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FULL PAPER

Percutaneous MR-guided whole-gland prostate cancer cryoablation: safety considerations and oncologic results in 30 consecutive patients

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Objective: To assess the safety and oncological efficacy of percutaneous MR-guided whole-gland prostate cancer (PCa) cryoablation (CA).

Methods and materials: Between July 2009 and January 2018, 30 patients (mean age 72.9 ± 5.13 years) with histologically proven, organ-confined ($\leq$ T2cNOMO), predominantly low/intermediate-risk PCa (median Gleason score 7; mean prostate specific antigen 6.05 ± 3.74 ng ml⁻¹) underwent MR-guided whole-gland CA. Patients were selected on the basis of prior pelvic radiotherapy ($n = 16$; 12 for previous PCa), or contra indication/refusal of surgery or radiotherapy. Complications, local progression-free survival (LPFS) and overall survival (OS) were retrospectively investigated.

Results: Eighteen [60%] patients reported procedure-related complications: 5/18 [28%] needed surgical/interventional treatments and 13 [72%] conservative or pharmacological treatment. Eleven [73%] complications were noted in the first 15 patients and 7 [47%] in the last 15 patients ($p = 0.26$). Mean nadir prostate specific

antigen was 0.24 ± 1.5 ng ml⁻¹ (mean follow-up 3.8 years; range: 2 – 2915 days). Seven [23%] patients developed histologically proven local progression (mean time to recurrence 775 days, range: 172 – 2014). Mean clinical follow-up was 3.8 years (range 1–2915 days). LPFS was 92.0, 75.7 and 69.4 % at 1-, 3- and 5 year follow-up, respectively. For patients in salvage treatment, LPFS was 100%, 75%, and 75% at 1-, 3- and 5 year follow-up. OS was 100%, 94.4 and 88.5 % at 1-, 3- and 5 year follow-up respectively, with no patients dying from PCa.

Conclusion: Whole-gland PCa CA offers good oncological efficacy, particularly in post-radiotherapy cases. Although the complication rate is significant, the majority is minor and is managed with conservative or pharmacologic management.

Advances in knowledge: MRI-guided whole-gland prostate cancer cryoablation offers good oncological efficacy, particularly in post-radiotherapy cases with a contained complication rate.

INTRODUCTION

Prostate cancer (PCa) is the most common malignant tumor in males, accounting for almost 1 in 5 new cancer diagnoses in the USA.¹ Despite recent reductions in age-standardized mortality, PCa remains the third most common cause of cancer-related mortality in males.^{1,2}

Standard curative treatment for prostate-confined disease includes radical prostatectomy and radiotherapy.³ According to 2017 American Urological Association guidelines, whole-gland cryoablation (CA) is a third intention alternative curative therapy for patients unsuitable for

standard treatments with good life expectancy (>10 years) and intermediate-risk disease (*i.e.* prostate specific antigen (PSA) 10.0–20.0 ng ml⁻¹, Gleason score = 7, cT2b-c); and may be offered to low-risk patients (PSA <10.0 ng ml⁻¹, Gleason Score <7, cT1c-T2a) following discussion of potential complications and absence of survival benefit compared with active surveillance.⁴ CA has also been proposed as salvage therapy for patients with local recurrence following radical radiotherapy.⁵

Several studies have established that whole-gland and focal CA for primary/radio-recurrent PCa provides acceptable

oncologic efficacy compared with standard treatments, and similar or lower morbidities (other than a higher rate of sexual dysfunction).^{6,7} However, side-effects remain common (up to 40% of primary and 72% of salvage treatments),^{5,8} and a contributory factor may be the technical limitations of transrectal ultrasound-guidance (TRUS) used in these studies.⁹

MR imaging-guided CA offers superior multiplanar ice-ball monitoring relative to vulnerable critical structures, accurate needle-guidance using MR-fluoroscopy sequences, and potential safety advantages over ultrasound-guidance.¹⁰ Several studies applying MR-guided focal CA to PCa recurrence post-prostatectomy/radiotherapy have shown promising initial results,^{11–13} although local control may be suboptimal.^{14,15} Two small studies investigating MR-guided whole-gland CA of PCa have demonstrated good early/mid-term PSA response, with variable complication rates,^{16,17} but the whole-gland technique has received less attention in the literature.

