Focal Salvage MR Imaging–Guided Cryoablation for Localized Prostate Cancer Recurrence after Radiotherapy: 12-Month Follow-up

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ABSTRACT

Purpose: To evaluate safety, quality of life (QoL), and local cancer control after focal salvage MR imaging–guided cryoablation in patients with local recurrence of prostate cancer (PCa) after radiotherapy.

Materials and Methods: A retrospective, single-center study was performed in 62 patients with radiorecurrent PCa who underwent MR imaging–guided cryoablation since May 2011 with a follow-up ≥12 months in December 2017. Rates and descriptions of adverse events were reported. Ablation complications were classified according to the Clavien and SIR systems. Validated questionnaires were used to observe functional outcomes and QoL before therapy and 6 and 12 months after therapy. Cancer control was defined as no biochemical failure according to Phoenix criteria and no other clinical evidence for local or metastatic disease.

Results: All procedures were technically feasible. The number of complications requiring major therapy (Clavien grade 3b/4 or SIR grade D/E/F) was low (2 [3.2%] and 1 [1.6%], respectively). After 12 months, the International Consultation of Incontinence Questionnaire–Short Form ($P < .001$) and 5-item International Index of Erectile Function ($P = .001$) scores became significantly worse, indicating increased symptoms of incontinence and diminished erectile function, without compromising QoL. Six patients developed metastases within 6 months. After 12 months, 36 patients (63%) were disease-free.

Conclusions: Focal salvage MR imaging–guided cryoablation is safe and is associated with a high technical success rate, preservation of QoL, and local PCa control. This treatment can be a reasonable alternative to salvage radical prostatectomy in properly selected patients with low morbidity and preservation of QoL; however, longer follow-up is needed.

ABBREVIATIONS

FACT-P = Functional Assessment of Cancer Therapy–Prostate, ICIQ-SF = International Consultation of Incontinence Questionnaire–Short Form, IIEF-5 = 5-item International Index of Erectile Function, IPSS = International Prostate Symptom Score, PCa = prostate cancer, PSA = prostate-specific antigen, QoL = quality of life, SRP = salvage radical prostatectomy

Biochemical recurrence of prostate cancer (PCa) after a form of radiotherapy occurs in approximately 26%–52% of patients (1,2). At the present time, salvage radical prostatectomy (SRP) is a treatment option. SRP has a curative intent, but it is technically challenging because of radiation-induced fibrosis and shrinkage of the prostate gland, resulting in high rates of urinary incontinence (0%–28%) and rectal injury (0%–67%) (3,4) which severely affect

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patients' quality of life (QoL). In addition, surgery is contraindicated in most patients because of their age and comorbidities. Androgen deprivation therapy can be an alternative treatment option. However, this option is unattractive because of its temporary effect, and it can lead to an increased risk of cardiovascular mortality and skeletal fracture and a decreased QoL (5,6).

Minimally invasive treatments, including high-intensity focused ultrasound, high-dose brachytherapy, and cryoablation, have emerged as alternative salvage therapies. In case of a local recurrence, these minimally invasive treatments can be applied locally (7–14). The goal is to treat localized tumors only to obtain local cancer control, while sparing the rest of the prostate to minimize potential morbidity. Accurate image guidance is of utmost importance to enable focal treatment. In contrast to ultrasound imaging, magnetic resonance (MR) imaging is able to target the lesion and monitor the treatment accurately during cryoablation. Iceball growth can be monitored in real time and in multiple planes, such that damage to adjacent critical structures, such as the rectal wall, can be minimized (15). Additionally, local recurrent disease after radiotherapy may be very suitable for focal treatment because it is more often unifocal (72%) compared with primary PCa (17%) and has a smaller cancer volume (0.68 cm^3 for local recurrence vs 3.43 cm^3 for primary PCa) (16,17). Furthermore, local recurrences are likely to occur at the same site as the index lesion before radiotherapy (18,19). Therefore, it was hypothesized that focal salvage MR imaging–guided cryoablation might be a reasonable alternative to SRP, particularly in patients with high risk of comorbidities but with a substantial life expectancy. The purpose of this study was to evaluate safety, QoL, and local cancer control in patients with locally recurrent PCa after radiotherapy using this novel treatment approach.

