



Evolution of non-perfused volume after transurethral ultrasound ablation of prostate: A retrospective 12-month analysis

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HIGHLIGHTS

- Tissue necrosis after heat-based ablation therapies can be measured by MRI.
- Most of the necrotic tissue after prostate ablation resolves within one year.
- Disappearance of necrotic tissue is slower for irradiated prostate tissue.

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ABSTRACT

Background: A detailed understanding of the non-perfused volume (NPV) evolution after prostate ablation therapy is lacking. The impact of different diseased prostate tissues on NPV evolution post-ablation is unknown. **Purpose:** To characterize the NPV evolution for three treatment groups undergoing heat-based prostate ablation therapy, including benign prostatic hyperplasia (BPH), primary prostate cancer (PCa), and radiorecurrent PCa. **Materials and methods:** Study design and data analysis were performed retrospectively. All patients received MRI-guided transurethral ultrasound ablation (TULSA). 21 BPH, 28 radiorecurrent PCa and 40 primary PCa patients were included. Using the T1-weighted contrast-enhanced MR image, the NPV was manually contoured by an experienced radiologist. All patients received an MRI immediately following the ablation. Follow-up included MRI at 3- and 12 months for BPH and radiorecurrent PCa patients and at 6- and 12 months for primary PCa patients.

Results: A significant difference between BPH and radiorecurrent PCa patients was observed at three months ($p < 0.0001$, Wilcoxon rank sum test), with the median NPV decreasing by 77 % for BPH patients but increasing by 4 % for radiorecurrent PCa patients. At six months, the median NPV decreased by 97 % for primary PCa. Across all groups, although 40 % of patients had residual NPV at 12 months, it tended to be < 1 mL.

Conclusion: The resolution of necrotic tissue after ablation was markedly slower for irradiated than treatment-naïve prostate tissue. These results may account for the increased toxicity observed after radiorecurrent salvage therapy. By 12 months, most necrotic prostate tissue had disappeared in every treatment group.

1. Introduction

Patients with either localized treatment-naïve or radiorecurrent prostate cancer (PCa) and in need of treatment are typically offered conventional treatments including radical prostatectomy or radiation

therapy [1]. While these therapies have demonstrated an efficacy benefit, they also carry safety risks, such as erectile dysfunction and urinary incontinence [1]. Newer therapies are therefore needed, which can offer equivalent cancer control but with an improved safety profile [2]. The situation is similar for patients seeking treatment for benign

Abbreviations: BPH, benign prostatic hyperplasia; CEM240, 240 cumulative equivalent minutes; HIFU, high-intensity focused ultrasound ablation; NPV, non-perfused volume; PCa, Prostate cancer; TULSA, transurethral ultrasound ablation of prostate.

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prostatic hyperplasia (BPH) [3]. BPH patients are commonly referred for transurethral resection of the prostate (TURP) treatment. Although TURP is effective, it also carries surgical risks and may not be suitable for all patients [4].

To address these limitations for both PCa and BPH patients, several researchers have used heat-based ablation therapies [2,5]. The most common image-guided heat-based ablation therapies include laser and transrectal high-intensity focused ultrasound (HIFU) ablation. These minimally invasive therapies deliver thermal energy to prostate tissue to achieve complete cell death in the targeted region while preserving the vitality of surrounding tissues to minimize genitourinary adverse effects. Both have been used for several decades, most commonly for the treatment of localized primary PCa [2,6]. Less common indications include salvage therapy for radiorecurrent PCa and for treating benign prostatic hyperplasia (BPH) [5,7].

MRI-guided transurethral ultrasound ablation (TULSA) is a newer option for prostate ablation [8]. TULSA uses high-intensity directional ultrasound to ablate prostate tissue under real-time MR thermometry guidance. Various researchers have used TULSA to treat both BPH, primary and radiorecurrent PCa [9,10].

A distinguishing feature of heat-based ablation therapy is that the extent of tissue necrosis after ablation can be measured immediately after treatment and months later. This measurement is performed using contrast-enhanced (CE)-MRI. The non-perfused volume (NPV) on CE-MRI corresponds to the region of histopathologic coagulation necrosis [11–14]. Particularly for heat-based ablation of PCa, the NPV has been traditionally used as a secondary marker to monitor treatment outcome after therapy [14–16].