The purpose of this study is to retrospectively assess safety and oncologic efficacy of MR-guided whole-gland CA for PCa in a series of 30 patients; and evaluate results in relation to existing second-line therapies for low/intermediate risk PCa.

METHODS AND MATERIALS

This retrospective case series was approved by the institutional review board with a waiver of informed consent. The study was compliant with the Health Insurance Portability and Accountability Act.

Patients

Between July 2009 and January 2018, 30 patients (mean age 72.9 ± 5.1 years; range 62–84 years) underwent percutaneous MR-guided whole-gland CA for PCa. All patients had biopsy-proven PCa on TRUS-guided non-targeted 16-core biopsy (mean Gleason score 6.73 (min 5 (2 + 3); median 7 (3 + 4); max 8 (4 + 4)), and a gland confined disease (TNM stage between T1N0M0 and T2cN0M0). Mean PSA was 6.05 ± 3.7 ng ml⁻¹ (range: 1.05–15.98 ng ml⁻¹).

Patients were referred for CA following multidisciplinary tumor-board discussion on the basis of: (i) prior pelvic radiotherapy relatively contraindicating surgery (4 cases with previous rectal cancer; 12 with locally radio-recurrent PCa); (ii) patient refusal of standard surgical/radiation therapies ($n = 14$); and life expectancy >10 years. For 18 patients (3/18 low-risk, 15/18 intermediate-risk), CA was the primary curative treatment. No patients received androgen deprivation therapy. Four patients had a history of transurethral resection of the prostate (TURP) due to obstructive urinary symptoms. Population data are summarized in Table 1. The first eleven patients of this study have been previously reported by Gangi *et al* in 2012¹⁶. This prior report mainly focused on the feasibility of the procedure as well as on tumor response at short-term. On the other hand, the current study expands on safety and oncological efficacy by evaluating these two aspects in a larger population in which a longer and detailed follow-up was available.

Procedure

All procedures were performed under general anesthesia and strict sterile conditions, by 1 of 6 interventional radiologists with at least 4 years of interventional oncology experience. Antibiotic prophylaxis (Ofloxacin 200 mg) was administered intravenously prior to CA. Treatment was deferred in the event of local/systemic infection or uncorrected coagulopathy. A large-bore 1.5 T interventional MRI scanner (Magnetom-Espree and Magnetom-Aera; Siemens, Erlangen, Germany), pelvic phased-array coil, and MR-compatible cryoablation system (MR-Seednet, Galil-Medical, Yokneam, Israel), were used for MR-guidance. Multiplanar T2 BLADE (Slice thickness = 2.5 mm, repetition time (TR) = 2000 ms, echo time (TE) = 137 ms) and/or three-dimensional T2 SPACE (Slice Thickness = 2 mm, TR = 1000, TE = 126 ms) and/or T2 TrueFISP (slice thickness = 5 mm, TR = 4 ms, TE = 2 ms) sequences were acquired for pre-procedural planning and thermoprotection, intraprocedural probe placement-confirmation and ice-ball monitoring, and assessment of post-procedural complications. BEAT-IRRT (Slice thickness = 4 mm, TR = 850 ms, TE = 2.5 ms) or T2 TrueFISP (slice thickness = 5 mm, TR = 4 ms, TE = 2 ms) real-time MR-fluoroscopy sequences were utilized for free-hand probe advancement under continuous imaging-guidance in at least two planes.

