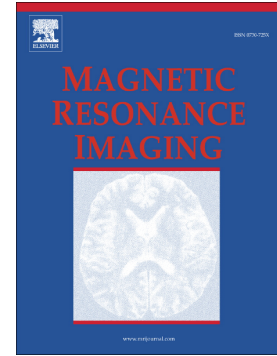


## Accepted Manuscript

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PII: S0730-725X(18)30646-5  
DOI: <https://doi.org/10.1016/j.mri.2019.02.003>  
Reference: MRI 9144  
To appear in: *Magnetic Resonance Imaging*  
Received date: 14 December 2018  
Revised date: 21 January 2019  
Accepted date: 10 February 2019

Please cite this article as: F. Giganti, A. Stabile, S. Giona, et al., Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome, *Magnetic Resonance Imaging*, <https://doi.org/10.1016/j.mri.2019.02.003>

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**Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome**

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**Prostate cancer treated with irreversible electroporation: MRI-based volumetric analysis and oncological outcome**

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**ABSTRACT**

**Background:** To assess multiparametric magnetic resonance imaging (mpMRI) characteristics in prostate cancer (PCa) before and after irreversible electroporation (IRE) and to investigate their correlation with the presence of post-operative recurrence of PCa.

**Methods:** MpMRI was performed in 30 men with PCa prior to treatment, after 10 days and at 6 months. An additional scan at 1 year was available for 18 men. Two radiologists assessed retrospectively the following parameters by planimetry: tumour volume, necrotic volume (early post-treatment scan) and residual fibrosis. Residual tumour/recurrence were defined as a suspicious area within the treatment field scored  $\geq 4$  on a 1-to-5 scale. Oncological outcome was also assessed.

**Results:** The median follow-up of the entire study was 16 months. Six men were undertreated and showed mpMRI recurrence after 6 months. At 1-year, three additional men had recurrence. Overall, four of these 9 men (44%) were retreated. The other five men did not receive any further treatment. Median time to re-treatment was 15 months. Median pre-treatment lesion volume was 0.65cc, 0.66cc and 0.43cc on the different mpMRI sequences (T2, DWI and DCE). Median necrotic volume was 10.77cc. Median overall residual fibrosis volume were 0.84cc and 0.95cc at 6-month and 1-year mpMRI. Pre-treatment, necrotic and residual fibrosis volumes were significantly different ( $p < 0.001$ ). Pre-treatment

tumour volumes on diffusion-weighted imaging and necrotic volumes were correlated ( $r = 0.18$ ;  $p = 0.02$ ).

**Conclusions:** MpMRI is able to visualise the IRE ablation effects in men with PCa. MpMRI-derived parameters - such as tumour, necrotic and fibrosis volumes - can be measured and are potentially useful for assessing efficacy in the medium term, as with other ablative techniques.

## 1. INTRODUCTION

Focal therapy has been increasingly proposed as an alternative strategy to radical treatment for prostate cancer (PCa) (1) and has been evaluated in different studies in its various forms (2,3). The majority of the available studies investigate the role of high intensity focused ultrasound (HIFU) in PCa, but other works have also reported the effects of cryotherapy and thermal laser techniques (4–6).

Irreversible electroporation (IRE) is another type of focal therapy that is being increasingly used in the treatment of different tumours (7,8), including PCa (9). This technique is based on the pulsatile application of non-thermal energy - delivered between two electrodes - that leads to cell death (i.e. irreversible) by the formation of nanopores within the cell membrane of tumour cells, without causing a thermal effect outside the ablation zone (10). The non-thermal approach allows to overcome the dissipation of energy - which may result in undertreatment - that occurs when using other types of thermal treatments such as HIFU or cryotherapy (9). As a result, IRE provides selective ablation with demarcated margins in the target area (9).

It is well known that imaging plays an important role in the diagnosis, management and follow up of PCa, but there is still a critical need of studies evaluating multiparametric magnetic resonance imaging (mpMRI) (T2-weighted imaging, T2-WI; diffusion-weighted imaging, DWI; dynamic contrast enhanced, DCE) findings after IRE and oncological outcome (11–13). Knowledge of early and late mpMRI findings after IRE, and their

correlation with pre-treatment findings, may give further insight to the ability of mpMRI to assess the efficacy of IRE in PCa.