Yet the potential influence of significant leftover necrotic tissue appearing as NPV on lower urinary tract irritation and voiding symptoms, particularly months after treatment, has largely been overlooked. While urinary symptoms tend to subside in the months after treatment, persistent necrotic tissue that does not disappear quickly may increase the risk of bladder outlet obstruction and urinary infections. For example, it is known that patients undergoing whole-gland ablation tend to incur worse side effects than those undergoing partial ablation [17, 18]. In addition to the increased risk of adverse effects on genitourinary organs, more extended ablation may cause prolonged irritation in the lower urinary tract due to the slower eradication of necrotic tissue from the prostate. Moreover, salvage therapy of patients with radiorecurrent PCa have higher toxicity than treatment-naïve patients [7,19]. The specific reasons for these discrepancies are poorly understood, but NPV and prostate volume changes likely play a role. A detailed understanding of this phenomenon could help physicians better anticipate and manage the associated side effects, and optimize follow-up.

Unfortunately, the evolution of NPV after prostate ablation therapy has not been well-studied, which makes it challenging for physicians to interpret these results. The majority of evidence on NPV evolution exists in the primary PCa setting [20–23]. Only one study reported NPV changes in the salvage setting [17]. In the BPH setting, no work has been published. Moreover, most studies have reported on changes in NPV after prostate ablation merely as incidental findings instead of as a primary endpoint.

The aim of this study was two-fold. The first objective was to evaluate the NPV evolution up to 12 months after TULSA. The second objective was to compare the change in NPV dynamics between BPH, radiorecurrent, and primary PCa treatment groups.

2. Materials and methods

2.1. Patient selection

All imaging data were acquired as part of an ethics-approved, single-center, phase 1–2 study of TULSA therapy for BPH and radiorecurrent PCa patients (NCT03350529), and phase 2 study for primary PCa patients (NCT03814252). Written informed consent was provided from all

patients. We retrospectively identified 97 consecutive patients who received TULSA between April 2018 and November 2021. After a detailed review, eight patients were excluded from the study for two reasons; three patients did not complete the necessary follow-up, and five patients (1 radiorecurrent and 4 primary PCa) were re-treated with TULSA due to residual tumor before the completion of follow-up. A total of 89 patients (21 BPH, 28 radiorecurrent, and 40 primary PCa) were included in the study. [Supplemental Material S1](#) shows the study flow-chart diagram.

Since this study was both retrospective, and therefore not geared towards proving superiority, equivalency or non-inferiority, the patient sample size of 89 was deemed sufficient to detect any potential differences in NPV evolution amongst the three patient groups. Each patient group had a minimum of 20 patients.

2.2. TULSA treatment

TULSA (TULSA-PRO, Profound Medical Inc., Canada) has been previously described by Chin et al. [8]. Briefly, TULSA delivers high-intensity ultrasound energy to the prostate via a transurethral catheter in order to achieve thermal coagulation. The extent of ablation (partial or whole-gland) is fully customizable by the user, and the heating is monitored in real-time using MR thermometry. The treatment objective is to ensure that all targeted tissue inside the physician-contoured boundary reaches at least 240 cumulative equivalent minutes (CEM 240) [24].

The TULSA transurethral catheter has an active treatment length of 50 mm. The active area is itself composed of ten individually controlled ultrasound elements. Each ultrasound element is 4.5 mm width × 5 mm length. Acoustic energy, originating from the prostatic urethra, is delivered from each element at two distinct ultrasound frequencies (4 and 13 MHz). These frequencies cannot be adjusted by the operator. Low frequency operation is used when the prostate boundary is larger than 14 mm from the prostatic urethra, otherwise high frequency operation is enabled. The acoustic power and rate of rotation are modulated by the TULSA closed-loop treatment controller, which can deliver up to 4 W and 2 W acoustic at low and high frequency, respectively. The treatment controller monitors boiling, ensuring that no temperature inside the prostate exceeds 100 °C. The ablation time for each patient is variable and depends on both the prostate size, tissue perfusion, heat conduction and the treatment plan, but typically ranges from 30 to 60 min. The vitality of the urethra and rectal wall are preserved by active water cooling.

The treatment strategy for primary and radiorecurrent PCa patients was partial or whole-gland ablation, depending on patient preference and individual disease characteristics. Conversely, depending on prostate size, all BPH patients received transition zone ablation, from either apex or midgland to the base. At least two heating sweeps of the targeted area were performed for all patient groups to ensure complete thermal coagulation. The only exception was the last 11 BPH phase 2 study cohort patients receiving only one heating sweep. [Table 1](#) highlights the patient characteristics and details of the treatment strategy, and [Supplemental Material S2](#) shows the extent of immediate NPV compared to baseline prostate volume.

