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Anatomical Changes in Resection Cavity during Brain Radiotherapy

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Abstract:	Background and purpose Brain tumors are in general treated with a maximal safe resection followed by radiotherapy of remaining tumor including the resection cavity (RC) and chemotherapy. Anatomical changes of the RC during radiotherapy can have impact on the coverage of the target volume. The aim of the current study was to determine the internal margin (IM) required to compensate for potential changes of the RC, and to identify risk factors for RC changes. Materials and methods Sixteen patients treated with pencil beam scanning proton therapy between October 2019 and April 2020 were retrospectively analyzed. The RC was delineated on pre-treatment computed tomography (CT) and magnetic resonance imaging, and weekly CT-scans during treatment. Isotropic margins were applied to the pre-treatment RC (1-5 mm). The percentage of volume of the RC during treatment within the expanded pre-treatment volumes was quantified. Potential risk factors (volume of RC, time interval surgery-radiotherapy and relationship of RC to the ventricles) were evaluated using Spearman's rank correlation coefficient. Results The average variation in relative RC volume during treatment was 26.1% (SD:34.6%). A margin of 4 mm was required to cover >95% of the RC volume in >90% of patients. There was a significant relationship between the absolute volume of the pre-treatment RC and the volume changes during treatment (Spearman’s ρ=-0.644; p=0.007). Conclusion

	RCs are dynamic after surgery. An internal margin in brain cancer patients with an RC should be considered, to avoid insufficient target coverage. Future research on local recurrence patterns is recommended.
Keywords:	Neuro-oncology; Radiotherapy; Resection cavity; Anatomical changes; Internal margin
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Professor Pierre Blanchard and professor Daniel Zips
Editors-in-Chief
Clinical and Translational Radiation Oncology

Maastricht, December 20th, 2022

Dear Prof. Blanchard and prof. Zips,

We would hereby like to submit our manuscript entitled *"Anatomical Changes in Resection Cavity during Brain Radiotherapy"* for publication in Clinical and Translational Radiation Oncology.

This manuscript describes the anatomical changes of resection cavities after brain surgery during the course of brain radiotherapy. Currently, little is known about potential anatomical changes of the resection cavity during radiotherapy and the potential need for internal margins to guarantee accurate coverage of the target volume. In addition, risk factors for changes in the resection cavity are identified.

We feel that this paper will be of interest to the readers of Clinical and Translational Radiation Oncology and suitable for publication.

On behalf of all co-authors,

Sincerely,

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Highlights:

- Resection cavities (RCs) are dynamic after surgery
- RC dynamics can have a negative effect on target coverage in neuro-oncology
- A margin of 4 mm was required to cover >95% of the RC volume in >90% of patients
- The absolute pre-treatment RC volume is a risk factor for RC volume changes
- It is recommended to apply an internal margin to the gross tumor volume delineation

Anatomical Changes in Resection Cavity during Brain Radiotherapy

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Abstract

Background and purpose: Brain tumors are in general treated with a maximal safe resection followed by radiotherapy of remaining tumor including the resection cavity (RC) and chemotherapy. Anatomical changes of the RC during radiotherapy can have impact on the coverage of the target volume. The aim of the current study was to determine the internal margin (IM) required to compensate for potential changes of the RC, and to identify risk factors for RC changes.

Materials and methods: Sixteen patients treated with pencil beam scanning proton therapy between October 2019 and April 2020 were retrospectively analyzed. The RC was delineated on pre-treatment computed tomography (CT) and magnetic resonance imaging, and weekly CT-scans during treatment. Isotropic margins were applied to the pre-treatment RC (1-5 mm). The percentage of volume of the RC during treatment within the expanded pre-treatment volumes was quantified. Potential risk factors (volume of RC, time interval surgery-radiotherapy and relationship of RC to the ventricles) were evaluated using Spearman's rank correlation coefficient.

Results: The average variation in relative RC volume during treatment was 26.1% (SD:34.6%). A margin of 4 mm was required to cover >95% of the RC volume in >90% of patients. There was a significant relationship between the absolute volume of the pre-treatment RC and the volume changes during treatment (Spearman's ρ=-0.644; p=0.007).

Conclusion: RCs are dynamic after surgery. An internal margin in brain cancer patients with an RC should be considered, to avoid insufficient target coverage. Future research on local recurrence patterns is recommended.

Keywords:
Neuro-oncology; Radiotherapy; Resection cavity; Anatomical changes; Internal margin.

1. Introduction

For the majority of brain tumors, radiotherapy is part of the standard treatment. For example, standard treatment for low-grade gliomas (LGGs) consists of maximally safe resection, i.e. resection without compromising neurological function preferably gross total resection, often followed by radiotherapy and chemotherapy [1,2].

Treatment volumes have traditionally been based on protocols of landmark trials, e.g. European Organization for Research and Treatment of Cancer (EORTC) 22033-2603 [3]. Although there is currently a lack of widely accepted international guidelines on radiotherapy target volume delineation of LGG, national or institutional guidelines [4] often reflect past trial protocols, and generally suggest contouring the resection cavity (RC) as well as any residual tumor identified on T1-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) as part of the gross tumor volume (GTV). A limited isotropic margin is added to the GTV to create the clinical target volume (CTV). As an example, the Dutch radiotherapy consensus guidelines suggest an isotropic margin of 5 mm for WHO grade II gliomas and 10 mm for grade III gliomas, adapted to anatomical barriers [5]. However, little is known about potential anatomical changes of the RC during radiotherapy and therefore if the current margins are sufficient to guarantee accurate coverage of the target volume.

Factors that influence the RC during treatment could be: 1) The size of the RC; the hypothesis is that the absolute volume of the RC on the planning computed tomography (CT) scan correlates to the variability of the relative volume changes of the RC during treatment. 2) A shorter time between brain surgery and planning CT could possibly lead to anatomical changes of the RC during treatment, since for example (early) wound healing processes would still be active in those patients. 3) Contact between the RC and ventricles could be a factor for RC changes due to changes in intracerebral pressure leading to increased or decreased pressure in the RC over time [6].