Patients were positioned supine with legs slightly elevated, the perineum was exposed by scrotal elevation and strap fixation. This positioning was maintained using a departmental custom-made MR-compatible support for the first 15 patients, and the Uni-Lift Prostate Intervention Device (NORAS GmbH, Hochberg, Deutschland) for the remainder; this device includes a template/grid to facilitate precise probe spacing/stability (Figure 1). Initially, multiplanar T2 sequences were acquired to target the prostate and plan probe trajectories. Using MR-fluoroscopic sequences, multiple (4–10) cryoprobes (Ice Rod[] for the first six patients and IceSeed[] for the remainder; Galil-Medical, Yokneam, Israel) were advanced into the prostate and positioned 1 cm apart (5 mm from the prostatic capsule). Adequate position was confirmed on multiplanar T2-sequences prior to ablation (Figure 2).

A variety of thermoprotective techniques were utilized throughout the study to protect the rectal wall through hydro-/hemo-dissection of the recto-prostatic space (Figure 1),¹⁸ and the urethral sphincter (Table 2); external urinary sphincter thermometry was performed by positioning a transurethral thermocouple at the level of the prostatic apex. Urethral and rectal warming catheters were continuously flushed with warm saline during freezing. The first two cases were performed without thermoprotection. All subsequent cases were performed using at least one rectal and one urethral protective technique.

CA was performed using a standard 10 min freeze—10 min thaw—10 min freeze protocol with intermittent MR-monitoring to assess ice-ball propagation and ensure ablation-zone margins (Figure 2). If required, a third freezing-cycle was performed with probe repositioning and/or additional probe deployment. Freezing was terminated prematurely if recorded urethral temperature was <10C (for cases with urethral

Table 1. Demographic characteristics and clinical features of study population

Patient	Age	PSA before Cryoablation (ng/ml)	TNM	Gleason	TURP	RT	Type of pelvic cancer treated by RT	Prostate volume (ml)
1	62	7.33	T1cN0M0	4 + 3	-	-		27.4
2	78	14.90	T2bN0M0	3 + 3	-	-		37.3
3	65	7.06	T2bN0M0	3 + 3	-	-		59.0
4	75	4.89	T2bN0M0	3 + 3	-	-		53.3
5	67	6.40	T2aN0M0	3 + 4	-	+	rectum	24.5
6	72	4.78	T2aN0M0	2 + 3	+	-		44.8
7	74	5.51	T2bN0M0	3 + 4	-	-		38.3
8	74	11.43	T2cN0M0	3 + 4	-	-		52.6
9	78	3.01	T1cN0M0	4 + 3	+	-		27.4
10	78	2.04	T1bN0M0	3 + 3	+	-		11.0
11	73	1.05	T2cN0M0	4 + 4	-	+	prostate	25.0
12	70	3.91	T2bN0M0	4 + 3	-	+	prostate	24.1
13	76	3.10	T2bN0M0	3 + 4	-	-		48.5
14	73	4.34	T2aN0M0	3 + 3	-	-		41.7
15	75	6.59	T2aN0M0	3 + 4	+	-		36.3
16	73	2.75	T2cN0M0	4 + 4	-	+	prostate	34.0
17	70	7.00	T2cN0M0	3 + 4	-	-		29.4
18	71	4.30	T2bN0M0	3 + 3	-	-		30.9
19	73	4.50	T2aN0M0	3 + 4	-	+	prostate	53.6
20	69	14.00	T2bN0M0	4 + 4	-	+	rectum	36.0
21	80	4.17	T2aN0M0	3 + 4	-	+	prostate	14.0
22	75	3.90	T2cN0M0	3 + 3	-	+	prostate	52.9
23	68	6.56	T2aN0M0	3 + 3	-	+	prostate	17.4
24	69	15.98	T2cN0M0	3 + 4	-	+	rectum	43.8
25	69	10.00	T2aN0M0	3 + 4	-	+	rectum	44.3
26	75	6.27	T2aN0M0	4 + 3	-	+	prostate	59.4
27	80	5.48	T2cN0M0	4 + 3	-	+	prostate	13.2
28	84	2.78	T2aN0M0	3 + 3	-	+	prostate	27.0
29	63	3.04	T2bN0M0	4 + 3	-	+	prostate	38.7
30	78	4.30	T2bN0M0	4 + 3	-	+	prostate	32.6

PSA, prostate specific antigen; RT, radiotherapy; TURP, transurethral resection of the prostate.

sphincter thermometry), or if the ice-ball contacted the anterior rectal wall. Post-procedural T2 MR-sequences assessed immediate complications. Following a short thaw-cycle, cryoprobes and thermoprotective devices were withdrawn; incision-sites were dressed; and urinary catheters were left *in-situ* to avoid post-procedural retention. Patients were transferred to a recovery ward, and discharged at the discretion of the referring urologist.