2.3. Imaging protocol

Most patients underwent baseline- and follow-up imaging on a 3 T MR system with a 32-channel torso coil (Ingenia 3 T, Philips Healthcare, Netherlands). The intravenous contrast media used was gadoterate meglumine (Dotarem, Guerbet, France).

BPH, radiorecurrent and primary PCa patients underwent baseline MR imaging before TULSA treatment (mean 64, 59, and 99 days, respectively) to establish baseline prostate volume. All patients were imaged with MRI during and immediately after the TULSA intervention. In the BPH and radiorecurrent cohorts, patients were imaged with MRI

Table 1
Patient and TULSA treatment characteristics.

	BPH (n = 21)	Radiorecurrent PCa (n = 28)	Primary PCa (n = 40)
Median patient age (yr, IQR)	68 (64–72)	73 (69–76)	69 (65–73)
Treatment strategy	transition zone	19 whole-gland 9 partial	9 whole-gland 31 partial
Median sonication time (min, IQR)	44 (24–58)	49 (39–63)	40 (30–64)
ISUP Grade Group (for Primary PCa group)	–	–	5 GG1 24 GG2 9 GG3 2 GG4
Median time between radiation therapy and TULSA (yr, IQR)	–	11 (8–14)	–

BPH, Benign prostatic hyperplasia; ISUP, The International Society of Urological Pathology; IQR, interquartile range; PCa, Prostate cancer.

at 3- and 12 months post-TULSA, while primary PCa patients were imaged at 6- and 12 months post-TULSA.

MRI sequences included T2-weighted (T2w), diffusion-weighted (DW), and T1-weighted (T1w) fat-saturated (fs) contrast-enhanced imaging. A detailed MRI sequence protocol is summarized in [Supplemental Material S3](#).

2.4. Non-perfused volume (NPV) and prostate volume

NPVs were manually contoured using the contrast-enhanced T1w fs images (slice thickness = 3 mm, TR = 496 ms, TE = 8 ms, in-plane resolution = 0.75×0.75 mm). The non-enhancing prostatic and periprostatic tissue was designated as the NPV. Prostate volumes were manually contoured (AW Server 3.2, GE Healthcare, Chicago, Illinois, United States) using the axial T2w images with 3 mm slice thickness. Post-procedural peri-prostatic fibrosis, fluid-filled cavities, and cyst formation were excluded from the contoured areas in prostate volume and NPV measurements.

Subgroup analysis was also performed. The difference in NPV evolution between whole-gland and partial ablation for the radiorecurrent and primary PCa group was assessed. Additionally, the influence of the number of heating sweeps on residual NPV was analyzed for the BPH cohort.

Since this study was retrospective, only one clinical reader (P.M.) was used to segment the NPV for all images. The reader had over five years of experience in prostate MRI and TULSA therapy. For this reason, inter- and intra-reader reliability were not evaluated.

2.5. Statistical analysis

JMP® (Version 16.2.0 Pro. SAS Institute Inc., Cary, NC, 1989–2021) was used for statistical analysis. Normality assumptions were confirmed using a normal quantile plot, box plot, kurtosis/skewness evaluation, and Shapiro-Wilk test. Normally distributed data were reported as mean, and the skewed distribution data as median values. Significance testing between two variables was performed using a two-sample t-test for normally distributed variables and Wilcoxon rank sum test as a nonparametric test. Levene's test was used to evaluate the assumption of equality of variances. Kruskal-Wallis test was used for multiple comparisons between all groups for the relative change of NPV at 12 months. P values of ≤ 0.05 were considered statistically significant.

3. Results

3.1. Non-perfused volume

[Table 2](#) summarizes the median (IQR25, IQR75) NPV values for each treatment arm as a function of different time points. [Fig. 1](#) is a box and whisker plot of the NPV, which shows the absolute and relative changes during the follow-up. Compared to the immediate post-treatment NPV, the median NPV decreased by 14.9 mL (77 % decrease) by three months for the BPH cohort. For the same BPH cohort, there was virtually no NPV left at 12 months (99 % decrease). For the radiorecurrent PCa cohort, the median NPV increased by 4 % at three months, but by 12 months, it had also virtually disappeared. For the primary PCa cohort, the NPV almost entirely disappeared by six months (97 % decrease) compared to immediately post-treatment, and the same trend continued at 12 months. There was no statistically significant difference between groups in the relative NPV change at 12 months ($p = 0.132$, Kruskal-Wallis). [Fig. 2](#) demonstrates a representative patient example of NPV change for each patient group.