The aim of the current study was to determine the isotropic internal margin (IM) required to compensate for potential anatomical changes of the RC, and to identify risk factors for RC changes of patients during brain radiotherapy.

2. Materials and methods

2.1 Patient population and imaging

Patients treated with intensity modulated proton therapy (IMPT; Mevion Hyperscan S250i) between October 2019 and April 2020 at Maastro, Maastricht, the Netherlands, were reviewed. Patients with a visible RC on the weekly CT-scans were included in this study.

All 16 included patients underwent a pre-treatment (planning) CT-scan (pCT) of the brain with a slice thickness of 1 mm (SOMATOM Drive or Confidence; Siemens, Erlangen, Germany). Additionally, a pre-treatment 3D T1-weighted neuronavigation MRI post-gadolinium contrast (pMRI) with a slice thickness of 1 mm was performed (Ingenia CX or Achieva; Philips, Best, The Netherlands). During radiation treatment, patients received cone-beam CT (CBCT) scans before administration of each fraction. Furthermore, a weekly repeat CT-scan without contrast (reCT) was performed. Thermoplastic immobilization masks (Orfit, Wijnegem, Belgium) were used during CT-scanning.

2.2 Radiotherapy delineation, planning and administration

Delineation of GTV and CTV was performed by experienced radiation oncologists specialized in neuro-oncological radiotherapy (DE, IC). The organs-at-risk (OARs) were defined according to the EPTN consensus-based atlas for CT- and MRI-based contouring in neuro-oncology [7]. The GTV and CTV were defined according to the Dutch guidelines [4,5], using a GTV to CTV margin of 0.5-1 cm depending on the tumor characteristics. Treatment schedule, dose, and if applicable adjuvant chemotherapy were also subscribed conform national guidelines [4,5,8].

Robust planning and optimization were used for IMPT planning, i.e. plan optimization was directly based on the CTV [9]. Plan objectives were: 98% of the CTV receiving at least 95% of the dose ($D_{98\%} \geq 95\%$) in the robust plan, 98% of the CTV receiving at least 94% of the dose ($D_{98\%} \geq 94\%$) in the voxel-wise minimum plan, a maximum dose (D_{max}) of 107% in ≤0.03 cm^3 in the robust plan, preferably in the CTV, and a D_{max} of <109% in ≤0.03 cm^3 in the voxel-wise maximum plan, with a mean dose (D_{mean}) to the GTV of at least 100% in the robust plan. Eclipse (Varian Medical Systems Inc, Palo Alto, California, USA) was used for delineation, and RayStation (RaySearch Laboratories AB, Stockholm, Sweden) was used for IMPT planning. Radiation treatments were administered using the Mevion S250i Hyperscan system (Mevion Medical Systems, Littleton, MA, USA).

2.3 Anatomical changes of the RCs

RCs were delineated in Eclipse on the pCT, T1-weighted pMRI, and reCTs using brain window settings (WW 120; WL 40) and high-resolution structures. All contours were evaluated with a specific focus on consistency. The reCT-scans made during treatment were rigidly registered to the pCT within Eclipse (Varian Medical Systemc Inc, Palo Alto, California, USA). These registrations allowed for the RC structures to be copied to the pCT structure set for further analysis.

The RC structures on the pCT were isotropically expanded with 1, 2, 3, 4, and 5 mm. MATLAB2020a (The MathWorks Inc, Natick, Massachusetts, USA) was used to calculate the percentage of the volume of the RC during treatment within the volume of the RC on the pCT, or within the isotropically expanded RCs as illustrated in Figure 1. RCs delineated on a reCT were compared to the RC delineated on the pCT.

The aforementioned volume percentages were used to calculate the minimal percentage of the volume of the RCs for *all reCTs per patient* contained within the original RC on the pCT and within the expanded volume per added millimeter of isotropic margin. The percentage of the volume that would be covered with the added isotropic margins for a certain number of patients, e.g. the percentage of volume covered when applying an added isotropic margin of +2 mm, for 90% of patients, was also calculated.

The absolute (in cm^3) and relative change in volume of the RCs during treatment compared to the RC on the pCT were calculated for every reCT. The relative variability was calculated using these individual relative values and the largest variability was further used for the analysis. For example, if a patient had a minimal relative volume change of -10% and a maximum relative volume change of +20%, the relative variability was 30%.

2.4 Potential risk factors

In this study we hypothesize that three factors influence the volume changes of the RC: 1) The absolute volume of the RC on the pCT; 2) The time between brain surgery and pCT in days; 3) The relationship between the RCs and the ventricles. This relationship was categorized into two categories: direct/potential contact (<0.5 cm between RC and ventricles), or no contact (>0.5 cm between RC and ventricles).

2.5 Statistical analysis

The correlation between the RC volume on pCT, the time between surgery and the pCT, and the relative change in the volume of the RCs were analyzed using Spearman's rank correlation coefficient. The relationship between the relative change in volume of the RCs and the relationship between RC and ventricle was analyzed using a Mann–Whitney U-test. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26, IBM Corporation, Armonk, New York, USA). A p-value of <0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

Sixteen consecutively treated patients with a visible RC and treated with proton therapy were included in this study. The patient characteristics are summarized in Table 1.

3.2 Anatomical changes of RCs

Relative change in volume of the RC during treatment ranged from -58.6% to 79.3%, with 35/78 (44%) RC measurements being positive, i.e. an increase of the RC volume on the reCT. The average variation in relative resection volume during treatment was 26.1 ± 34.6% (range: 2.0 – 137.9%). An example patient is shown in Figure 2.

Expanding the RC structures with an isotropic margin substantially increased the percentage of the volume of the RC on the reCTs that were within the expanded volume of the RC (Figure 3). Additionally, two (visual) 'outliers' could be identified.