The primary aim of this study was to assess mpMRI-derived volumes in PCa before and after IRE. The secondary endpoint was to investigate the recurrence rate of PCa over time (6 months and 1 year, if available), assessing the number of men who showed imaging or biochemical evidence of recurrence.

## **2. MATERIALS AND METHODS**

This is a single-centre, retrospective analysis of men with localised biopsy-proven PCa treated with IRE. All patients gave their written consent after thoroughly discussing the potential risks along with the possible advantages of this procedure.

Three urology fellows (SG, AS, JM) searched a local database for men with organ-confined PCa treated with IRE between August 2011 and June 2016. Inclusion criteria were: i) biopsy proven tumour; ii) serial mpMRI scans before and after the procedure, as follows: pre-treatment, early (within 10 days from the procedure, to evaluate the effect of the treatment, including any evidence of rectourethral fistula) - and at 6 months.

### **2.1 MpMRI analysis**

All patients underwent mpMRI using a 3T system (Magnetom Verio, Syngo MR B 17; Siemens Healthcare, Erlangen, Germany) and a pelvic

phased-array coil. The protocol included T2-WI (sagittal, coronal and axial), DWI ( $b$  values: 0, 100, 500 and 1000 s/mm<sup>2</sup>, with a dedicated long  $b$  value sequence: 2000 s/mm<sup>2</sup>) and DCE imaging (intravenous injection of 0.1 mmol/kg of body weight of gadoterate meglumine (Dotarem<sup>®</sup>, Guerbet, Roissy, France) at a rate of 2 ml/s.

All lesions were visible on mpMRI and were concordant with initial histology.

Two board-certified radiologists (FG and SP, each one reporting more than 1,500 prostate mpMRI scans/year) who were privy to clinical and histopathological data but blinded to the original reports, re-scored all lesions on baseline scans according to Prostate Imaging Reporting and Data System (PI-RADS) v. 2 guidelines (14) and assessed tumour volumes on all sequences by planimetry (and using also the ellipsoid formula for T2-WI) in consensus. For the analysis, we considered the volume by planimetry from the sequence best showing the tumour.

Then, after IRE, the radiologists contoured the necrotic volume (in the early post-treatment scan, using both planimetry and the ellipsoid formula) and residual fibrosis (at follow-up scans, by planimetry) on DCE images (Fig. 1).

The presence of residual tumour/recurrence was defined as a suspicious area within the treatment field scored  $\geq 4$  on a 1-to-5 Likert scale.

Qualitative and quantitative analyses were carried out using commercial image viewing software (Osirix <sup>®</sup> v. 4.1.2; Geneva, Switzerland).



## 2.2 IRE procedure and follow up

After the first scan, all men underwent treatment with Nanoknife system (AngioDynamics, New York, USA) by a dedicated urologist (ME) highly experienced in focal therapy of PCa. This device uses a biplanar transrectal ultrasound probe and a template grid to transperineally place electrode needles in the planned treatment area according to mpMRI, as previously described by Valerio et al. (15)

All men had either a suprapubic catheter placed (that was removed after 2 to 6 weeks after treatment depending on individual patient voiding) or a urethral catheter (for 3 to 7 days) postoperatively.

After treatment, clinical visits occurred every 3 months to record adverse events and prostate specific antigen (PSA) level. In five patients with a clinically suspicious rise in PSA or an mpMRI score  $\geq 4$  a transperineal template biopsy was performed. For one patient the imaging findings were considered definitive and retreatment was performed without a rebiopsy.

## Statistical analysis

Continuous variables were summarised by their median values and interquartile ranges -IQR- [1<sup>st</sup> to 3<sup>rd</sup> quartile] and by means of frequencies and percentages. Wilcoxon test was used to assess differences between continuous variables.

The analysis of variance (ANOVA) test was used to analyse the differences between pre-treatment T2-WI, necrotic and fibrosis volumes.

Corresponding box-plots were generated.

Retreatment-free survival curves were fitted by means of Kaplan-Meier estimator.