MATERIALS AND METHODS

Study Design and Patients

Between May 2011 and December 2017, 83 consecutive patients underwent focal salvage MR imaging–guided cryoablation of the prostate after previous radiotherapy. Before treatment, all patients underwent multiparametric MR imaging to localize the recurrence. Furthermore, all patients had negative results on macroscopic metastatic screening with abdominal and pelvic MR imaging. In December 2017, 62 patients had a follow-up of ≥ 12 months and were included in this study. No restrictions were placed on characteristics of pre-radiotherapy cancer, prostate-specific antigen (PSA) levels, Gleason score, and stage of recurrent disease. Ethical approval of the local institutional review board was waived. All patients gave written informed consent for treatment with MR imaging–guided focal cryoablation and use of their anonymized data for publication. A small study describing the feasibility results of the first 10 patients was published previously (20).

Table 1. Patient and Procedure Characteristics (N = 62 Patients)

	Value
Patient Characteristics	
Age, y, median (IQR)	67.0 (64.0–70.8)
Type of radiotherapy, n (%)	
External-beam radiation therapy	40 (64.5)
Brachytherapy	21 (33.9)
External-beam radiation therapy and brachytherapy	1 (1.6)
Time between RT and MR imaging cryoablation (months), median (IQR)	69.5 (49.3–95.0)
Characteristics before RT	
PSA (ng/mL), median (IQR)	12.0 (7.6–18.2)
Gleason score, n (%)	
≤ 5	5 (8.1)
6	22 (35.5)
7	23 (37.1)
8	9 (14.5)
9	1 (1.6)
Unknown	2 (3.2)
Tumor stage, n (%)	
T1c–T2	29 (46.8)
T3	30 (48.4)
Unknown	3 (4.8)
Cryoablation characteristics before MR imaging	
PSA (ng/mL), median (IQR)	4.1 (2.5–6.8)
Gleason score, n (%)	
6	7 (11.3)
7	22 (35.5)
8	11 (17.7)
9	12 (19.4)
10	1 (1.6)
Unknown	9 (14.5)
Tumor stage, n (%)	
T2	40 (64.5)
T3	22 (35.5)
Prior ADT use	23 (37.1)
Procedure characteristics, median (IQR)	
Total anesthetic time, min	180.0 (160.0–197.0)
Procedure time, min	103.0 (92.3–125.0)
Number of cryoablation needles	3.0 (2.0–4.0)
Hospitalization, d	1.0 (1.0–2.0)

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen; RT = radiotherapy.

A total of 62 men were treated with MR imaging–guided focal cryoablation. One patient died 5 months after MR imaging–guided cryoablation from an unrelated stomach perforation. One patient was lost to follow-up. In 1 patient, colon cancer was diagnosed 2 months after MR imaging–guided cryoablation; in another patient, lung cancer was diagnosed 9 months after treatment. Both patients were excluded from follow-up analyses. Characteristics of all patients are summarized in **Table 1**.

Patients were admitted to the hospital on the night before (n = 19) or a few hours before (n = 43) treatment. Antibiotic prophylaxis (ciprofloxacin; Bayer AG, Leverkusen, Germany) was started 14 days before admission, and patients were given a cleansing enema to remove feces. All patients were treated in a closed-bore 1.5T (n = 14) or 3T (n = 48) MR imaging system (MAGNETOM Avanto or Skyra; Siemens Healthcare, Erlangen, Germany) under general anesthesia. Cryoablation was performed with an MR imaging–compatible cryoablation device (MRI-SeedNet; Galil Medical, Yokneam, Israel). Multiple cryoneedles (IceSeed or IceRod; Galil Medical) were transperineally inserted in the tumor under MR imaging guidance. All MR imaging parameters are described in a previous study (20). During freezing, the urethra and the rectal wall were protected with warming catheters. In every patient, 2 freeze-thaw cycles were performed. After the procedure, the cryoneedles and the rectal warmer were removed, and the urethral warmer was changed for a Foley catheter. Patients were discharged the day after treatment. When spontaneous voiding was not possible, a Foley catheter was inserted for another 7 days.