A dose of at least 95% of the nominal dose or higher is preferred in at least 90% of the patients, or alternatively 85% of the patients, which results in excluding the 2 outliers. The volume covered by expanding the RC with the additional isotropic margins are detailed in Table 2 for both 90% and 85% of patients. An objective of covering 95% of the volume results in a required additional isotropic margin of 4 mm and 3 mm to compensate for 90% and 85% of patients, respectively. Results in terms of volume percentage covered for all patients and all reCTs are visualized in Figure 4.

3.3 Potential risk factors

The three risk factors were evaluated for RC changes. Firstly, the absolute volume of the RC at time of pCT showed significant, negative correlation to the variability of the relative volume changes during treatment (Spearman's $\rho = -0.644$; $p=0.007$). Figure 5 details the variation in the relative volume of the RCs compared to the pCT per patient, sorted by absolute volume on the pCT.

Secondly, there was a large range in time interval between surgery to planning CT (48 – 1534 days; see Supplementary Material Figure S1), however no significant relationship between the time interval and the variability of the relative volume changes during treatment was observed (Spearman's $\rho = -0.165$; $p=0.542$, see Supplementary Material Figure S2).

Thirdly, when comparing the group of patients with a direct or potential (<0.5 cm distance) relationship between RC and ventricle to the group with no relationship between RC and ventricle (>0.5 cm distance), no significant differences were found with regards to the variability/spread of the relative volume changes during treatment (Spearman's $\rho = -0.123$; $p=0.650$, see Supplementary Material Figure S3).

4. Discussion

In this study, anatomical changes of the RC during cranial radiotherapy treatment were analyzed using weekly imaging in neuro-oncological patients. The aim was to determine the (additional) isotropic internal margin required to compensate for the anatomical changes of the RC and to identify potential risk factors.

The average variation in relative resection volume during treatment was 26.1%, with a range of 2.0 – 137.9%. In current literature, the RC changes during brain radiotherapy have not been systematically analyzed for patients with a primary brain tumor. However, cavity volume dynamics have been reported after resection of brain metastases in the context of stereotactic radiotherapy (SRT). Several studies have reported a decrease of RC volume [10–13]. Nevertheless, these studies often report several patients with an increase in RC volume. Jarvis et al. for example analyzed 43 RCs and found that 20 cavities (46.5%) were stable, 10 cavities (23.3%) decreased in volume by >2 cm^3, and 13 cavities (30.2%) increased in volume by >2 cm^3 [14]. Of these 13 cavities that increased in volume, progression of local disease was only the reason for this enlargement in 2 patients. Yang et al. analyzed RC volume changes in 11 glioma patients (4 grade II, 5 grade III and 2 grade IV) [15]. They demonstrated a significant decrease in RC volume when comparing contrast-enhanced CT- and MRI-scans performed at the last day of radiotherapy to the pCT and pMRI scans. Changes in RC volume have also been reported for glioblastomas. Mehta et al. obtained daily MRI-scans of three glioblastoma patients using a magnetic resonance image guided radiotherapy (MR-IGRT) system [16]. The cavity volume of all three patients generally decreased during treatment. In contrast to these results, the currents study shows an increase in resection volume during radiation treatment for 44% of the included reCT-scans, thereby needing additional internal margins.

This study investigated three potential risk factors, which potentially influence the variability in resection cavity changes during treatment. The absolute volume of the RC at time of pCT turned out to be a significant risk factor, which was negatively correlated to the variability of the relative volume changes during treatment. Previously, Aghmadi et al. reported that dural involvement, maximum tumor diameter and time from surgery were significant predictors of RC volume reduction [10]. Atalar et al. however did not find a statistically significant association between the post-resection time and volume changes [17]. Ahmed et al. demonstrated a significant correlation between extent of post-operative vasogenic edema and subsequent cavity contraction, whereas Shash et al. did not find a significant relationship between post-operative edema and cavity volume reduction [11,18].

To the best of our knowledge, no studies have tried to determine the (additional) margin required to compensate for anatomical changes of the RC. When determining the isotropic margin required to compensate for the anatomical changes of the RC, it is important to set an objective at a specified probability (percentage of patients to compensate for). Van Herk et al. lists as an example (regarding the minimal dose) “for 90% of the patient population, the minimum dose to the CTV must be 95% of the nominal dose (i.e., the dose at the specification point) or higher” [19]. In the current study, it was determined that based on covering 95% of the volume, an (additional) isotropic margin of 3-4 mm is required to compensate for potential anatomical changes of the RC during treatment for 85-90% of patients respectively.

This study has some limitations. First, the covering of the target volume using additional margins was investigated. However, increasing margins will also have influence on the dose to surrounding OARs. This evaluation was considered out of scope of the manuscript, but would be worthwhile to investigate in future research. Secondly, small errors during registration, or small (software-related) errors by copying structures to different structure/imaging sets can occur. These unintentional differences have a larger impact on patients with smaller RCs. Thirdly, anatomical changes of the RCs were mostly evaluated on (re)CT-scans due to practical/logistical limitations in clinical practice. However, MR-imaging is the golden standard with its superior soft-tissue contrast compared to CT. Weekly MRI-scans were not available for all patients, but this would be recommended for further research. Finally, this is a single institutional, retrospective study with a limited number of patients. Because of these reasons, the results should be verified in a fully prospective study with a larger cohort, with a diverse neuro-oncological patient population and MR-imaging during radiation treatment to evaluate anatomical changes of the RC.

In conclusion, both this study and the currently available literature indicate that RCs are dynamic after surgery, unlike often assumed during target volume delineation of brain tumors. Especially with the current trend towards decreasing margins in neuro-oncological radiation therapy, RC dynamics might have a negative effect on target coverage in brain cancer patients. It is recommended to apply an internal margin to the GTV delineation to account for the volume differences of the GTV during radiotherapy treatment. Future research on local recurrence patterns is strongly recommended.