Statistical significance level was set at p-value <0.05.

All statistical analyses were performed using R software (Version 3.4.2; Foundation for Statistical Computing, Vienna, Austria).

### **3. RESULTS**

A total of 30 men met the inclusion criteria and were included in the study. All 30 men had a scan at 6 months, and 18 of them (60%) had also an additional scan at 1 year.

The median age was 63 years [IQR: 60-67]. Median PSA at baseline was 6.4 ng/mL [5-8.8].

Seven patients had Gleason 3+3, twenty Gleason 3+4 and three Gleason 4+3 at initial biopsy. At baseline, 1/30 lesion (3%) was scored as PI-RADS 3, 16/30 (53%) as PI-RADS 4 and 13/30 (44%) as PI-RADS 5.

Twenty-five out of 30 (83%) lesions were in the transitional zone and 5/32 (17%) in the peripheral zone.

#### 3.1 Outcome

The median follow-up period of the entire study was 16 months (range 6 - 24 months).

At early mpMRI, undertreatment (i.e. a suspicious lesion still scoring  $\geq 4/5$ ) was observed in 6/30 men (20%) and the residual volume fraction (i.e. tumour volume at early mpMRI / pre-treatment tumour volume at mpMRI \* 100) was calculated (Table 1). All of these 6 men had recurrence ( $\geq 4/5$ ) at 6-month mpMRI, and two men were retreated (Table 2). At 1-year mpMRI three new patients (10%) showed evidence of recurrence on mpMRI (Table 3).

Overall, four patients (13%) were retreated, 3 of which had histological confirmation at subsequent biopsy. Specifically, one patient underwent HIFU, two were treated with IRE and one with radiotherapy.

The median time to re-treatment was 15 months (range 12-24 months).

### 3.2 Volumetric analysis

The median pre-treatment tumour volume on T2-WI was 0.65 cc [0.31-1.32] by planimetry and 0.72 cc [0.34 – 1.43] using the ellipsoid formula, with no significant difference between the two methods ( $p=0.73$ ). The median overall pre-treatment lesion volume on DWI by planimetry was 0.66 cc [0.17-1.05] and 0.43 cc [0.20 – 0.83] on DCE.

The overall median necrotic volume on DCE on early post-treatment mpMRI was 10.77 cc [7.64-14.71] by planimetry and 11.28 cc [9.65 – 14.13] using the ellipsoid formula, with no significant difference ( $p = 0.43$ ).

The overall residual fibrotic volume calculated by planimetry on DCE was 0.84 cc [0.55-1.44] and 0.95 cc [0.42 – 1.66] at 6-month (n=30) and 1-year scans (n=18), respectively.

When analysing the two populations (non-recurrence vs recurrence), there was a significant difference a) between the overall pre-treatment T2-WI tumour volume and the necrotic volume (by planimetry) at early post-treatment mpMRI ( $p < 0.001$ ), and b) between the necrotic volume (by planimetry) at early post-treatment mpMRI and the residual fibrosis volume at 6 months and one-year mpMRI (both  $p < 0.001$ ).

Specifically, in men with no recurrence the median pre-treatment tumour volume on T2-WI was 0.65 cc [0.31 – 1.16], the median necrotic volume on DCE was 10.9 cc [7.88 – 15.59], the residual fibrotic volume was 0.85 cc [0.57 – 1.92] at 6 months (n=30) and 1.21 cc [0.45 – 1.94] at one year (n=18) (Fig. 2a).

In men with recurrence the median pre-treatment tumour volume on T2-WI was 1.13 cc [0.22 – 1.72], the median necrotic volume on DCE was 8.93 cc [5.84 – 13.08], the residual fibrotic volume was 0.69 cc [0.39 – 1.38] at 6 months and 0.61 cc [0.30 – 1.35] at one year (Fig. 2b). There was a significant correlation between pre-treatment tumour volume on DWI and the early necrotic volume ( $r = 0.18$ ;  $p = 0.02$ ). No significant differences were observed for pre-treatment tumour volumes on T2-WI ( $r = 0.11$ ;  $p = 0.06$ ) and DCE ( $r = 0.05$ ;  $p = 0.25$ ).