Follow-up consisted of urologic checkups at 1, 3, 6, and 12 months for PSA tests and adverse event reporting. At 3, 6, and 12 months, multiparametric MR imaging was performed to determine local cancer control. MR imaging–guided biopsies were performed when a suspected tumor was seen on multiparametric MR imaging. Beginning in August 2013 (n = 44), multiparametric MR imaging at 12 months was followed by 2 or 3 targeted MR imaging–guided biopsy samples of the edge or rim of the ablated region to confirm treatment success with histopathology. If biopsies were positive, patients could be retreated with MR imaging–guided cryoablation after multidisciplinary consensus with the urologist, radiation oncologist, and interventional radiologist. Beginning in January 2013, patients (n = 42) were asked to complete validated questionnaires (International Prostate Symptom Score [IPSS], International Consultation of Incontinence Questionnaire–Short Form [ICIQ-SF], 5-item International Index of Erectile Function [IIEF-5], and Functional Assessment of Cancer Therapy–Prostate [FACT-P]) (21–24) before therapy and 6 and 12 months after therapy.

Primary outcomes of the study were safety, functional outcome, and QoL. Safety was assessed with rates and description of adverse events. Complications were classified according to the modified Clavien system for reporting surgical complications and the Society of Interventional Radiology (SIR) classification system for complications by outcome after radiologic interventions (25,26). IPSS (including the IPSS-QoL questionnaire) and ICIQ-SF were used to assess urinary function and to define the proportion of men who were leak-free (< 1time/d urinary leakage). High IPSS, IPSS-QoL, and ICIQ-SF scores indicated poor urinary functioning. The IIEF-5 questionnaire was used to assess potency, defined as being capable of having erectile function sufficient for penetration, as well as total IIEF-5 score. A low IIEF-5 score indicated poor erectile function. QoL was assessed with FACT-P with summary measures of the FACT-Prostate score, Functional Assessment of Cancer Therapy–General score, and Trial Outcome Index (TOI) score. High scores indicated a better QoL. Secondary outcome of the study was to determine cancer control, which was defined as no biochemical failure according to the Phoenix definition (PSA nadir + 2 ng/mL) and/or no other clinical, radiologic, or histopathologic evidence for local recurrent or metastatic disease.

Statistical Analysis

Missing values for individual questions were imputed based on known clinical data as reported to the urologist. Because of the retrospective design of this study, not every patient filled in questionnaires at every time point. Data of all patients who filled in the questionnaires of at least 1 time point (n = 54) were used in generalized least squares analyses using unstructured covariance matrix for residuals to accommodate the repeated measurements. Outcomes were reported as point estimates with 95% confidence intervals to demonstrate level of precision. P values < .05 were considered significant. All statistical analyses were performed with IBM SPSS Version 25 (IBM Corp, Armonk, New York).

RESULTS

Procedure characteristics are summarized in **Table 1**. All procedures were technically feasible, and no intraprocedural complications were reported. Of all patients, 56 (90.3%) were discharged the day after treatment. One patient was monitored for 2 nights and went home without complications. Three patients had to stay 1 more night because of acute urinary retention and went home with a Foley catheter for 7 days. One of these patients developed a urethral stricture 6 months later, which was surgically treated (Clavien grade 3b, SIR class C). Afterward, the patient needed clean intermittent catheterization. Another patient was hospitalized for 17 days because he experienced a myocardial infarction the day after the cryoablation. This patient had a medical history of cardiac disease and had undergone cardiovascular interventions before. Although it is not clear that the myocardial infarction was related to the cryoablation procedure, it was defined as a Clavien grade 4a/SIR class D complication. Eight other patients had acute urinary retention, and 7 of them went home with a Foley catheter for 7 days (Clavien grade 1/SIR class B). In the eighth patient, placement of a Foley catheter was not possible owing to prostate swelling, and a temporary suprapubic catheter was placed (Clavien grade 3a/SIR class C). None of the patients experienced voiding problems after removal of the catheter.