Post-procedure follow-up

Clinical and biochemical follow-up was performed by the referring urologist at 1, 3, 6, 9 and 12 months post-CA, and annually thereafter provided PSA remained stable. Multiparametric MRI follow-up was scheduled at 2 months post-CA, and at urologist discretion thereafter. In the event of clinical/radiological suspicion of local disease progression, ultrasound-guided transrectal 16-core biopsy was systematically performed.

Figure 1. Current patient preparation and positioning before cryoprobes insertion. After general anesthesia and antibiotic administration, a dissection of the Denonvillier's fascia is performed under ultrasound guidance (A). Autologous blood injection (B) allows a reversible but long-lasting enlargement of the recto-prostatic space. The ultrasound probe and the needle are then withdrawn, the grid is placed on its support and the patient is draped sterile (C).

Local tumor progression was defined as tumor recurrence on follow-up MRI, positive biopsy or biochemical failure according to the Phoenix criteria (PSA nadir + 2 ng ml⁻¹).¹⁹

Data collection and analysis

Procedural data collection included number of cryo-probes/freezing-cycles, total freezing-time, ice-ball volume (measured at end of final freezing-cycle on T2 BLADE/SPACE MR sequences), pre-ablation prostatic volume (electronically measured on planning T₂ weighted MR images), procedural duration and immediate complications. Retrospective chart/imaging review analyzed hospital stay; duration of clinical follow-up; PSA nadir; minimum prostatic volume on follow-up MR; local tumor progression (defined as tumor recurrence on follow-up MR, positive biopsy or biochemical failure according to Phoenix criteria (PSA nadir + 2 ng ml⁻¹)¹⁹; and complications (graded according to Clavien–Dindo classification²⁰ as well as their management.

Statistical analysis was performed using R statistical software (v 3.4.5). Descriptive statistics were used to present results; paired Wilcoxon tests were used to compare pre- and post-procedural parameters; Fisher's exact test was used to assess correlation between variables; and Kaplan–Meier survival curves were plotted to evaluate local progression-free survival (LPFS) and overall survival (OS); $p < 0.05$ was considered statistically significant.

RESULTS

All procedures were undertaken successfully using 4–10 cryo-probes (mean 5.7 ± 1.2), and at least two freezing-cycles. Three cycles were undertaken in six patients to ensure whole-gland ablation; in three cases ablation was terminated prematurely due to ice-ball proximity to the rectal wall. Mean freezing time was 21.1 min (range 10–30 min, median = 20 min). Mean ice-ball volume at end of final freezing cycle (50.8 ml; range 21–90 ml) was significantly larger than mean pre-CA prostatic volume (35.9 ± 13.6 ml; range 11–59.4 ml), with a mean difference of 50% ($p <$

0.001). Mean procedural duration was 180 min (range 110–270 min); significantly longer for the first 15 patients than the last 15 (207 vs 160 min; $p < 0.001$). There were no immediate complications. Mean hospital stay was 5.7 days (range 3–13 days).

Mean clinical follow-up was 3.8 years (median 4.9 years; range 1–2915 days). All patients demonstrated significant reduction in PSA, from mean 6.05 ± 3.7 ng ml⁻¹ (range 1.05–15.98 ng ml⁻¹) pre-treatment, to a mean PSA nadir of 0.82 ± 1.50 ng ml⁻¹ (range 0.02–6.92 ng ml⁻¹; $p < 0.001$). Mean prostate volume significantly decreased from 35.9 ml (range 11–59.4 ml) to 20.5 ml (range 4–84 ml) at mean 423 days (range 25–1712 days) post-procedure; mean volume reduction was 49% ($p = 0.001$).

