the fused CE-MRI and the embedded surgical clip. The CT was displayed in grayscale with a soft tissue window/level and the MRI displayed as a heatmap overlaid on the CT with a window/level determined by an expert external to the study and ensured that the window/level settings used were reasonable for all patients. Observers were not allowed to change the display map for the CE-MRI or the window/level though they were able to change the transparency of the CE-MRI heatmap from 0 (only CT shown) to 1 (only CE-MRI shown). The ROs were blinded to each others' contours. After at least 1 month, ROs were asked to recontour the images (randomized again), blinded to their first contouring session and given identical delineation instructions. In accordance with the SIGNAL trial [9], clinical target volumes (CTV) were created by adding a 0.5 cm margin to the GTV.

Data analysis

The contours were exported from MIM as RTStructs and imported into MATLAB as binary label maps. All metrics were calculated using MATLAB v. 2017a (Mathworks Inc., Natick, MA) using in-house programs.

Reporting of multiple metrics is required for accurate characterization of data and comparison to previous results [18]. We chose to use metrics that fall under different categories of characterizing observer agreement: descriptive metrics, spatial or overlap metrics, and statistical metrics [18]. The descriptive and spatial metrics

used the first contouring session for analysis [19]. The statistical methodology for comparing groups for each metric is described in the statistical section.

For the descriptive metrics, we compared the volumes of the contours and the coefficient of variation (CV). The mean, median, standard deviation, and range of the volume contoured across observers for each patient and both groups were calculated. The CV was calculated for each patient and is defined as the standard deviation of the volume across observers normalized by the average volume across observers [20].

We used three spatial measures to assess differences in contours between observers: the conformity index (CI), the generalized conformity index (CI_{gen}), and the distances between centres of mass (dCOM). The CI is a simple measure of overlap and is defined as [10]:

$$CI_{ij} = \frac{V_i \cap V_j}{V_i \cup V_j} \quad (1)$$

where *i*and *j*are a pair of observers and V is the volume of the contour. It has a value between 0 and 1 where 1 indicates perfect agreement. For each patient, CI was calculated between all pairs (10 pairs) and averaged across observers [21] and the groups statistically compared.

The generalized conformity index (CI_{gen}) can be used to compare any number of observers simultaneously and is unbiased by the number of observers included [21]. It is defined as:

$$CI_{gen} = \frac{\sum_{pairs\ ij}(V_i \cup V_j)}{\sum_{pairs\ ij}(V_i \cap V_j)} \quad (2)$$

where *i* and *j*are a pair of observers and V is the volume of the contours for those respective observers. It has the same limits as CI (0–1).

We used the distance between centres of mass (dCOM) to determine if there tended to be any difference in systematic shifts between observers. For each patient, the dCOM was calculated for each pair and was averaged across observer and the groups were statistically compared.

Finally, we assessed inter- and intra-observer variability using a statistical methodology that results in two measures termed the reliability coefficients [19,22–24]. This method allows for the concurrent assessment of inter- and intra-observer reliability using at least two successive measurements by the same set of observers. In brief, this method ascribes portions of the total variance in the volume measurement to the patients, observers, and inter-/intra-observer random error. These variances are estimated using a two-way random analysis of variance (ANOVA) [23,24]. We report the variance for each component. From the variances, the inter-observer (ρ_{inter}) and intra-observer (ρ_{intra}) reliability coefficients, defined as the proportion of the total volume variance ascribed to inter- and intra-observer effects, are reported and compared statistically. Values close to unity indicate perfect reliability.

In addition to the above metrics, we also attempted to quantify differences in the shape of contours between groups. This was done by calculating the shape circularity (SC):

$$SC = \frac{Area\ of\ Contour\ Slice}{Area\ of\ Bounding\ Circle} \quad (3)$$

This method assumes more jagged contours will occupy less space of a bounding circle than a "simple" contour. We are interested in the most jagged contour for each patient. As such, this analysis worked as follows: (1) For each expert, for each patient, average (SC_{avg}) and minimum (SC_{min}) SC across all slices was recorded, (2) for each patient, the minimum (and range) across observers was calculated for each patient for SC_{min}. In addition, the average value across observers for each patient (and standard deviation of the average values) was calculated for both SC_{avg} and SC_{min}, (3) full and half dose groups were compared statistically.

