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# Medium-term oncological outcomes of intermediate-risk prostate cancer treated with HIFU or cryotherapy. A single center 10-year experience

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**Summary** ***Objectives: Focal therapies (FTs) are promising techniques for the treatment of localized prostate cancer. We assessed the medium-term oncological outcomes of intermediate-risk prostate cancer (PCa) treated with HIFU or cryotherapy.***

***Materials and methods: One-hundred and fifty consecutive patients with intermediate-risk PCa, treated between 2009 and 2018 at a single center were included. Primary study outcome was failure-free survival (FFS), defined as absence of additional treatment, systemic progression or prostate cancer related death.***

***Results: Thirty-seven (25%) patients underwent cryotherapy and 113 (75%) HIFU. Median age was 69 (IQR 62-72) years, with 36 (24%) presenting palpable disease on rectal examination, and median total PSA of 7.85 (IQR 5.75-10.62) ng/mL. Patients were followed for a median of 61 (IQR 48-82) months. FFS at 2 and 4 years was of 75.6% and 53.6%, respectively. Survival from whole gland or systematic treatment at 2 and 4 years was of 78.9% and 53.9%, respectively. Patients with FFS presented lower total PSA nadir (1.89 vs 3.25 ng/mL, p < 0.001), higher % PSA reduction at 3 months (66.1% vs 49.3%, p < 0.001), and at nadir (75.5% vs 55.8%, p < 0.001). Other characteristics such has the treatment modality, age, prostate size, initial total PSA, cT stage, International Society of Urological Pathology (ISUP), tumor location and biopsy results by region did not differ between patients failing and not failing FT. Complications were uncommon (13%), with only onr (1%) patient having Clavien-Dindo grade > II. No deaths due to treatment were registered.***

***Conclusions: At medium-term, FTs for intermediate-risk PCa presented good oncological results, with an excellent safety profile.***

*KEY WORDS: Prostatic neoplasms; Cryotherapy; Focal therapy; Ablation.*

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## INTRODUCTION

Current standard treatment options for localized *prostate cancer* (PCa) include active surveillance and radical treatment (surgery or radiotherapy) (1), which has been known to have negative impacts on quality of life (2). ProtecT trial results (3), first published in 2014, have shown that active monitoring of PCa would achieve a similar overall survival as radical treatment, while enduring less treatment related side-effects (2). However, in this same cohort, *Active Surveillance* (AS) had a higher risk of disease progression and of metastatic disease (3).

If for low-risk PCa, AS is looked at as the mostly consensual choice, for intermediate-risk PCa, *focal therapies* (FTs) are being studied in an attempt to allow a treatment that assures less morbidity while allowing acceptable oncological outcomes. The improvement in imaging modalities, mainly the MRI, has allowed to improve diagnostic accuracy and localization of regions of interest for directed treatment, which allows FT to be considered in selected patients (4).

Despite being considered experimental treatments, FTs are viewed by some as a potential treatment choice for intermediate-risk PCa with a favorable safety profile (5).

Our goal was to describe medium-term oncological outcomes for patients with intermediate-risk localized PCa treated primarily with *High-Intensity Focused Ultrasound* (HIFU) or Cryotherapy.

## METHODS

We conducted an observational, single-center, cohort study, evaluating data on all consecutive patients undergoing FT (HIFU or cryotherapy) for intermediate-risk localized PCa.

Patients were included if they fulfilled the following criteria: > 18 years, treatment naïve for PCa at the moment of FT, *multi-parametric Magnetic Resonance* (mpMRI) and subsequent biopsy, diagnosis of intermediate-risk localized PCa having primary FT (either HIFU or Cryotherapy) between the years 2009 and 2018. Patients were excluded if: no mpMRI was performed by any reason or if they had hormonal therapy as a bridge for FT. Using these criteria, we identified 150 patients after querying our continuously maintained institutional database.

### *Definitions*

We defined intermediate-risk PCa as per the current NCCN Prostate Cancer Guidelines (6): at least one of the intermediate-risk factors – cT2b-cT2c, Gleason Grade

No conflict of interest declared.