Post-procedural complications occurred in 18 patients (60%), including 11/15 former cases (73%) and 7/15 latter cases (47%; $p = 0.26$). Major complications (grade ≥ 3) occurred in 6 cases (20%); 4 in the first 15 procedures (27%), and 2 in the last 15 (13%; $p = 0.65$). Five cases required surgical/interventional management, including TURP for persistent obstruction/retention ($n = 3$; 10%); endoscopic urethrotomy for stricture ($n = 1$; 3.3%) and artificial sphincter surgery for incontinence ($n = 1$; 3.3%). A single case of recto-urethral fistula (3.3%) was managed minimally invasively using a urinary probe. All minor complications were managed conservatively/pharmacologically (Table 3). There was no significant difference in major/minor complication rates between non-radiotherapy and post-radiotherapy treatment groups; or between patients with/without prior TURP. Among all tested variables, only use of >5 cryo-probes predicted development of major/minor complications (OR = 10.00, $p = 0.02$); Table 4.

In total, seven patients (23.3%) met criteria for local disease progression (mean time to progression 775 days; range 172–2014 days), including four patients with tumor progression on MRI (mean 514 days; range 285–652 days) and three biochemical failures. All progressions were confirmed via ultrasound-guided

Figure 2. Intraprocedural MRI monitoring during whole-gland CA procedure. Following placement of the urethral warming catheter, dissection of the recto-prostatic space and placement of thermocouples, the patient is installed on the MRI table and multiplanar T2 images are acquired. In this patient, Axial (A) and Sagittal (B) T2 TrueFISP images demonstrate intermediate-signal fluid in the recto-prostatic space (arrows) following initial hemodissection. Cryoprobes are then inserted under MR fluoroscopy; and a 3D T2 SPACE sequence is acquired to check probe placement (arrows) in the axial (C) and Sagittal (D) planes. During the freezing cycles, T2 space acquisitions are regularly obtained to evaluate the extension of the iceball. Axial (E) and Sagittal (F) 3D T2 SPACE reconstructed images showing the largest ice-ball size obtained at the end of the second freezing cycle; as clearly shown the posterior margins of the ice-ball (arrows) are relatively distant from the anterior rectal margin (arrowhead). 3D, three-dimensional; CA, cryoablation.

Table 2. Thermoprotective techniques utilized over study duration

Rectal wall protection	28/30 [93%]
Warmed intrarectal balloon	17/30 [57%]
Hydrodissection	3/30 [10%]
Hemodissection	8/30 [27%]
Urethral sphincter protection	28/30 [93%]
Urethral heating	27/30 [90%]
External urinary sphincter thermometry	7/30 [23%]

transrectal 16-core prostatic biopsy. No patients demonstrated metastatic disease on MR, or on subsequent re-staging isotope bone scan or ^{18}F -Choline positron emission tomography-CT. All were treated with androgen deprivation therapy.

Overall, LPFS was 92.0% [95% confidence interval (CI) (81.9–100)], 75.7% [95% CI (59.1–97.1)] and 69.4% [95% CI (51.3–93.9)] at 1-, 3- and 5 year follow-up, respectively (Figure 3). For patients treated primarily, LPFS was 88.9% [95% CI (75.6–100)] at 1 year, 75.2% [95% CI (56.7–100)] at 3 year, and 67.7% [95% CI (47.8–96.1)] at 5 year; compared with 100% [95% CI (100–100)] at 1 year, 75.0% [95% CI (42.6–100)] at 3 year, and 75.0% [95% CI (42.6–100)] at 5 year for salvage CA ($p = 0.82$) (Figure 4). OS was 100% [95% CI (100–100)], 94.4% [95% CI (84.4–100)] and 88.5% [95% CI (74.8–100)] at 1-, 3- and 5 year follow-up (Figure 5). There were two patient deaths due to lymphoma (Patient 20; 823 days) and pyelonephritis (Patient 9; 1693 days), but no mortality was observed due to PCA progression or treatment.