In the months after cryoablation, patients reported urinary retention needing clean intermittent catheterization

Table 2. Complications after First MR Imaging–Guided Cryoablation Procedure in 62 Patients Classified According to Modified Clavien System for Reporting Complications and SIR Classification System for Complications

Grade/Class	Definition	n (%)
Clavien system		
1	Any deviation from normal postoperative course	33 (53.2)
2	Complications needing intravenous medication or antibiotics	5 (8.1)
3a	Complications needing intervention under local anesthesia	2 (3.2)
3b	Complications needing intervention under general anesthesia	1 (1.6)
4a	Life-threatening: single-organ dysfunction	1 (1.6)
4b	Life-threatening: multiple-organ dysfunction	0 (0)
5	Death of the patient	0 (0)
SIR classification system		
Minor complications		
A	No therapy, no consequence	16 (25.8)
B	Nominal therapy, no consequence; includes overnight admission for observation only	20 (32.3)
Major complications		
C	Require therapy, minor hospitalization (< 48 h)	5 (8.1)
D	Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 h)	1 (1.6)
E	Permanent adverse sequelae	0 (0)
F	Death	0(0)

once a day (n = 3, Clavien grade 1/SIR class B); urinary incontinence needing several pads per day (n = 2, Clavien grade 1/SIR class A); lower urinary tract symptoms (n = 11, Clavien grade 1/SIR class A); a perineal wound, which resolved after 2 weeks (n = 1, Clavien grade 1/SIR class C); pain (perianal and on the glans penis) (n = 3, Clavien grade 1/SIR class A); a fungal infection (n = 1, Clavien grade 1/SIR class B); and urinary tract infections needing antibiotics (n = 5, Clavien grade 2/SIR class B). After 3 months, 1 patient developed a rectovesical fistula, which was conservatively treated by placing a suprapubic catheter (Clavien grade 3a/SIR class C). Another patient developed a rectoprostatic fistula 1 month after treatment. A Foley catheter was placed for a few weeks as a precaution (Clavien grade 1/SIR class C). This fistula resolved spontaneously within 3 months. A third patient developed a rectoprostatic fistula after 3 months. He experienced some fluid loss by his anus but mainly experienced consecutive urinary tract infections, which were treated with antibiotics (Clavien grade 2/SIR class B). The fistula diminished in size and symptoms decreased over time. All adverse events defined according to the Clavien and SIR classifications are summarized in **Table 2**.

All scores are summarized in **Figure 1**. Between baseline and 12 months, ICIQ-SF scores increased significantly ($P < .001$), indicating increased symptoms of incontinence. No significant differences were seen in IPSS or IPSS-QoL scores when comparing baseline scores with scores 12 months after treatment. At baseline, 91% (41 of 44) of the patients were leak-free; this declined to 71% (27 of 38) after 12 months. Only 2 patients (3.2%) reported needing to use several pads per day for their leakage. IIEF-5 scores decreased significantly ($P = .001$) 1 year after treatment, indicating decreased erectile function. Before treatment, 59% (24 of 41) of the patients reported having erections sufficient for penetration; after 12 months, this declined to 41% (15 of 37) of the patients. Despite increased incontinence symptoms and diminished erectile function, no significant differences were seen in the QoL scores for total FACT-P, Functional Assessment of Cancer Therapy–General, and TOI between baseline and 12 months.

The cancer control outcomes are summarized in **Figure 2**. Six months after MR imaging–guided cryoablation, 49 patients (83%) were disease-free. One patient died for reasons not related to PCa; 1 patient was lost to follow-up; 1 patient developed colon cancer and was excluded; 1 patient developed biochemical recurrence; and 3 patients had local disease diagnosed based on suspicious findings on multiparametric MR imaging, 1 of whom was retreated with MR imaging–guided cryoablation. Metastatic disease was diagnosed in 6 patients. Between 6 and 12 months, 1 patient was excluded from follow-up because he developed lung cancer, and another 12 patients showed disease progression. Of the 12 patients with progression, 4 had metastases, 7 had local disease, and 1 showed biochemical recurrence according to the Phoenix definition. After multidisciplinary consensus with the urologist, radiation oncologist, and interventional radiologist, 3 of the patients with local disease were retreated with MR imaging–guided cryoablation. Consequently, 36 patients were disease-free, showing a 63% chance at disease-free survival at 12 months, based on Kaplan-Meier analyses.