Group 2-3, total PSA 10-20 ng/mL; without having high or very high-risk factors – any of cT3+, Gleason Grade Group 4-5, PSA ≥ 20 ng/mL or >4 cores with Gleason Grade Group 4 or 5. We further stratified patients between the categories of favorable intermediate (all of the following: having 1 intermediate-risk factor, Gleason Grade Group 1 or 2, and < 50% of biopsy cores positive) and unfavorable intermediate-risk (at least one of the following criteria: having 2 or 3 intermediate-risk factors, Gleason Grade Group 3, and ≥ 50% of biopsy cores positive) prostate cancer.
Clinically significant prostate cancer (csPCa) was defined as Gleason Grade Group [or *International Society of Urological Pathology* (ISUP) Grade] ≥ 2.

***Data collection***
Data was collected from our continuously updated database and patient records. We recorded age at time of treament, pre-operative total PSA, clinical T staging, prostate volume, initial mpMRI results, initial biopsy results, date of FT and type of FT performed. We obtained follow-up data including total PSA values, MRI and biopsies results. We registered if patients developed disease biochemical, imagiological and histological recurrences; if there was a need for subsequent treatment and its indication, overall survival, prostate cancer specific survival and last follow-up date.

***Procedures***
Multi-parametric MRI was performed at community centers. If there was a disagreement between radiologist and urologist interpretation, it was reviewed with an in-house urologist specialized in uro-oncological imaging, and repeated if advised.
Prostate biopsies were performed in our center, transrectally, with a 12-core systematic biopsy and 2-4 targeted samples being obtained from suspicious lesions, defined as score *Prostate Imaging Reporting & Data System* (PI-RADS) ≥ 3.
Among patients with suspicious lesions on imaging, 3 regions of interest were considered. Target zone cancer was considered when PCa was identified on the targeted samples obtained from suspicious MRI lesions. Near target zone cancer was considered when PCa was identified on randomized samples obtained from a region adjacent to the suspicious lesion location. Away from target zone cancer was considered when PCa was identified on randomized samples obtained from a region not adjacent to the suspicious lesion location.
Cryotherapy (n = 37) was performed using the various devices, using a previously described standard technique (7), for all cases.
HIFU was performed using *Ablatherm® Fusion* (EDAP) (n = 29) and *Focal One®* (EDAP) (n = 84), through an evolving technique (8), until arriving at what we use today.
After an initial learning period, the energy to use was typically chosen based on lesion location, with cryotherapy being preferred for anterior tumors and HIFU for peripheral tumors.
In patients with well delimited lesions on MRI and no extra-lesion csPCa disease we performed uniquely a targeted FT. Patients with MRI lesions and ipsilateral peri-lesion csPCa disease on systematic biopsy, we performed targeted FT with a widened field. Patients with MRI lesions and ipsilateral csPCa disease on systematic biopsy cores non-adjacent to the lesion site, we performed hemi-ablation.
Patients with bothering emptying symptoms underwent TUR-P in the 2 weeks prior to the FT procedure.

***Study outcomes***
Primary study outcome was *Failure Free Survival* (FFS), defined as absence of additional gland-directed (being focal or radical) or systemic treatment, metastatic disease or PCa related death.
Other study outcomes included biochemical recurrence free survival, metastasis free survival, overall survival, adverse events and complications classified by the *Clavien-Dindo* system.

***Follow-up***
The recommended follow-up strategy consisted in performing PSA measurements every 3 months during the 1st year after treatment and every 6 months thereafter, performing mpMRI 1 month and 1, 2 and 3 years after treatment and performing control biopsies 1, 2 and 3 years after FT. Additional repeat MRI and biopsies were performed if clinically judged indicated, based on various criteria. If patients declined to perform imaging and/or biopsies, they would remain in surveillance based on total PSA measurement alone, on a 3-6 months basis.
Treatment failure was considered when a patient was submitted to any additional PCa directed treatment, apart from complementary FT during the first 3 months after initial treatment. Patients were classified as having biochemical recurrence using the PHOENIX criteria (4) - measurement of total PSA higher than nadir total PSA + 2 ng/mL. In patients with recurrent or persistent disease, treatment was decided on a case-by-case basis.