Statistics

Statistical analysis was performed using GraphPad Prism v. 6.01 (GraphPad Software, La Jolla, CA) except for the reliability coefficient analysis which was performed using SPSS v. 25 (SPSS, Inc, IBM, Armonk, NY, USA).

The descriptive, spatial and shape circularity were not normally distributed as determined by a Shapiro Wilks test and so a Mann–Whitney *U* was performed for comparison of the groups. For the reliability coefficients, we used a left-sided *F*-test with the methods outlined in Eliasziw et al. [24]. A *p*-level of 0.05 was used.

Results

Table 1 shows patient characteristics for each dose group. In the process of contouring, no expert missed the tumour for any patient, so each contour was included in the analysis. The average ± standard error of the mean post-contrast image timepoint used for the full and half dose groups was 7.30 ± 0.72 min and 7.44 ± 0.76 min respectively signifying essentially no difference in selection of the post-contrast image selected.

Fig. 1a,b shows the GTV delineations of the five observers on the CT image (grayscale) fused with the CE-MRI image (heat-map) for a representative patient from the full dose group (Fig. 1a) and the half dose group (Fig. 1b). In terms of descriptive measures of variability, Fig. 2a,b shows the volumes for each patient and Fig. 2c,d shows the CV. There was no significant difference in the volume or CV for the GTV and CTV between the full and half dose groups, though there tended to be a reduced volume in the half dose group compared to the full dose group as seen by both the mean (Fig. 2 a,b) and median values (median [range] of 0.83 [0.37–3.63]cc and 0.57 [0.29–3.33]cc for the full and half dose of the GTV, 5.95 [3.79–15.01] and 4.68 [3.34–13.65] for the full and half dose of the CTV). Additionally, there was no significant difference in the CTV between the full and half dose groups for both the GTV and CTV.

For the spatial metrics, there was a significant difference between the full and half dose groups for CI_{gen}, but no significant difference between for CI and dCOM (Table 2).

From the statistical comparison, the variability was predominantly due to patients, though there was a larger variability due to inter-observer effects for the full dose group for both the GTV and CTV, though this difference was small. This is reflected in the reliability coefficients (Table 3), which show the full dose group had 10% less inter-observer reliability than the half dose group. Following this, a sensitivity analysis was conducted to determine if there was a volume effect in the full dose group. Excluding the top four patients with the largest tumours in the full dose group and recalculating the inter-observer reliability coefficient resulted in a difference of the inter-observer reliability coefficient of approximately 5% between groups.

Table 1
Patient characteristics for the two groups.

Characteristic	Full dose group	Half dose group
Age (years)		
Median	61	69
Range	57–76	58–80
Side		
Left	7	6
Right	7	3

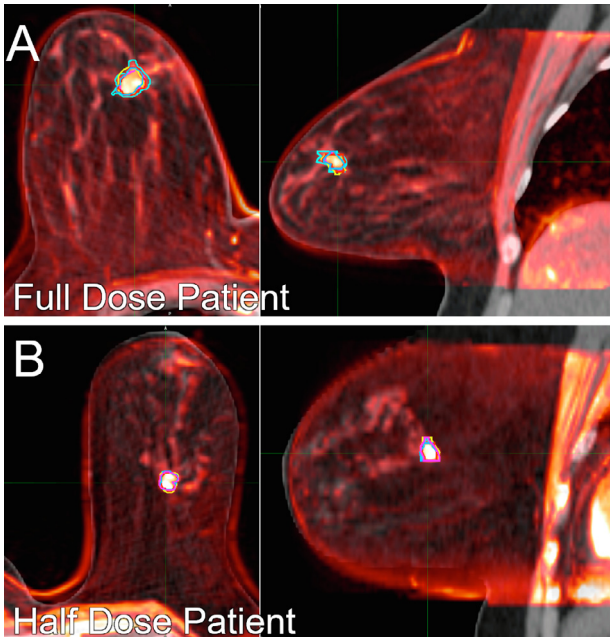

Fig. 1. 3D delineations of the five observers in the axial (left) and sagittal (right) planes for representative patients from the full dose group (A) and the half dose group (B).