Acknowledgements

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Tables and figures:

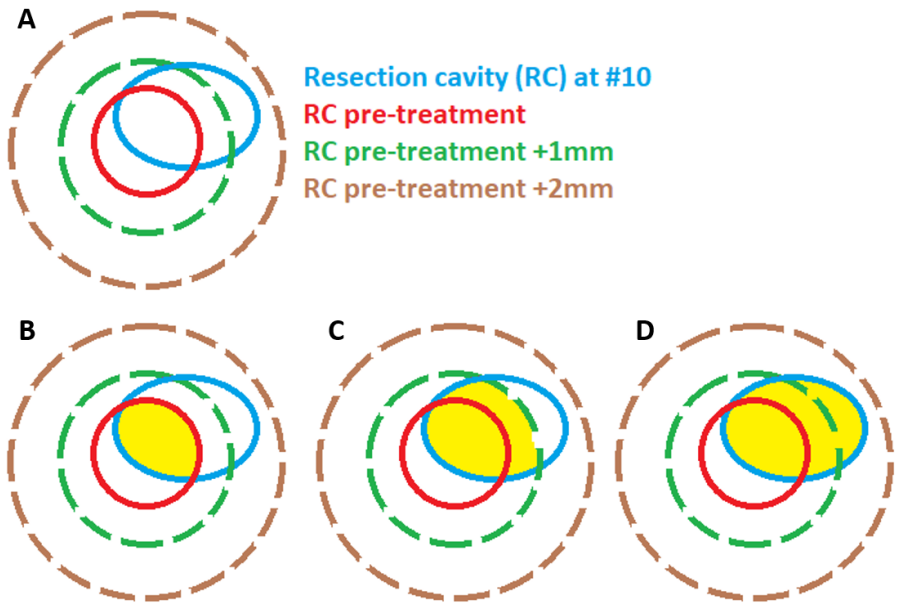

Figure 1 – An example of the analysis of the RCs using MATLAB. A) Red contour = RC pre-treatment, blue contour = RC during treatment, green contour = pre-treatment RC + 1 mm isotropic margin, brown contour = pre-treatment RC + 2 mm isotropic margin. B) Overlap of RC during treatment with original pre-treatment RC (yellow area). C) Applied 1 mm isotropic margin to pre-treatment RC. D) Applied 2 mm isotropic margin to pre-treatment RC.

Table 1 – Overview of patient characteristics (n=16). WHO grade = World Health Organization grade.

Characteristic	**Median or value**	**Range**
Age at first fraction (years)	41.9	24.2-60.6
Tumor type + WHO grade (no. patients)		
Astrocytoma WHO grade 2	5	
Oligodendroglioma WHO grade 2	6	
Oligodendroglioma WHO grade 3	3	
Meningioma WHO grade 1	1	
Meningioma WHO grade 2	1	
Number of planned fractions	28	28-33
Time between surgery & planning CT (days)	172	48-1534
Relationship RC - ventricles		
Direct or potential (<0.5 cm)	9	
None (>0.5 cm)	7	
Volume RC at pCT (cm^3)	16.8	2.1-135.5

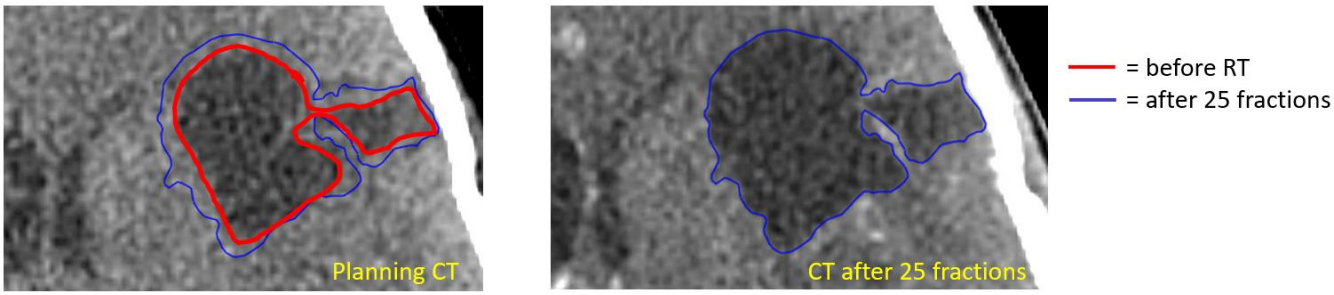

Figure 2 – Visually noticeable anatomical changes of an RC. Both images were captured using brain window settings (WW 120; WL 40). Left image: planning (pre-treatment) CT. The RC is delineated in red. The blue contour is the RC after 25 fractions. Right image: reCT after 25 fractions. The RC is delineated in blue. This contour is copied over to the left image. As can be seen on the images, the RC increased in size during treatment.