DISCUSSION

Percutaneous MR-guided whole-gland CA of PCA is a novel technique which aims to reduce complications and maintain oncologic efficacy compared with ultrasound-guidance. Unlike TRUS (where field of view is small, visualization of deep ablation-zone is limited by artifact, and recto-prostatic distance is narrowed to optimize image quality),^{9,21} MR-guidance offers superior multi-planar ice-ball visualization over a wide field of view, improved precision of cryo-probe placement, and applicability to post-surgical cases (e.g. abdominoperineal resection) without need for transrectal access.^{11,17} MR-guidance may therefore avoid collateral freezing of the urinary sphincter and rectum; more easily facilitate rectal thermoprotective techniques; and potentially reduce complication rates.

In the present study, major complication rate was 20%; including 3.3% recto-urethral fistula, incontinence requiring surgical management, and urethral strictures (respectively), and 10% requiring TURP for persistent retention. This is similar to previous reports for TRUS-guided and MR-guided whole-gland/focal CA for primary/salvage treatment of PCA, allowing for paucity of MR-guided CA data.^{5,8,11,14,16,22} Minor complications were frequent but gradually resolved with conservative/pharmacologic management; similar to prior ultrasound-guided studies,^{8,23} although higher than reported for MR-guided focal CA in post-prostatectomy cases.^{13,24} The cause of persistent/delayed urinary symptoms is unknown, but may partly be

secondary to evolution of treated prostatic tissue. Several present cases demonstrated marked necrosis/increased prostatic volume (persisting for 9–12 months), followed by gradual fibrosis/retraction on serial MR-examinations (Figure 6); this correlated with onset of irritative/obstructive symptoms (respectively) in a few patients. Early/mid-term symptoms may therefore putatively result from necrosis, and late-onset symptoms from fibrosis; in addition to post-CA effects on urinary sphincter function.

Absence of significant differences in complication-rates between patients with/without prior radiotherapy (mainly for previous/recurrent PCA), and cases with/without prior TURP, is contrary to previous reports suggesting higher complication rates for salvage CA in radio-recurrent PCA,^{5,25} and high risk of incontinence post-TURP.²⁶ However, although individual complications (e.g. 37.5% lower urinary symptoms) in post-radiotherapy cases were less frequent than in some ultrasound-guided reports (up to 72%),^{5,8} numerous alternative series have shown more comparable results.^{8,22} It is therefore possible that the discrepancy is due to small sample size rather than true outcome improvements.

Slightly higher than expected overall complication rates may partially be secondary to learning-curve effects. Fewer major complications were observed in the latter 15 cases than the former (statistically non-significant; likely due to small sample). Several factors could explain this tendency. Previous studies showed improvements in prostate biopsy results or in prostate brachytherapy dwell positioning when a template/grid is used.^{27,28} The template allows easier probe positioning, better probe stability and reliable probe spacing. Thus with easier probe positioning, improved cryo-probe technology and MR-fluoroscopic sequences (particularly T2 TrueFISP, permitting accurate needle positioning), and evolving thermoprotective techniques (interprostate-rectal space hemodissection and urinary sphincter thermometry,¹⁸ operator confidence to perform procedures time-efficiently and safely increased over the study period. Additional external urinary sphincter thermoprotection using hydrodissection below the prostatic apex is planned for future cases without apical tumor involvement, to minimize local freezing and hopefully reduce urinary morbidity. Major complication rates are thus anticipated to reduce as technique is refined.

Oncologic efficacy is difficult to compare between studies due to variable local recurrence definitions, heterogeneous populations, and systematically high OS for low/intermediate-risk disease and relatively short follow-up. In addition, the oncology results of this study should be interpreted taking into account the small sample size and the small number of patients with a 5 year follow-up (15) as confirmed by wide 95% CI intervals. However, the present biopsy-proven 3 year 24.3% overall local recurrence rate is comparable to the 20.4% 1 year local recurrence reported by Barqawi *et al* following ultrasound-guided primary whole-gland CA²⁹; and broadly similar to other biopsy-proven estimates in similar studies.³⁰ For primary treatment, the 5 year local recurrence rate of 32.3% is slightly higher than estimates of biochemical recurrence at similar time-points in comparable ultrasound-guided CA series,^{6,31,32} but significance is difficult to interpret due to small sample size and variable definitions.