Shape circularity was used to determine how round a given contour was with **higher** values indicating **rounder contours**. We found there was a statistically significant increase in the SC_{min} for the half dose group compared to the full dose group with an average ± standard deviation value of 0.48 ± 0.11 for the full dose group and 0.58 ± 0.11 for the half dose group for the case where the minimum was taken across observers, indicating contours were less round when using the full dose of contrast. However, there was no significant difference in the average value across all observers for the full dose group (0.5 ± 0.07) versus for the half dose group (0.57 ± 0.08, $p = 0.7$) for SC_{min}. For SC_{avg}, there was also no significant difference between the full dose group (0.60 ± 0.04) compared to the half dose group (0.63 ± 0.02, $p = 0.07$).

Discussion

Over the past decade, there has been a large increase in the use of MRI scanning for radiation treatment planning, particularly in the case where soft-tissue contrast is highly desirable. Accurate localization for neoadjuvant radiotherapy or screening requires the use of a GBCA as these lesions are often difficult to localize using CT alone. Due to the finding of long-term retention in brain and bone for gadolinium-based CAs, if it is possible to reduce the dose of GBCA to a patient without affecting tumour delineation, then it is imperative we do so. This study showed that it is feasible to reduce the dose of contrast given to early stage breast cancer patients while not affecting both the inter- and intra-observer variability

Apart from tumour volume delineation, CE-MRI is finding increased use in the clinical workflow for patients [25]. For example, studies have found that it has strong potential as a tool for selecting patients best suited for conserving therapies as well as a screening tool [26,27]. If CE-MRI is to be used more routinely, reducing the dose of GBCA is an important way to mitigate the deposition in brain and bone [12]. In the context of screening, it is reassuring that even in the half dose group, no targets were missed, especially since tumours included in this study were small (Fig. 2 a,b).

Regarding the reliability coefficients, an inter-observer reliability > 0.6 implies a substantial agreement and an intra-observer reliability > 0.8 implies an almost perfect agreement [22].

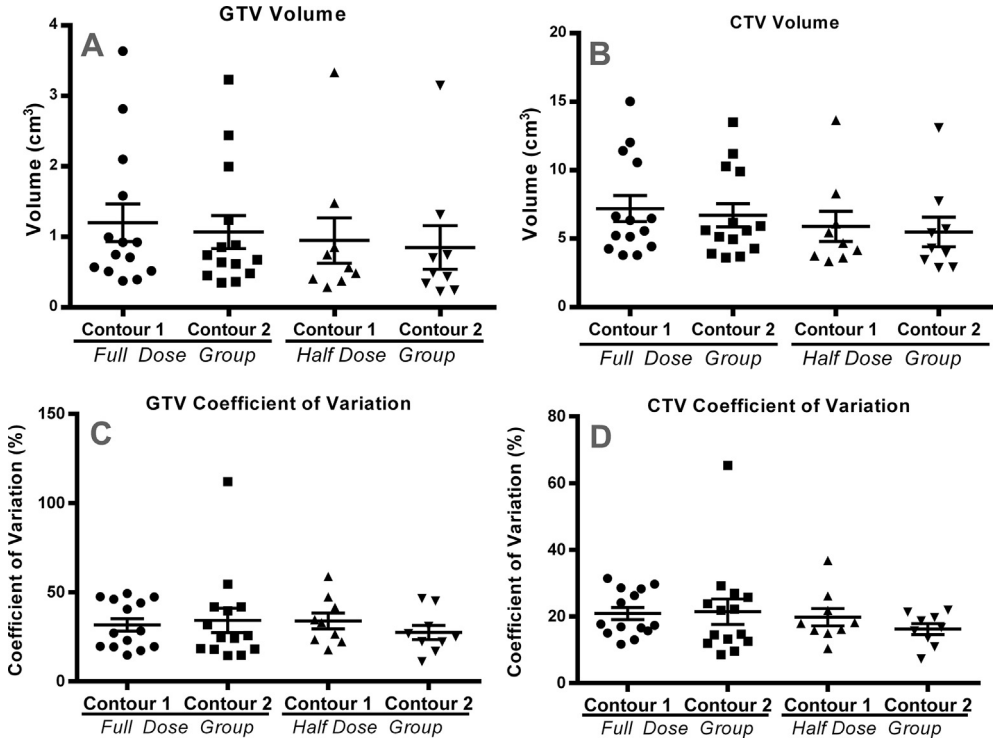

Fig. 2. Scatter plots of the volume measurements (A,B) and coefficient of variation (C,D) from each patient for the GTV (left column) and CTV (right column) for the full dose group and the half dose group. "Contour 1" and "Contour 2" represent the repeated session. The horizontal bar represents the mean volume across patients and the whiskers represent the standard error of the mean.