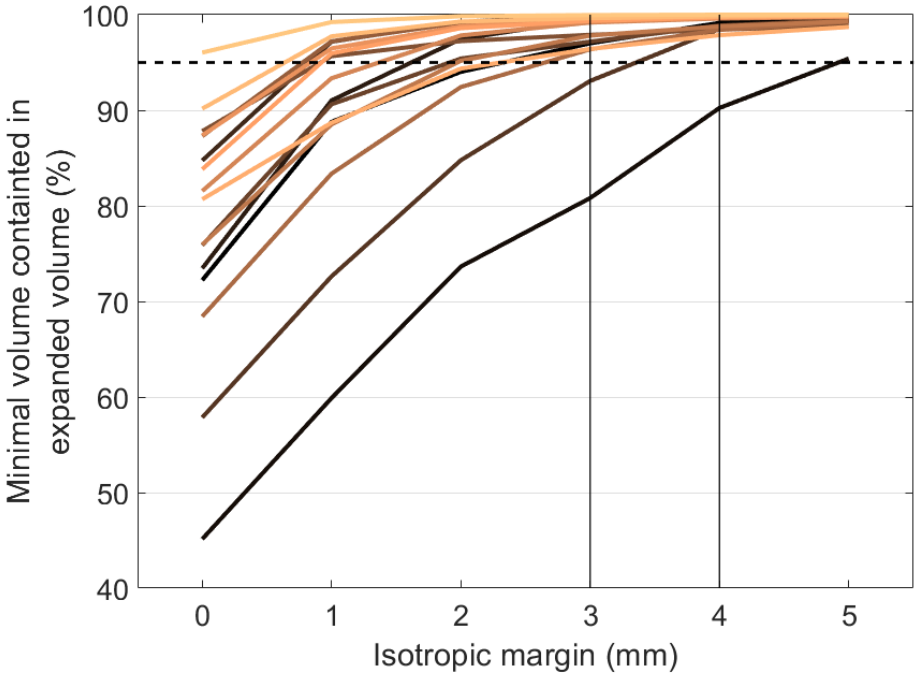

Figure 3 – Minimal percentage of the volume of the RCs for all fractions per patient located within the volume of the RC at start of treatment (0 mm) or within the isotropically expanded structures per millimeter of margin. The x-axis displays the added isotropic margin (0-5 mm). The y-axis displays the minimal percentage of the volume of the RCs for all fractions located within the volume of the RC at intake or within the isotropically expanded structures per patient. The dotted line represents the objective of covering 95% of the volume, which requires an additional isotropic margin of 4 mm and 3 mm (vertical lines) to compensate for respectively 90% and 85% of patients.

Table 2 – Minimal percentage of the volume of the RCs for all fractions for respectively 90% and 85% of patients contained within the volume of the pre-treatment RC or within the isotropically expanded structures per millimeter of additional isotropic margin.

90% of patients (n=15)		**85% of patients (n=14)**	
Additional isotropic margin (mm)	*Volume (%)*	*Additional isotropic margin (mm)*	*Volume (%)*
5	98.7%	5	98.9%
4	97.9%	4	98.4%
3	93.1%	3	96.4%
2	84.8%	2	92.4%
1	72.6%	1	83.4%
0	57.9%	0	68.4%

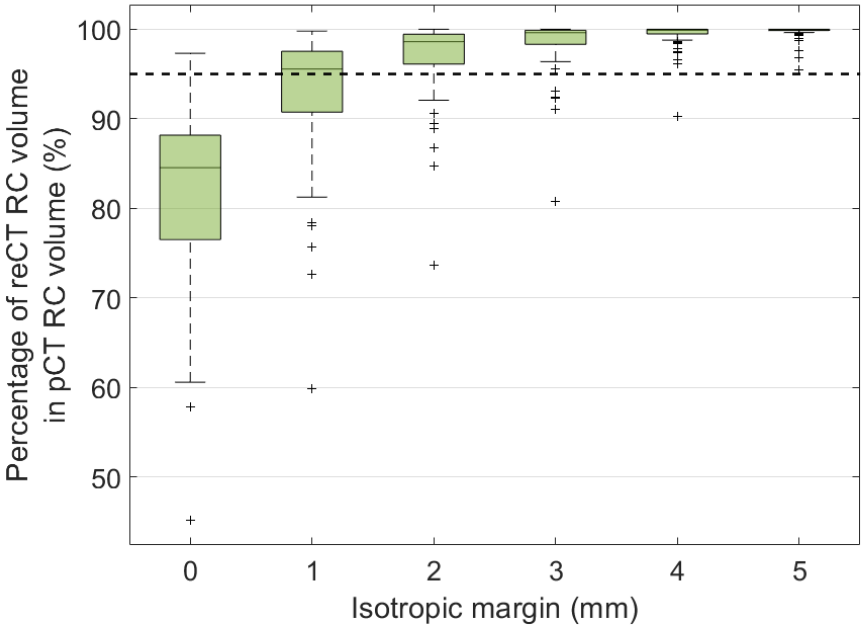

Figure 4 – Percentage of RC volume of the weekly CT-scans (reCTs) covered by the RC volume of the planning CT-scan (pCT) for the given isotropic margins, for all reCT-scans and all patients.

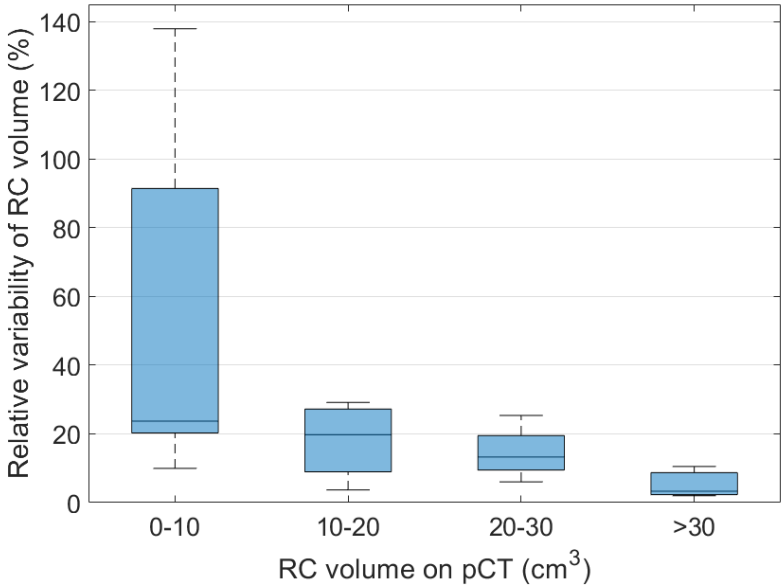

Figure 5 – The variation in relative variability of the resection cavity (RC) compared to the RC volume on the planning CT (pCT), divided in four groups. Number of patients per group: 0-10 (n=5), 10-20 (n=4), 20-30 (n=4), >30 (n=3).