At 12 months, measurable NPV remained in 12/21, 12/28 and 12/40 patients in the BPH, radiorecurrent and primary PCa groups, respectively. If NPV was leftover, the total amount was mainly small, typically less than 1 mL. There were, however, two notable outliers in the whole-gland radiorecurrent PCa cohort, whereby two patients had residual NPV of 16 and 17 mL at 12 months, respectively.

There was a significant difference in the median relative change of the NPV at three months between the BPH and radiorecurrent PCa cohorts ($p < 0.0001$, Wilcoxon rank sum test), with the latter harboring considerably more necrotic tissue based on NPV. In the radiorecurrent and primary PCa cohorts, subgroup analysis between partial and whole-gland treatment groups were made, and one significant difference was found at three months: radiorecurrent PCa patients undergoing partial salvage ablation had a median NPV change of -14% , while whole-gland salvage patients had a median NPV change of $+13\%$ ($p = 0.024$, Wilcoxon rank sum test).

In a BPH subgroup analysis, phase I patients who received two sweeps of transitional zone and phase II patients with only one sweep, had no statistically significant difference on the immediate mean NPVs ($p = 0.606$, two-sample t-test), nor in the relative NPV change at 3 months ($p = 0.698$, Wilcoxon rank sum test) or at 12 months ($p = 0.435$, Wilcoxon rank sum test).

[Supplemental Material S4](#) shows NPVs by treatment strategy for radiorecurrent and primary PCa groups, and a 3D illustration of NPV measurement and evolution is provided in [Supplemental Material S5](#).

3.2. Prostate volume

For the BPH cohort, the median prostate volume decreased by 29 % at three months compared to baseline and by 34 % at 12 months. For the radiorecurrent PCa cohort, a slight median prostate volume increase of 1 % was recorded at three months, followed by a noticeable 85 %

Table 2
Median (IQR) prostate volumes and NPVs.

	BPH mL	Radiorecurrent PCa mL	Primary PCa mL
Baseline prostate volume	55 (47–67)	24 (20–30)	30 (26–39)
3mo prostate volume	40 (30–50)	24 (21–35)	NA
6mo prostate volume	NA	NA	20 (14–24)
12mo prostate volume	33 (31–43)	5 (2–12)	17 (12–22)
Immediate NPV	20 (13–26)	14 (10–20)	10 (9–14)
3mo NPV	5 (1–9)	16 (10–22)	NA
6mo NPV	NA	NA	0 (0–1)
12mo NPV	0 (0–1)	0 (0–1)	0 (0–0)

BPH, Benign prostatic hyperplasia; NA, not applicable; PCa, Prostate cancer.