#### 4. DISCUSSION

To our knowledge, this is the first study that involves an mpMRI-based volumetric analysis in men with PCa treated with IRE.

We found that mpMRI is able to visualise the IRE ablation effects in men with PCa. MpMRI-derived parameters - such as tumour, necrotic and fibrosis volumes - can be measured and are potentially useful for assessing efficacy in the medium term after IRE, as with other ablative techniques.

There is very limited experience at present with the interpretation of mpMRI findings following IRE, and data from mpMRI have yet to be quantitatively validated in the follow-up. Scheltema and colleagues provided an overview on several imaging modalities used in conjunction with IRE, including mpMRI (12). They reported the mpMRI appearance of the prostate gland four weeks, six months and one year following IRE (12). The same author reported that mpMRI is able to detect high-volume residual significant PCa with a specificity of 72% and negative predictive value of 70% for the whole gland, even though low-volume or high-volume Gleason 3+3 can still be missed. It was suggested that follow-up biopsies should still be performed, given the current lack of robust studies at this regard (16).

Van de Bos and colleagues (17) have compared the volumetric ablation zone after IRE on grey-scale transrectal ultrasound (TRUS), contrast-enhanced ultrasound (CEUS) and mpMRI with histopathology findings in

16 men scheduled for radical prostatectomy. Imaging was performed prior to and four weeks after treatment. Radical prostatectomy was then carried out. They concluded that the effects of IRE are visible on mpMRI and CEUS but not on TRUS, suggesting that mpMRI is a feasible imaging modality to visualise IRE the ablation zones in the prostate gland (17). Consensus guidelines stated that DCE is considered to be the most sensitive sequence to detect residual PCa (18), and this is in line with our results. Our early post-IRE mpMRI scans revealed a notable volume increase of the gland due to the necrotic area that was visible on DCE. This was followed by a notable decrease during follow-up, and the volume of the residual fibrosis on DCE (both at 6-month and 1-year scans) was much smaller than the initial necrotic volume, both in men with or without recurrence (Fig. 2).

We have also observed a significant correlation between pre-treatment volume on DWI and the early necrotic volume, and also the results from T2-WI were close to the levels of statistical significance. Such findings confirm that pre-treatment lesion volume is one of the main drivers for the operator when it comes to the delineation of the treatment zone. Our group has previously evaluated the safety and clinical feasibility of focal IRE for PCa in a different group of 34 men by mpMRI (1 week and at 6 months) and targeted/template biopsy (19). Focal IRE had a low toxicity profile with encouraging genitourinary functional outcomes. MpMRI showed suspicious residual disease in six patients (18%) at a median follow-up of 6 months, of whom four (12%) underwent another

form of local treatment. Our current results are in line with these findings, as six men (20%) showed suspicious residual disease at 6-month MRI scan, and three of them (10%) were retreated.

We acknowledge that several important limitations apply to our study. The first is that not all suspicious lesions after IRE underwent routine biopsy to confirm the absence of tumour; same applies for the areas defined as necrosis or fibrosis at mpMRI. Additionally, this is a retrospective analysis with a small sample size, and multivariable analyses could not be performed. Two radiologists in consensus, although highly experienced in prostate MR reporting, re-reported the scans, so we cannot comment on the interobserver variability. Lastly, we did not assess the genitourinary outcomes (i.e. erectile dysfunction and urinary continence) of the men included in this study, but our previous work from a similar population reported encouraging results at this regard (19).

## **5. Conclusion**

Our study, although preliminary, shows that mpMRI is a promising imaging modality to evaluate pre-treatment tumour volume and to visualise IRE ablation zones and residual fibrosis in men with PCa.

Future studies from multi-centre, longitudinal cohorts should investigate whether imaging characteristics post-IRE can predict treatment outcome and stratify patients for potential retreatment in order to establish optimal protocols based on this technique.

These studies should include template-mapping biopsy of the residual prostate to verify and correlate findings from post-treatment MRI with regards to PCa recurrence.