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Figure 1

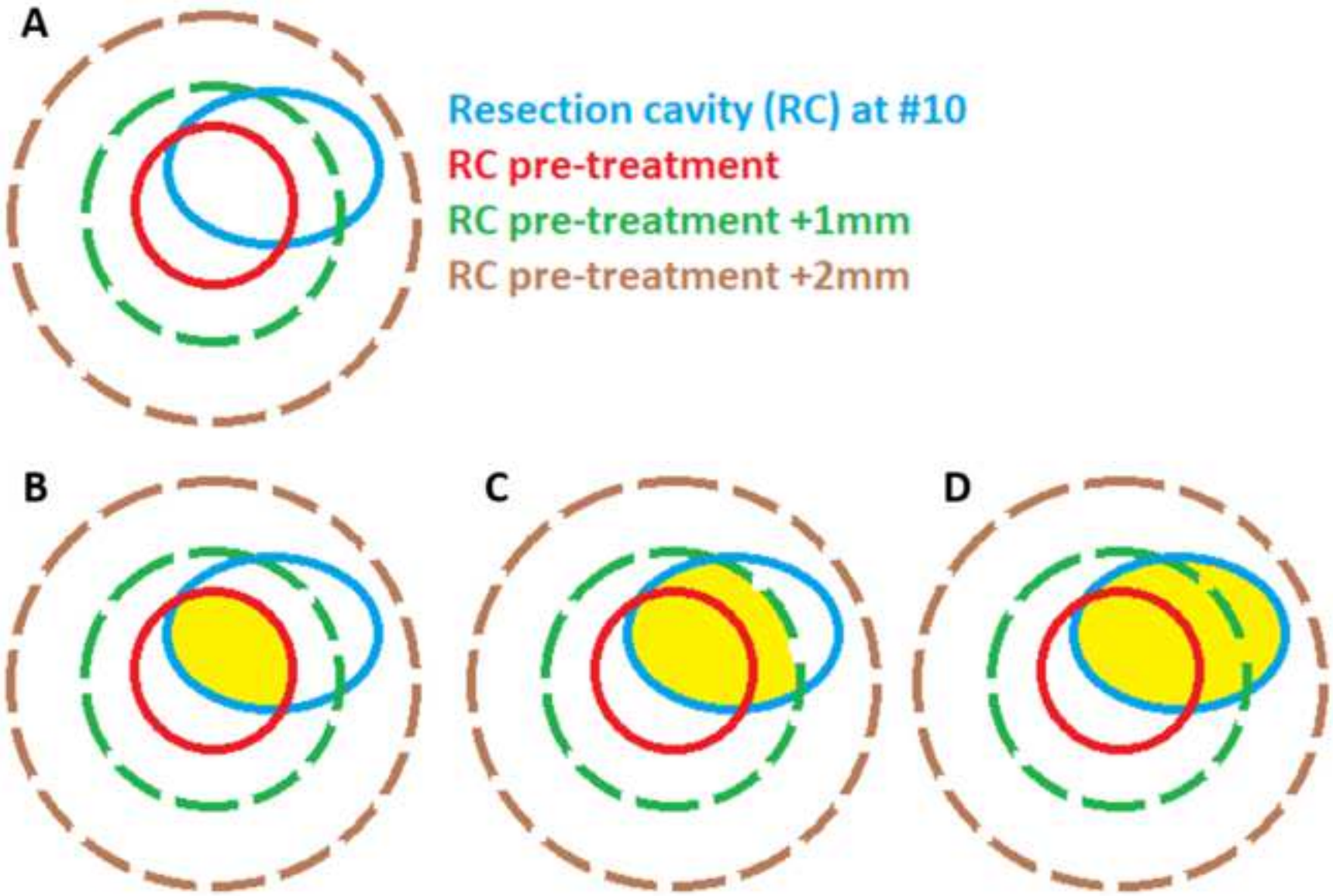

Figure 2

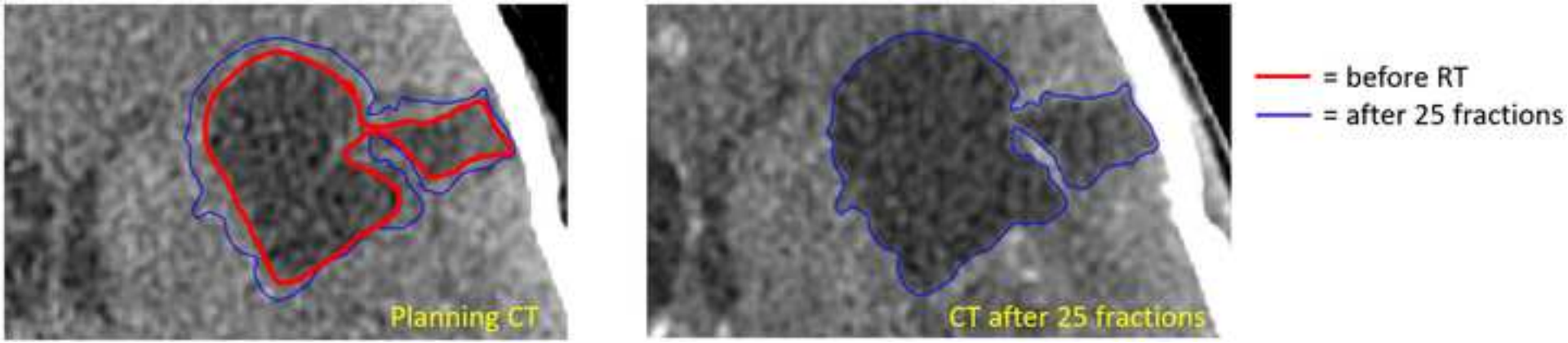