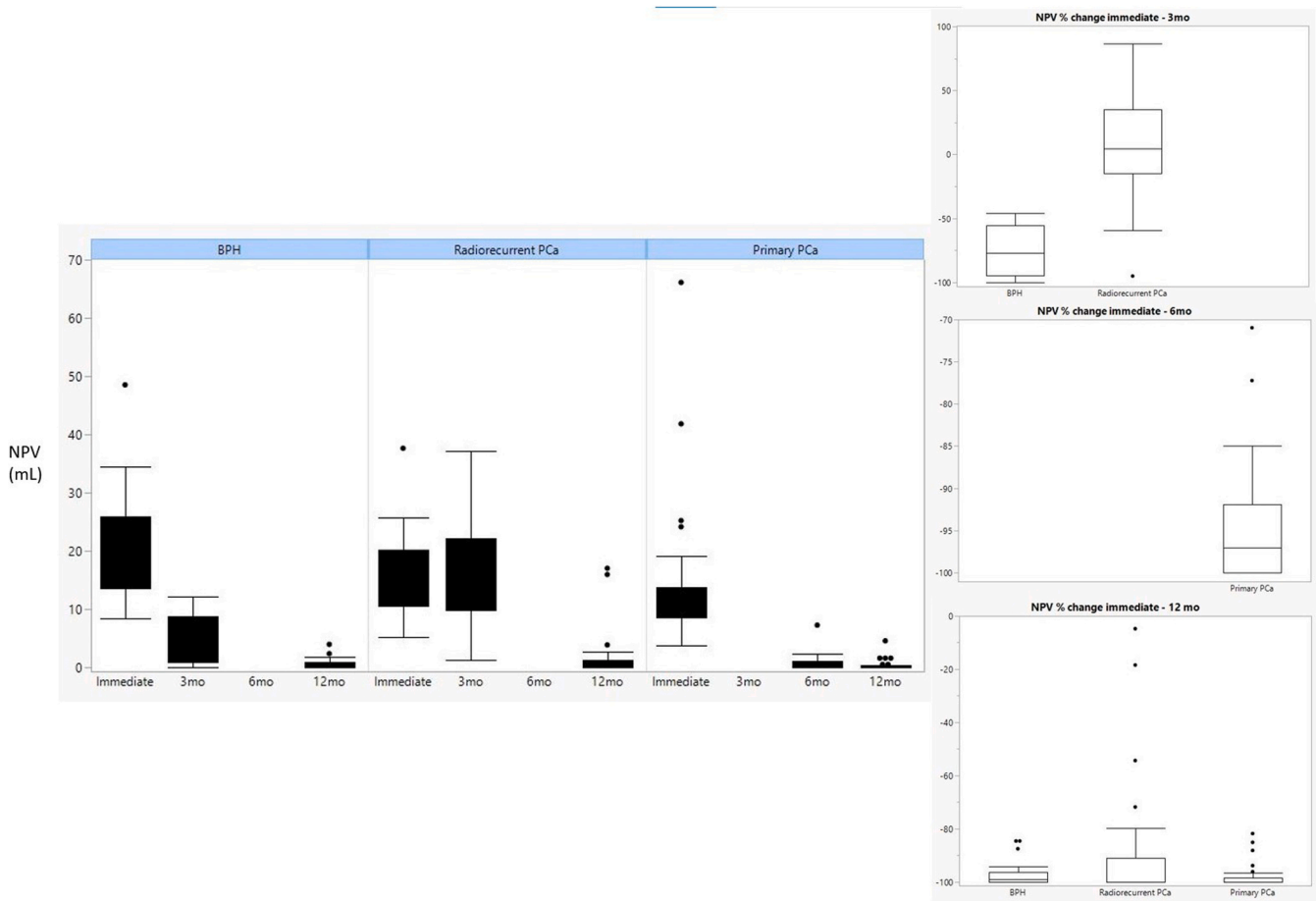


Fig. 1. Absolute and relative NPV change by treatment group at different time points.

decrease at 12 months. Finally, for the primary PCa cohort, the median prostate volume decreased by 36 % at six months and 41 % at 12 months. Fig. 3 is a BPH patient example highlighting the NPV evolution and gradual disappearance of prostatic tissue post-TULSA.

4. Discussion

This study measured the NPV at different time points after TULSA ablation for different treatment cohorts, including BPH, radiorecurrent, and primary PCa. It was shown that the resolution of necrotic prostate tissue after ablation, as measured by the disappearance of NPV, was substantially slower for previously irradiated than treatment-naïve prostate tissue. However, by 12 months, most of the necrotic prostate tissue had disappeared in each treatment group.

Some researchers have reported NPV changes after prostate ablation therapy. In an ultrasound-guided transrectal HIFU study conducted by Rouvière et al. [22] on primary PCa patients (n = 15), which included both whole-gland and lesion-targeted treatments, 11 patients had their CE-MRI control at 3–5 months post-treatment. At this timepoint, only 2/11 (18 %) patients had measurable NPV. In another study with 14 patients undergoing ultrasound-guided HIFU for primary PCa, Kirkham et al. [21] reported that roughly 60 % of patients still had measurable NPV at six months. The residual NPV, if it existed, was small (less than 1 mL for all save for one patient with 4 mL). The results from the current study agree with these prior observations at six months. In the primary PCa group, 26/40 (65 %) patients had leftover NPV. If residual NPV was detected, it tended to be very small, with a median (IQR25–75) value of 0.4 mL (0–1.1).

Despite the absence of NPV evolution studies for BPH patients, one

study by Mueller-Lisse et al. [25] reported treatment-induced lesion core volume evolution after laser ablative therapy for treatment of BPH. In this case, only T2w imaging on a 1.0 T MRI scanner was used to determine the lesion core size at future time points by comparing to a control scan shortly after treatment. This was performed by contouring the T2 hypointense area surrounded by a hyperintense rim. The authors reported lesion core volumes for four patients at two months (mean 55 % decrease) and only one patient at 6 months (96 % decrease). These results are not directly comparable to the current study because no contrast-enhanced images were used. However, there is prior evidence that T2w assessment of lesion core volume correlate with T1 contrast-enhanced measurements [15]. In that regard, the Mueller-Lisse study does align with our results as well.