Table 2
Summary of the spatial metrics CI, CI_{gen}, and dCOM and significance results comparing the first contouring session for both the GTV and CTV and both dose groups. Normality was violated for most cases and so a Mann–Whitney *U* test was used. No significance was found in comparing the two groups except for CI_{gen} though the difference in median value was small.

	Full dose group		Half dose group		*P*-value
	Median	Range	Median	Range	
CI					
GTV	0.58	0.29–0.73	0.52	0.46–0.69	NS
CTV	0.73	0.60–0.81	0.72	0.65–0.79	NS
CI_{gen}					
GTV	0.61	0.49–0.62	0.66	0.61–0.69	SIG
CTV	0.73	0.65–0.74	0.78	0.74–0.79	SIG
dCOM (mm)					
GTV	1.23	0.45–2.09	1.24	0.37–2.30	NS
CTV	1.46	0.49–2.66	1.14	0.46–2.09	NS

Table 3
Inter- and intra-observer reliability coefficients for volume measurements from 5 observers and 1 repetition (2 contour sessions) for both the GTV and CTV.

		Reliability coefficients (%)		
		Full	Half	*P*-value
ρ_{inter}	GTV	82.84	91.97	0.002
	CTV	80.41	91.13	0.001
ρ_{intra}	GTV	89.94	95.94	0.103
	CTV	89.19	95.62	0.105

Importantly, using a half dose of GBCA still maintained this threshold i.e., using a half dose of contrast does not alter the inter- or intra-observer variability compared to using a full dose of GBCA.

There is scant literature on observer agreement in the setting of neoadjuvant target volume delineation. In comparing CI and CI_{gen} reported here to those previous studies, it is important to note that CI and CI_{gen} are sensitive to the overall volume of the contour [10] which makes comparing to traditional whole-breast contouring studies difficult. In any case, the values of CI for both the GTV and CTV are well within reported ranges [6,10 *see* Table 3].

The shape circularity assessment was used to try and account for the better inter-observer agreement in the half-dose group compared to the full dose group as assessed by CI_{gen} (Table 3) and the reliability coefficients – which showed a 5% increase in the half dose group after the sensitivity analysis was performed. This metric was able to detect differences between groups (using the minimum across observers) when using the slice with the maximum deviation from a circle (minimum SC value). However, averaging across observers and slices resulted in only a trend to significance, most likely due to inadequate sample size and sensitivity of the metric as it is non-specific and only assess deviation from a circle. There may be other metrics more sensitive to differences in shapes between groups.

Furthermore, other factors not considered here that may affect contour variability should be investigated. For example, the use of a heatmap for the overlaid MRI and its window/level was mostly arbitrary which will add a systematic bias to the absolute tumour volume contoured, but because the same expert set the window/level, should not have a large impact on the systematic bias of the gross target volume delineation. However, it may be more appropriate to set the window/level of the MRI based on some characteristic of the signal intensity or to overlay subtraction images (a post-contrast image – a pre-contrast image). However, doing so requires good intra-imaging session registration to avoid motion artifacts and this is not currently being done clinically at our centre. In addition, there may be a confounding effect due to different injection flow rates of the GBCA [28]. Finally, providing additional MRI sequences or imaging modalities (PET) as additional information may be beneficial.

One other notable limitation was that the data were unpaired. This makes absolute comparison between groups difficult since patient biological variability becomes a confounding factor. Furthermore, it does not allow us to make any conclusions on the accuracy of the tumour volume delineated which would require confirmation with pathological specimens. In addition, our sample size was small, though larger than other studies investigating contouring effects [10,18].

MRI-guided radiotherapy is showing increasing promise for screening and APBI techniques, though due to recent findings concerning the deposition of contrast agents in brain in bone, it is important we minimize exposure of patients to these contrast agents. The results presented here suggest it is possible to reduce the dose of contrast agent delivered to patients without significantly affecting the efficacy to delineate the volume. Further studies are needed to examine the accuracy of the volumes delineated using a half dose of gadolinium-based contrast agents. The results of this study have prompted our centre to reduce the dose of gadolinium in all patients enrolled in the SIGNAL trial.

Conflicts of interest

None.

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