*Conflict of interest:*

*Dr Francesco Giganti is funded by the UCL Graduate Research Scholarship and the Brahm PhD scholarship in memory of Chris Adams. Dr Alex Kirkham receives research support from the UCLH/UCL NIHR Biomedical Research Centre. Prof. Mark Emberton is a UK National Institute of Health Research (NIHR) Senior Investigator. In addition, he receives research support from the UCLH/UCL NIHR Biomedical Research Centre. Prof. Shonit Punwani receives research support from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre.*



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**Figure legends:****Fig. 1**

MRI scan in a 71-year-old man with presenting PSA of 7.4 ng/ml and Gleason 3+4 at entry biopsy, scored as PI-RADS 5. The arrow indicates the lesion on T2-WI (A), DWI (B) and DCE (D). The asterisk (\*) in (D) shows the necrotic area on DCE at early scan (15.8 cc) and the arrow head in (E) indicates the residual fibrosis on DCE (0.65 cc) at 6-month scan. No recurrence was observed in this patient.

**Fig. 2**

Comparison of the volumes from MRI at different time points in men without (A) and with (B) recurrence.

**Table 1**

Residual tumour volume at early mpMRI (within 10 days from procedure).

	Baseline lesion volume (cc)	Residual tumour volume (cc)	Relative volume (%)
Patient 1	1.05 (DWI)	0.67 (DWI)	64
Patient 2	0.28 (DCE)	0.09 (DCE)	32
Patient 3	0.97 (DWI)	0.15 (DWI)	15
Patient 4	0.29 (DCE)	0.11 (DCE)	38
Patient 5	0.43 (DCE)	0.19 (DCE)	44
Patient 6	0.17 (DCE)	0.03 (DCE)	18

Legend – In parentheses the sequence in which the lesion was best seen; DWI: diffusion-weighted imaging; DCE: dynamic-contrast enhanced.

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**Table 2**

Residual tumour volume at 6-month mpMRI.

	Baseline lesion volume (cc)	Residual tumour volume (cc)	Relative volume (%)	Gleason score at rebiopsy	Decision	Time to retreatment/last follow up
Patient 1	1.05 (DWI)	0.97 (DWI)	92	-	Radiotherapy	13 months
Patient 2	0.28 (DCE)	0.08 (DCE)	29	-	Surveillance	-
Patient 3	0.97 (DWI)	0.16 (DWI)	16	-	Surveillance	-
Patient 4	0.29 (DCE)	0.23 (DCE)	79	-	Surveillance	-
Patient 5	0.43 (DCE)	0.36 (DCE)	84	3 + 4	IRE	11 months
Patient 6	0.17 (DCE)	0.03 (DCE)	18	-	Surveillance	-

Legend – In parentheses the sequence in which the lesion was best seen; DWI: diffusion-weighted imaging; DCE: dynamic-contrast enhanced; IRE: irreversible electroporation



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**Table 3**

Residual tumour volume at 1-year mpMRI (n=18).

	Baseline lesion volume (cc)	Residual tumour volume (cc)	Relative volume (%)	Gleason score at rebiopsy	Decision	Time to retreatment/last follow up
Patient 1	-	-	-	-	-	-
Patient 2	0.28 (DCE)	0.13 (DCE)	46	-	Surveillance	24 months
Patient 3	0.97 (DWI)	0.40 (DWI)	41	-	Surveillance	11 months
Patient 4	-	-	-	-	Surveillance	12 months
Patient 5	-	-	-	-	-	-
Patient 6	0.17 (DCE)	0.04 (DCE)	24	3 + 4	IRE	15 months
Patient 7	0.22 (DCE)	0.43 (DCE)	-	3 + 3	Surveillance	24 months
Patient 8	2.29 (DWI)	0.1 (DWI)	4	4 + 3	HIFU	24 months
Patient 9	1.56 (DWI)	0.08 (DCE)	5	-	Surveillance	24 months

Legend – In parentheses the sequence in which the lesion was best seen; DWI: diffusion-weighted imaging; DCE: dynamic-contrast enhanced; IRE: irreversible electroporation; HIFU: high intensity focused ultrasound