At the longer timepoint of 12 months, only one study conducted by Bonekamp et al. [20] reported NPV changes after prostate ablation. In this phase-1 study, 29 patients undergoing whole-gland TULSA with a conservative 3 mm safety margin for the treatment of primary PCa were included. Median (IQR25–75) NPV values of 19 (15–26) and 9 (6–12) mL were reported immediately after ablation and at 12 months, respectively. In contrast, the results from the current study showed that by 12 months only 12/40 (30 %) patients had any residual NPV at 12 months, and if there was any, it tended to be very small, with a median (IQR25–75) value of 0 mL (0–0.1). It is possible that discrepancies may have arisen from the NPV measurement technique. For example, including fluid-filled cavities or cysts in the NPV would inflate the post-ablation NPV measurement. Also, different treatment strategies may have impacted. However, difference persisted regardless of whether whole-gland or partial gland treatment was performed, with our primary PCa cohort including 9 whole-gland treatments with a

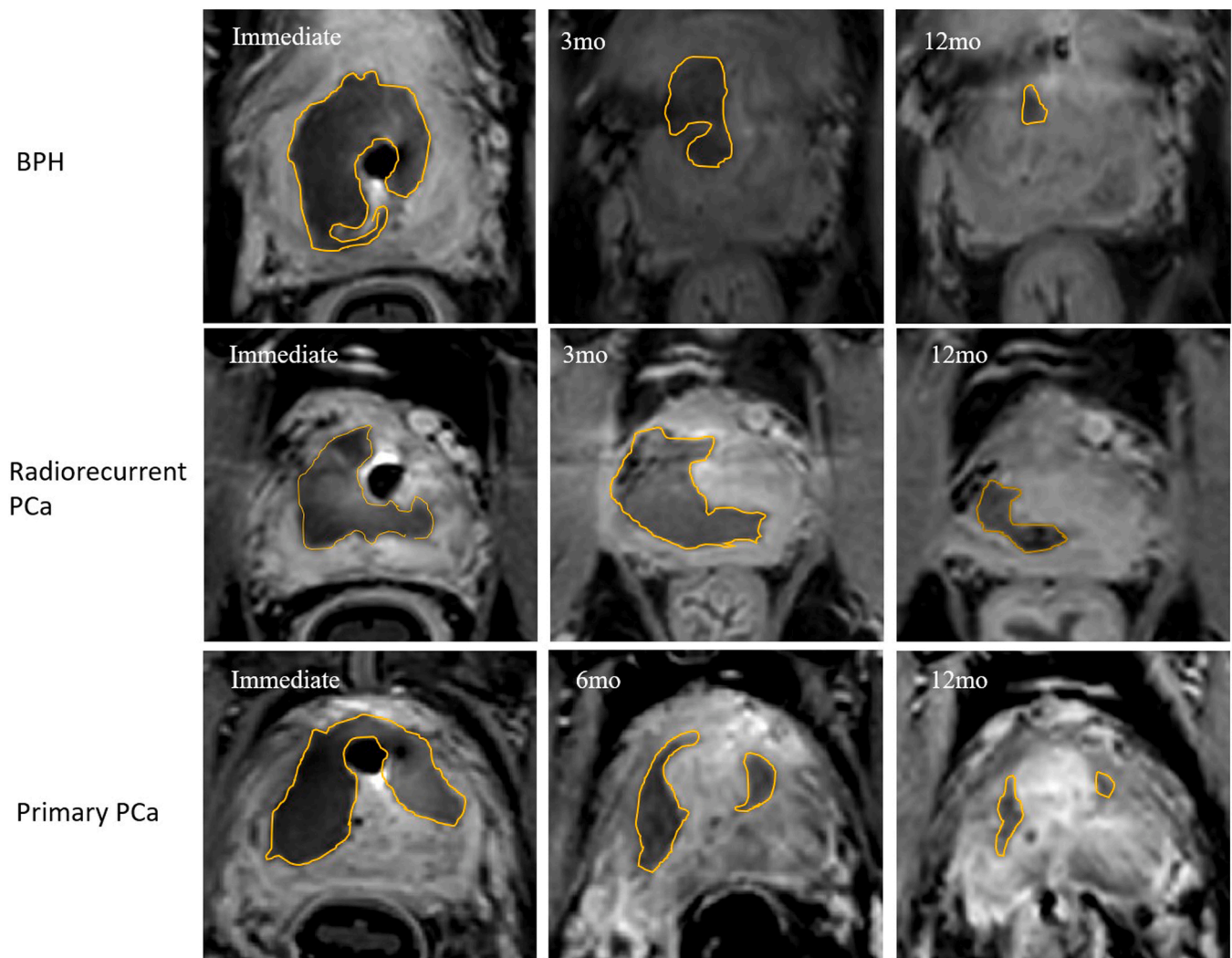


Fig. 2. Examples of NPV evolution for a BPH (upper row), a radiorecurrent PCa (middle row) and a primary PCa (bottom row) patient.

median (IQR25–75) NPV of 16 mL (13–24) immediately and 0 mL (0–1) at 12 months post-TULSA.