MR imaging–guided biopsy of the edge of the ablation zone was performed in 30 of 44 patients after 12 months. Biopsy was not performed in 14 patients because they had already received a diagnosis of local recurrence (n = 3), had tumors that had metastasized (n = 7), had a history of a fistula (n = 2), or refused to undergo biopsy (n = 2). In 23

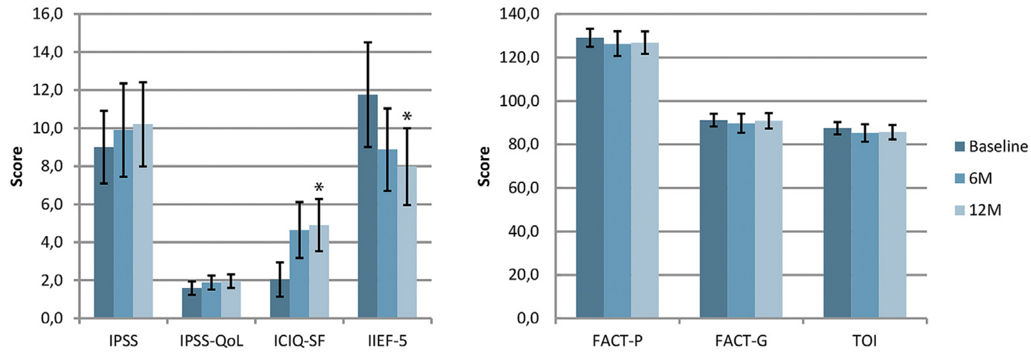
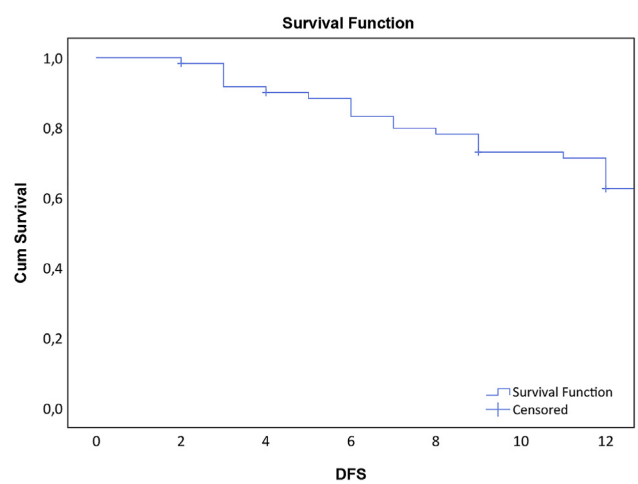


Figure 1. Results of validated questionnaires for functional outcome measured with IPSS, IPSS-QoL, ICIQ-SF, and IIEF-5 questionnaires and for QoL outcome measured with FACT-P questionnaires, including Functional Assessment of Cancer Therapy–General (FACT-G) and TOI. Plots show mean values (bars) with 95% confidence interval (whiskers). Two-tailed *P* values were calculated comparing baseline and 12-month mean scores. Asterisk indicates $P < .05$.

of 30 (77%) patients, no malignancy was found. In 3 patients (10%), an area suspicious for tumor was seen on 12-month multiparametric MR imaging, which was histopathologically proven to be tumor by targeted MR imaging–guided biopsy. In 4 of 30 (13%) patients, vital tumor cells were found even though multiparametric MR imaging showed no signs of disease. In 2 patients, only a few individual tumor cells were found, and in the other 2 patients, maximal tumor lengths of 1 mm and 4 mm, respectively, were found. One of these patients was retreated with MR imaging–guided cryoablation. The other 3 patients chose a watchful waiting trajectory.

Four patients were retreated with MR imaging–guided cryoablation within 12 months. None of these patients showed biochemical failure yet; however, regions suspicious for tumor were seen on MR images, which were histopathologically proven to be prostate cancer. Retrospective analysis of the intraoperative MR images showed that in 2 of 4 patients the iceball did not cover the complete tumor.



Months	0	3	6	12
No at risk	61	55	49	36
%	100	91.7	83.2	62.6

Figure 2. Kaplan-Meier curve for cancer control according to the Phoenix definition for biochemical disease-free survival (DFS) in combination with any clinical, radiologic, or histopathologic evidence for local or recurrent disease.