Table 3. Complications in the study population

Patient	Type of complication	Clavien–Dindo Grade	Delay of occurrence	Management
1	Urinary tract infection	1	3 days	Antibiotic therapy
	Difficult urination	3A	1 month	TURP
2	Urethro-rectal fistula	3A	1 month	Wound healing on a urinary probe
3	Nocturnal frequent urination	2	1 month	Clinical monitoring +alpha-blocker
4	Acute urinary retention	2	3 days	Urethral Probe +alpha-blocker
	Difficult urination	2	1 month	Clinical monitoring +medical treatment
5	Acute urinary retention	1	3 days	Clinical monitoring
	Difficult urination	2	1 month	Clinical monitoring +medical treatment
6	Scrotal pain	1	1 day	Clinical monitoring
	Chronical urinary retention	3A	1 month	TURP
7	Macroscopic hematuria	1	1 day	Clinical monitoring
8	Acute urinary retention	2	3 days	Urethral Probe +alpha-blocker
	Urinary tract infection	2	3 days	Antibiotic therapy
10	Difficult urination	2	2 years	Clinical monitoring +alpha-blocker
	Nocturnal frequent urination	2	2 years	Clinical monitoring +alpha-blocker
11	Difficult urination (urethral stenosis)	3A	2 years	Endoscopic urethrotomy
13	Acute urinary retention	2	3 days	Urethral Probe +alpha-blocker
	Scrotal Hematoma	1	1 day	Clinical monitoring
	Urinary tract infection	2	2 months	Antibiotic therapy
19	Nocturnal frequent urination	2	2 months	Clinical monitoring +alpha-blocker
21	Incontinence	3B	1 year	Artificial urinary sphincter
23	Nocturnal frequent urination	2	1 month	Clinical monitoring +alpha-blocker
24	Acute urinary retention	2	3 days	Urethral Probe +alpha-blocker
	Nocturnal frequent urination	2	1 month	Clinical monitoring +alpha-blocker
25	Acute urinary retention	2	3 days	Urethral Probe +alpha-blocker
	Urinary tract infection	2	7 months	Antibiotic therapy
26	Nocturnal frequent urination	2	1 month	Clinical monitoring +alpha-blocker
	Difficult urination	3A	1 month	TURP
28	Difficult urination	2	3 months	Clinical monitoring +alpha-blocker

TURP, Transurethral resection of the prostate.

Notably, for patients with radio-recurrent PCa, 5 year local recurrence was only 25% in the present series. This is lower than biochemical recurrence estimates in most comparable ultrasound-guided salvage whole-gland CA studies^{5,22}; and lower than those in MR-/ultrasound-guided focal CA series.^{11,12,14} The result is unexpected, since salvage treatment is traditionally

associated with poorer outcomes than primary therapy.²⁵ Interpretation is limited due to sample size, but MR-guided whole-gland CA may potentially optimize local control, postpone use of androgen deprivation therapy (and its side-effects),³³ and offer similar complication rates to alternative therapies in these challenging second-line cases.

Table 4. Predictive value of pre- and post-operative risk factors for all complications

Risk factor	Patients [Frequency]	OR	p-value
Pre-operative parameters			
TURP -	16 [61%]	0.63	1
TURP +	2 [50%]		
Radiotherapy -	9 [64%]	0.71	0.72
Radiotherapy +	9 [56%]		
Operative parameters			
No grid/template (first 15)	11 [73%]	0.31	0.26
Grid/template (last 15)	7 [47%]		
≤5 cryoprobes	6 [43%]	10.00	0.02
>5 cryoprobes	12 [75%]		
≤2 freezing-cycles	14 [58%]	1.43	1
>2 freezing-cycles	4 [67%]		
Rectal balloon warming -	6 [46%]	1.67	0.71
Rectal balloon warming +	10 [59%]		
Dissection -	11 [58%]	0.60	0.71
Dissection +	5 [45%]		
Urethral sphincter thermometry -	12 [52%]	1.22	1
Urethral sphincter thermometry +	4 [57%]		

OR, odds ratio; TURP, transurethral resection of the prostate.