While some authors have reported NPV evolution after prostate ablation for treatment-naïve prostate tissue, there is no evidence for previously irradiated tissue. Radiation therapy induces several delayed tissue changes, including fibrosis, necrosis, atrophy, and vascular damage [26], thereby prolonging the tissue recovery process. In the current study, a significant difference in NPV was found at three months between the BPH and radiorecurrent PCa groups. In the BPH cohort at three months, the median NPV change was -77% . Conversely, in the radiorecurrent PCa cohort, the NPV had not diminished but increased by 4% . Based on previous studies, patients who undergo salvage TULSA for radiorecurrent PCa tend to experience more severe and more frequent urinary symptoms within the first few months after treatment than those who undergo TULSA for treatment-naïve prostate diseases [19]. Urinary symptoms for TULSA-treated radiorecurrent PCa patients seem to relieve within one year [17,27]. The results from this study, which demonstrated that radiorecurrent PCa patients have a slower disappearance of necrotic tissue after TULSA, might partially explain this phenomenon.

One significant difference was found during subgroup analysis regarding partial vs. whole-gland salvage ablation of radiorecurrent PCa at three months: NPV decreased after partial ablation and increased after whole-gland ablation. These results suggest that the more necrotic tissue present, the longer it takes to remove. In contrast, after six months for

the primary PCa group, no statistical differences were found in leftover NPV between partial vs. whole-gland ablation subgroups. However, this time point may be too long to capture the possible difference. By 12 months, no statistical differences were found for either treatment group.

Another interesting aspect of NPV evolution is how the amount of accumulated thermal dose might influence the evolution of NPV. Thermal damage due to heating is not only dependent on elevated temperature but also on the duration of heat exposure. The thermal dose can be increased in TULSA by performing multiple heating sweeps. Interestingly, no significant difference in NPV immediately post-treatment, nor in the relative NPV change at three or 12 months, was observed for the BPH cohort, whether they received a single or double heating sweep. These findings suggest that increased accumulated thermal dose does not impact the NPV evolution.

There remains uncertainty about how necrotic prostate tissue disappears after coagulative therapies. Prior thermal ablation studies have shown that tissue resorption by macrophages and other inflammatory cells is one route [11,28]. However, based on the work by Mäkelä et al. [17], who reported that after salvage TULSA for radiorecurrent PCa, 11/18 fiducial markers had disappeared from the ablation zone by 12 months, sloughing of necrotic tissue via the prostatic urethra likely also plays a role since this is the only viable pathway for markers to disappear.

This study has several limitations. The present study was retrospective as opposed to prospective making the results more prone to bias.