DISCUSSION

This study demonstrated that focal salvage MR imaging–guided cryoablation in patients with PCa recurrence after radiotherapy is safe and is associated with a high technical success rate, preservation of QoL, and local cancer control. The number of complications needing major therapy (Clavien grade 3b/4 and SIR class D/E/F) was low (n = 2 [3.2%] and n = 1 [1.6%], respectively). After 12 months, only ICIQ-SF and IIEF-5 scores became significantly worse, without compromising the QoL. This seems contradictory; however, for some patients, the knowledge that their cancer had been eradicated seemed to compensate for the fact that their functional outcomes had slightly worsened.

A low complication and morbidity rate is also reported by other studies of focal salvage therapy (7–14,27,28). This is in contrast to the results after SRP. A systematic review averaging the results of 24 studies reported incontinence in 50%, bladder neck stricture in 26%, rectal injury in 5%, and rectal fistula in 2.4% of patients after SRP (29). This study reported an incontinence rate of 3.2%, 1 urethral stricture (1.6%) needing surgical intervention, no rectal injury, and 3 rectal fistulas (4.8%), which were conservatively treated and resolved or diminished within a few months. The present study is not directly comparable to these previous studies. Reasons for this are different inclusion criteria and therefore diverse patient groups, other treatment methods (ie, hemi-ablation vs focal ablation), and distinct definitions for functional outcomes and disease-free survival. Furthermore, some studies lump functional outcomes along with complications instead of reporting objective validated questionnaire-based data. Preferably, baseline, short-term, and long-term urinary, sexual, and bowel function should be ascertained using patient-reported questionnaires.

However, these instruments are underused, and data are sparse. In the present study, these data were collected in most of the patients, yielding unique information.

Proper patient selection is important when performing focal salvage therapy. In this study mp-MR imaging was used to detect and localize clinically significant disease after radiotherapy. It has shown a 95% negative predictive value in detecting local recurrences (32). Despite this, tumor could have been missed or treated incompletely, because it was not (completely) visible on the MR images. In contrast to previous focal salvage studies, this study also included patients with extracapsular extension and/or seminal vesicle invasion. This might have had a negative influence on the cancer control rate because these patients have a higher chance of developing metastatic disease. Micrometastatic disease was probably present in 6 patients at the time of their MR imaging–guided cryoablation because metastatic disease was diagnosed within 6 months after treatment. This was not detected during imaging before treatment, probably because the current radiologic work-up to detect distant metastases is not sensitive enough (30). Recently, lymphotropic nanoparticle-enhanced MR imaging became available in our center. This technique has shown high sensitivity (65–92%) and specificity (93–98%) in detecting PCa lymphnode metastases (30) and may improve our patient selection (31).

Currently, there is no consensus how to determine biochemical failure after salvage focal therapy. The Phoenix definition was originally developed to define biochemical failure after radiotherapy. It is not suitable and validated for use after focal therapy because part of the prostate remains untreated, and the mechanism of cell death is different between cryoablation and radiotherapy. Because of the absence of a validated definition, in this study, cancer control was defined as no biochemical recurrence according to the Phoenix definition and/or no clinical, radiologic, or histopathologic evidence for local recurrent or metastatic disease. Although this combined approach influenced the cancer control rate in a negative way, this study shows it has added value, as 4 patients who did not have biochemical failure yet were diagnosed with recurrent disease after multiparametric MR imaging and targeted MR imaging–guided biopsy. For this reason, targeted biopsy of the rim of the ablation zone is recommended.

Limitations of this study are its retrospective design, the relatively small number of patients, and a potential patient selection bias. The retrospective design led to an incomplete follow-up and hampered an objective comparison in functional outcome and QoL before and after treatment. For the same reason, not all patients underwent MR imaging–guided targeted biopsy of the ablation zone.

A future step will be to study which prognostic factors (eg, PSA, stage, androgen deprivation therapy use) have influenced the outcome of the present study. This will improve the current patient selection methods. Furthermore, future trials could combine MR imaging–guided cryoablation with adjuvant therapy or immunotherapy.

In conclusion, focal salvage MR imaging–guided cryoablation is safe and is associated with a high technical success rate, preservation of QoL, and local cancer control. This treatment may be a reasonable alternative to SRP in properly selected patients. However, longer follow-up is needed.

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