Focal CA is increasingly utilized for radio-recurrent disease,³⁰ due to potentially lower complication rates, preserved sexual function, and satisfactory local control compared with whole-gland ablation.^{14,29} Several studies investigating MR-guided focal salvage CA for radio-recurrent PCa have demonstrated promising results,^{11–13,24} but a 49% 12 month local recurrence rate has

been reported in predominantly high-risk patients¹²; and several ultrasound-guided primary/salvage studies have suggested a trend towards inferior local control compared with whole-gland CA.^{14,29,30} While proponents advocate isolated treatment of “index lesions” to minimize clinically significant cancer risk and avoid morbidity,^{15,22,34} detractors note that up to 80% of cases

Figure 3. Overall local progression-free survival of all patients undergoing MR-guided whole-gland CA of PCa in the study population (solid line; 95% CI, dotted lines). CA, cryoablation; CI, confidence interval; PCa, prostate cancer.

Figure 4. Local progression-free survival in primary treated patients (dotted line) or in salvage therapy (solid line).

are multifocal and may be occult on 3 T MRI,^{15,34} and focal approaches may risk residual untreated tumor. Our current institutional preference is for whole-gland CA, in line with current American Urological Association guidance.⁴

Study limitations include retrospective design; small, heterogeneous sample; and short follow-up. There was significant missing data (precluding analysis of sexual function, in particular) due to many International Prostate Symptom Score questionnaires, urinary flowmetry, and MR follow-ups being variably performed/available at distant referring institutions. The sample comprised different risk levels, variable prior radiotherapy, and heterogeneous CA technique (as new methods were adopted during the study period), significantly limiting generalizability

and obscuring effects of technical improvements on outcomes. Nevertheless, a significant evolution in the technique was represented by the introduction of the rigid template/grid which facilitated probe deployment and spacing thus probably making the procedure faster and reproducible.

Follow-up data >5 years were available in only half of cases, limiting evaluation of oncologic efficacy and factors affecting complications/local progression, particularly in low/intermediate-risk patients. Finally our oncologic results also need to be consolidated by long follow-up periods. Indeed, prostate cancer is a slow evolving cancer leading to the questions of over diagnosis and over treatment. Thus more and more recent studies evaluate the efficacy and side-effects of treatment at 10 years or more.³⁵

Figure 5. Overall survival in the study population (solid line; 95% CI dotted lines). CI, confidence interval.

Figure 6. MRI follow-ups in the same patient showed in Figure 2. Axial T2 (A), Sagittal T2 (B), and Axial contrast-enhanced T1 fat-saturated (C) sequences obtained at 1 month follow-up show heterogeneous high signal throughout ablated volume (arrows in A, B) and absence of contrast-enhancement in the center of the ablated volume, consistent with necrotic changes; a peripheral posterior rim of contrast enhancement is noted (arrowhead in C), consistent with early physiologic inflammatory changes. The same MRI sequences acquired at 12 month follow-up (D-F) demonstrate significant fibrotic shrinkage of the ablated volume without significant contrast-enhancement thus being consistent with a complete ablation of the entire prostatic tissue; the central focal signal on contrast-enhanced T1 fat-saturated sequence (arrow in F) corresponds to urethra.

In conclusion, MR-guided whole-gland CA offers comparable oncologic efficacy to ultrasound-guided studies, with encouraging results for salvage cases. Although complications are frequent, the majority are minor, requiring conservative/pharmacologic treatment only. Further prospective controlled trials

are required to evaluate this novel technique in relation to existing PCa therapies.

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