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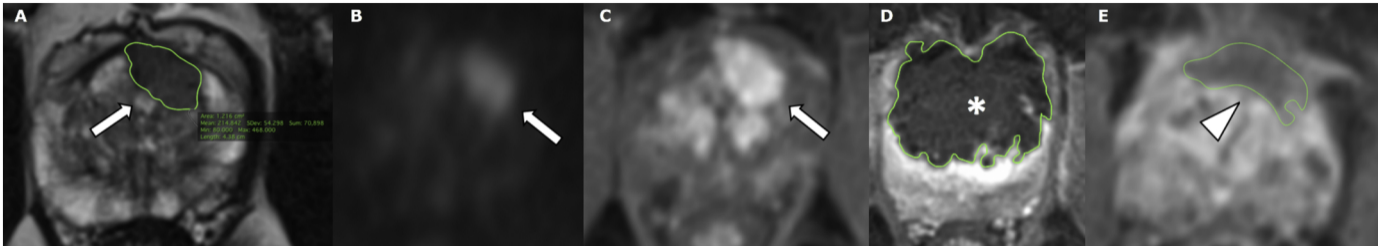


Figure 1

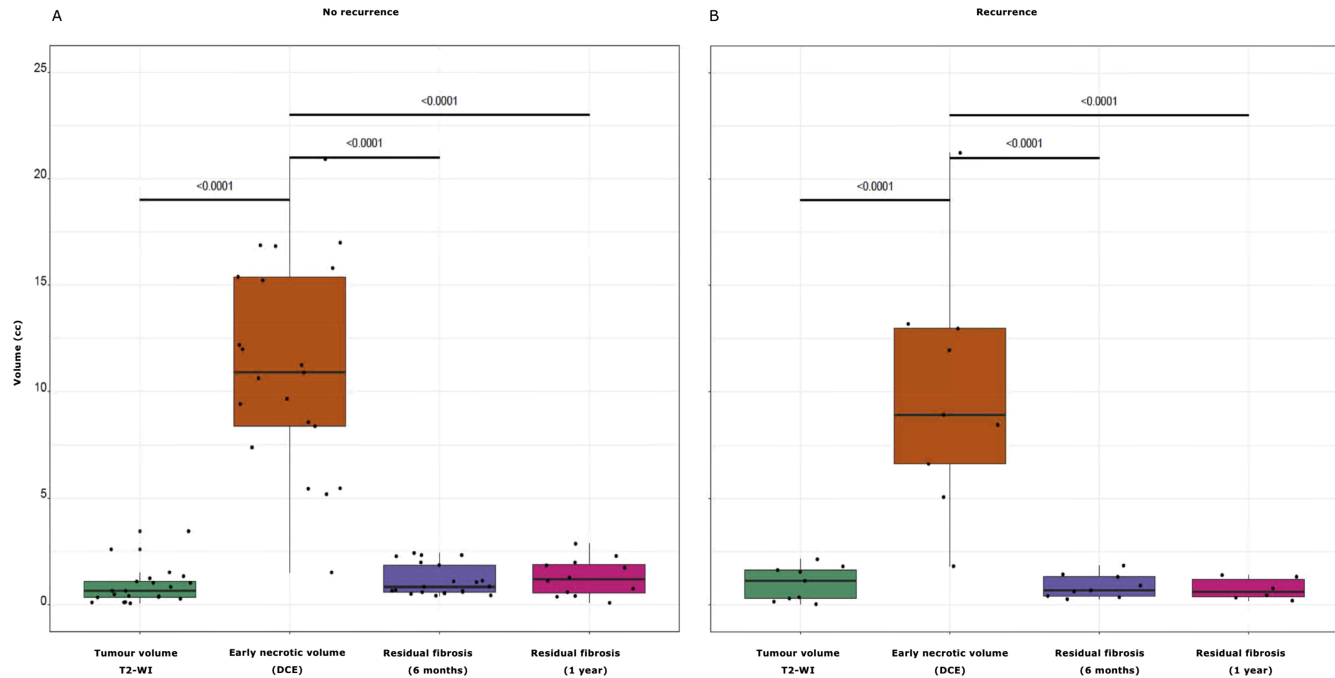


Figure 2