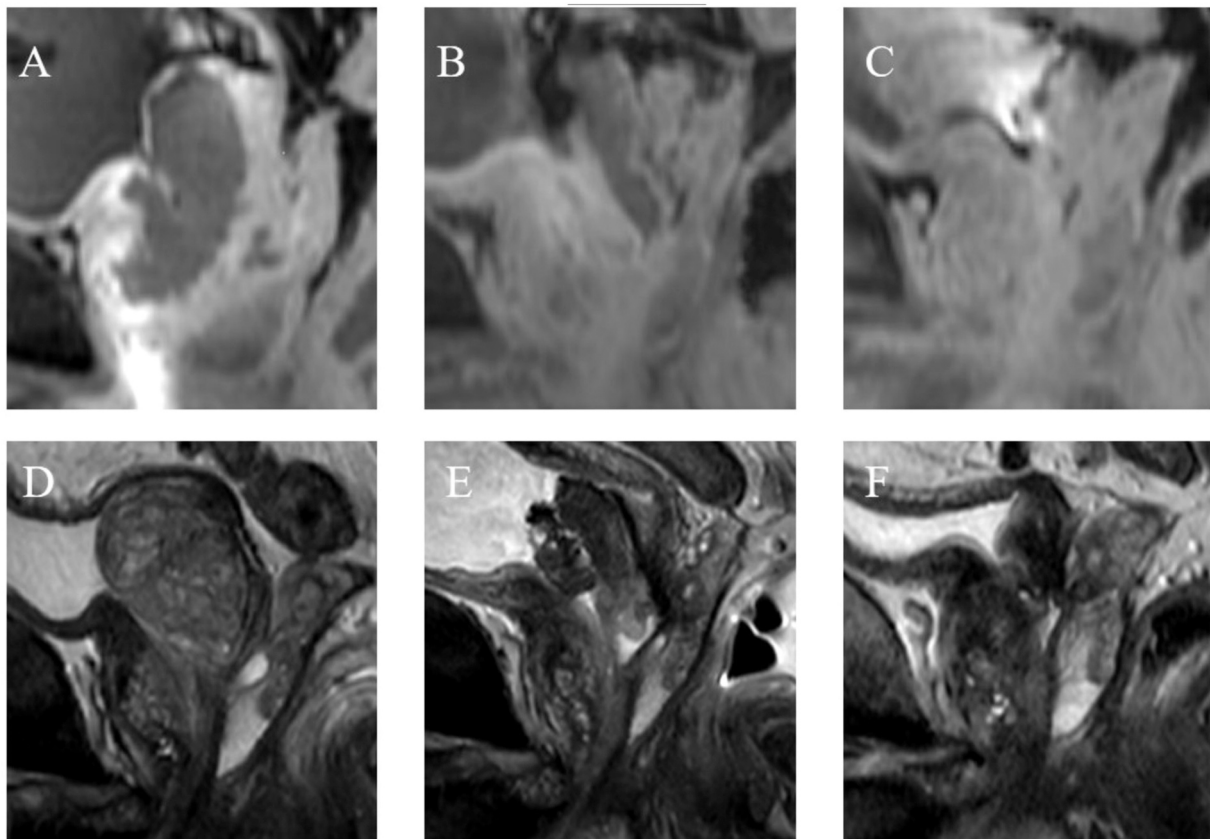


Fig. 3. Gradual disappearance of NPV and prostatic tissue in patient nr 13 in BPH group. In the upper row T1fs + c sag images; immediately (a), 3 months (b) and 12 months (c) after treatment. Lower row shows T2 sag images; pre-treatment (d), 3 months (e) and 12 months (f) post-TULSA. At 3 months, NPV has clearly diminished compared to large immediate NPV, and disappeared at 12 months.

Furthermore, patient disease characteristics, prostate sizes, and ablation volumes were variable across and within the different treatment cohorts. This could confound the results since underlying physiological mechanisms that influence necrotic tissue removal may not have been properly accounted for. Additionally, post-procedural prostate and surrounding tissue changes complicate the task of prostate and NPV contouring. Since only a single reader was used, these complications may add some systematic bias to the current results, potentially over- or underestimating the prostate and NPV volumes. Multiple readers with repeat measurements would have facilitated measurements of inter- and intra-reader variability and addressed this limitation. Finally, the primary PCa had their interim follow-up at six months instead of three, which makes intra-group comparison more challenging at this particular time point.

To conclude, the resolution of necrotic tissue after TULSA was markedly slower in previously irradiated prostate tissue than in treatment-naïve prostate tissue. Furthermore, salvage patients undergoing whole-gland ablation tended to have more residual NPV compared to those who had partial ablation. These results may account for the increased toxicity observed after radiorecurrent salvage therapy, as well as those who undergo whole-gland therapy. Also noteworthy is that by 12 months, most necrotic tissue had disappeared, irrespective of cohort. Future research includes confirming these results through a prospective study with more consistent disease characteristics and treatment plans in each study group, and the inclusion of multiple readers. Additionally, a detailed comparison of the correlation between the amount of leftover necrotic tissue and the number of urinary side effects should be directly explored. This will give physicians more tools to both anticipate and manage potential unwanted complications after heat-based ablation therapies.

CRediT authorship contribution statement

Pietari Mäkelä: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mikael Anttinen:** Validation, Methodology, Investigation, Data curation, Conceptualization, Writing – original draft, Writing – review & editing. **Peter Boström:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Roberto Blanco Sequeiros:** Investigation, Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. **Cameron Wright:** Data curation, Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Teija Sainio:** Writing – review & editing, Software, Methodology, Investigation, Conceptualization.

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Ethical statement

All imaging data in this study were acquired as part of an ethics-approved, single-center, phase 1–2 study of TULSA therapy for BPH and radiorecurrent PCa patients (NCT03350529), and phase 2 study for primary PCa patients (NCT03814252). In these abovementioned studies all patients have signed the appropriate Ethics Committee (EC) approved informed consent documents in the presence of the designated staff.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mikael Anttinen reports a relationship with Profound Medical that includes: funding grants. Cameron Wright reports a relationship with Profound Medical that includes: employment. Peter Bostrom reports a relationship with Profound Medical that includes: speaking and lecture fees.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejro.2023.100506](https://doi.org/10.1016/j.ejro.2023.100506).

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