Figure 3

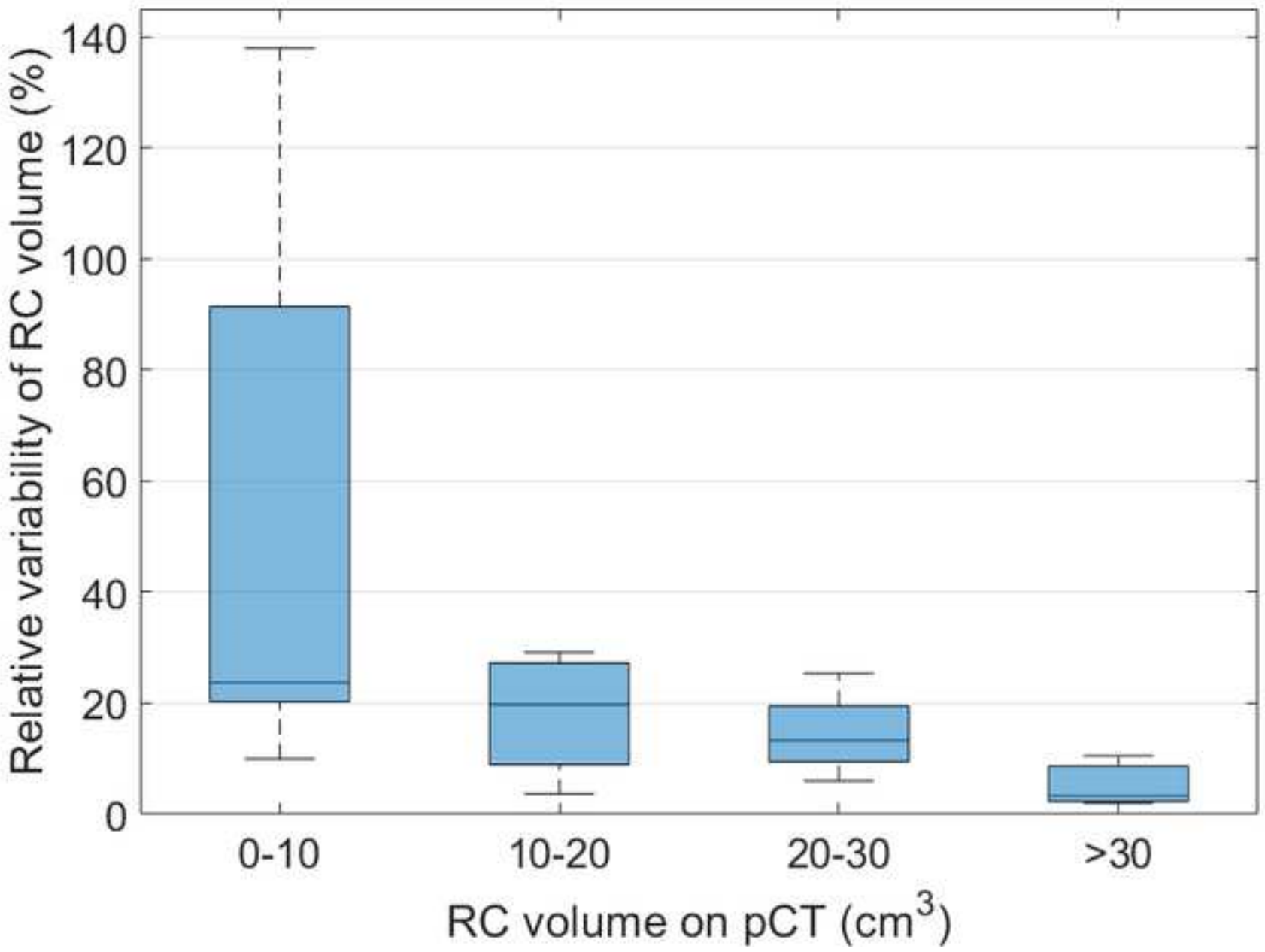

Figure 4

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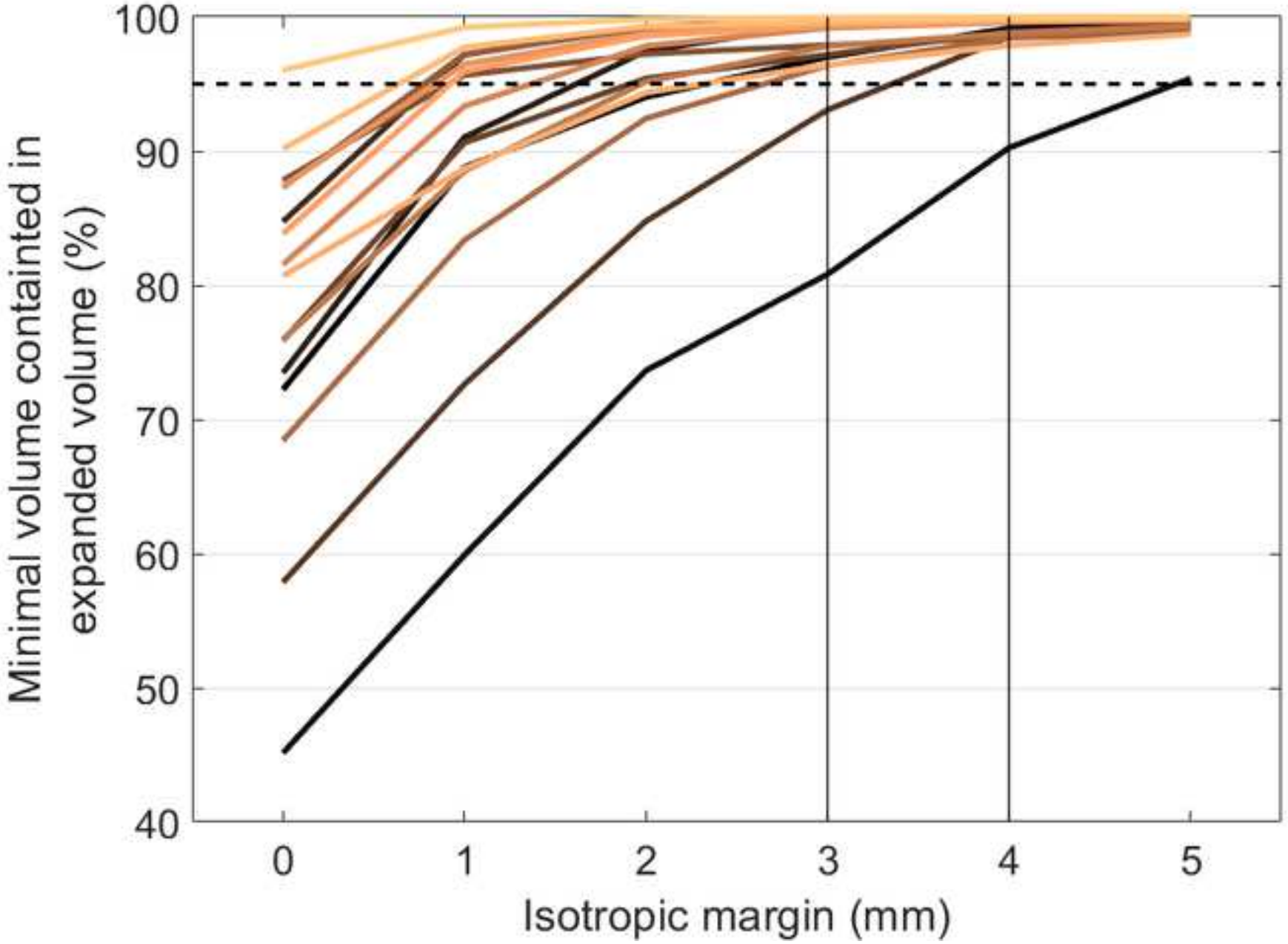

Figure 5

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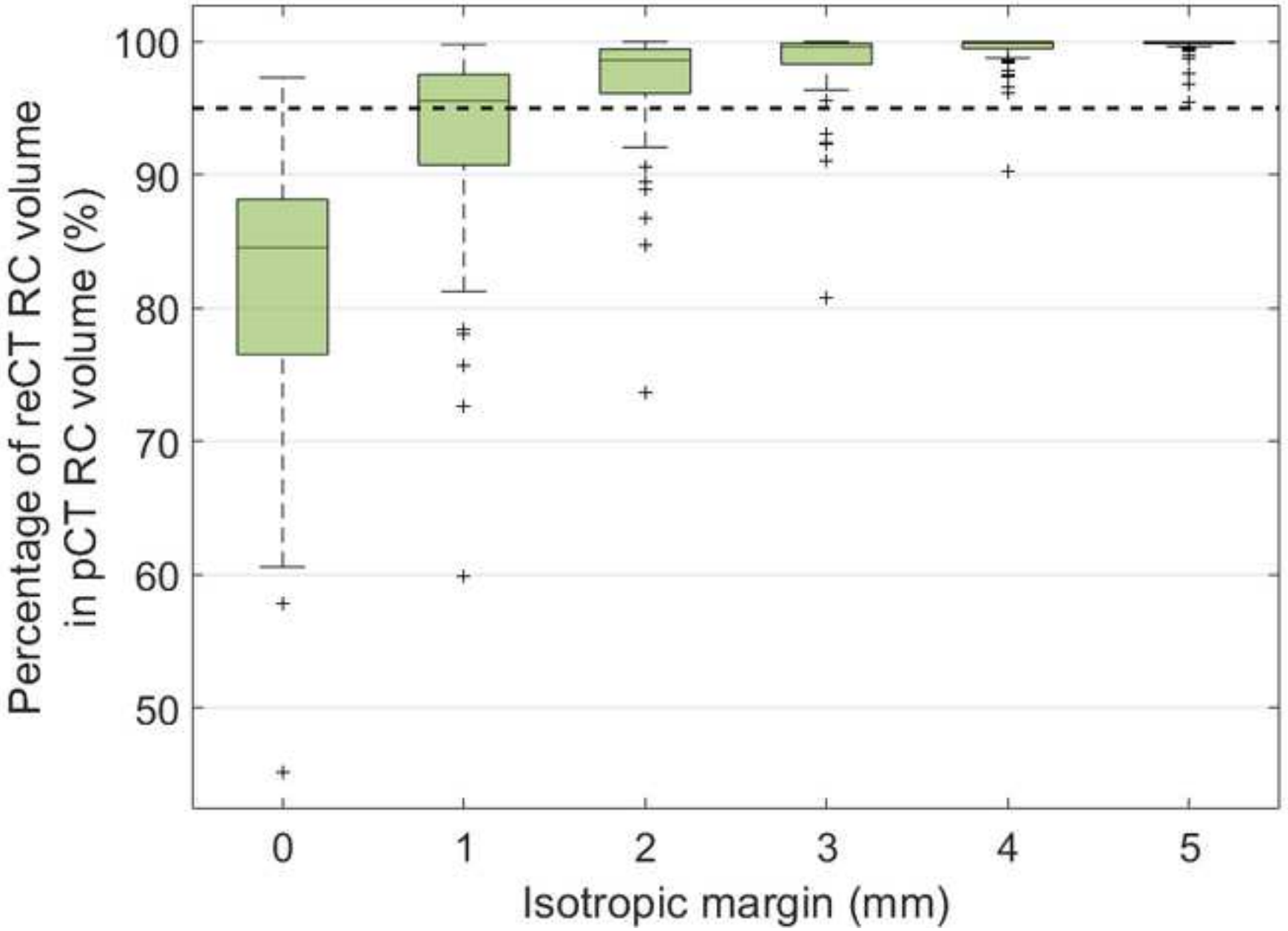

Conflicts of Interest:

None.

Patient Consent Statement:

Not applicable.