***Statistics***
Statistical analysis was performed with IBM® SPSS® v27 software. Categorical variables are presented as frequencies and percentages, and were compared using Chi-squared analysis or Fisher's Exact Test, as appropriate. Continuous variables are presented as means and interquartile ranges (IQR), and were compared using non-parametric Mann-Whitney U tests. Statistically significance was set as $p < 0.05$. All reported p values are two-sided. Kaplan-Meier survival curves were calculated for failure-free survival according to described variables. Log-rank test was used to calculate for difference between groups. Patients with peri-treatment *transurethral prostate resection* (TUR-P) were excluded from total PSA reduction analysis.
The study has received approval from the local Ethics Committee, and all research was conducted respecting the latest version of Helsinki's declaration. Patients were provided information on their PCa disease and available standard treatment modalities (active surveillance, radical prostatectomy, radiotherapy), that FTs were not standard of care and have chosen FT as their desired treatment choice. They provided consent agreeing to participate in this research on FT oncological results.

## Results

### *Pre-treatment patient characteristics*

Among 150 patients with intermediate-risk PCa, 37 (25%) underwent cryotherapy and 113 (75%) HIFU (Table 1). The median age was 69 (IQR 62-72) years, with 114 (76%) patients having no palpable disease on digital rectal examination. Median total PSA was of 7.85 (IQR 5.75-10.62) ng/mL, with 46 (31%) of patients having an initial total PSA between 10-20 ng/mL and none higher than 20 ng/mL. The mean prostate volume was 40 (IQR 35-48) mL.

Regarding NCCN risk groups, 117 (78%) patients had intermediate favorable PCa and 33 (22%) intermediate unfavorable PCa; 37 (25%) presented with ISUP 1, 109 (73%) with ISUP 2 and 4 (3%) with ISUP 3 PCa. A total of 115 (77%) patients had suspicious lesions present on mpMRI.

When analyzing biopsy results by region among the 126 (84%) patients with suspicious lesions on MRI: 93 (74%) had csPCa - 46 (37%) had csPCa only on suspicious lesions; 31 (25%) had csPCa on suspicious lesions and lesion-adjacent systematic biopsy cores; 8 (6%) had csPCa only on lesion-adjacent systematic biopsy cores; 4 (3%) had csPCa only on non-lesion-adjacent systematic biopsy cores; 3 (2%) had csPCa on suspicious lesions, lesion-adjacent and non-lesion-adjacent systematic biopsy cores; 1 (1%) had csPCa on lesion-adjacent and non-lesion-adjacent systematic biopsy cores but not on suspicious lesions; 0 (0%) had csPCa on suspicious lesions and non-lesion-adjacent systematic biopsy cores.

**Table 1.**
*Patient clinical characteristics.*

| Characteristics | Value (n = 150) |
|---|---|
| Treatment, n (%) | |
| Cryotherapy | 37 (25) |
| HIFU | 113 (75) |
| Treatment year, n (%) | |
| 2009-2012 | 22 (15) |
| 2013-2015 | 65 (43) |
| 2016-2018 | 63 (42) |
| Age, Median (IQR) | 69 (62-72) |
| Prostate volume (mL), Median (IQR) | 40 (35-48) |
| Total PSA (ng/mL), Median (IQR) | 7.85 (5.75-10.62) |
| Initial total PSA < 10 ng/mL, n (%) | 104 (69) |
| Initial total PSA 10-20 ng/mL, n (%) | 46 (31) |
| cT stage, n (%) | |
| cT1c | 114 (76) |
| cT2a | 18 (12) |
| cT2b | 13 (9) |
| cT2c | 5 (3) |
| Biopsy overall ISUP Grade, n (%) | |
| 1 | 37 (25) |
| 2 | 109 (73) |
| 3 | 4 (3) |
| NCCN risk group, n (%) | |
| Intermediate favorable | 117 (78) |
| Intermediate unfavorable | 33 (22) |
| PI-RADS score | |
| 1-2 | 24 (16) |
| Suspicious MRI, with no PI-RADS score * | 11 (7) |
| 3 | 27 (18) |
| 4 | 65 (43) |
| 5 | 23 (15) |
| Biopsy results by region, n (%) ** | |
| csPCa @ suspicious lesion(s) | 80 (63) |
| csPCa @ lesion-adjacent systematic biopsy cores | 43 (34) |
| csPCa @ non-lesion-adjacent systematic biopsy cores | 8 (6) |
| Tumor per specific locations, n (%) | |
| Anterior zone | 16 (11) |
| Apex | 23 (15) |
| Base | 51 (34) |
| Bilateral | 11 (7) |
| If peri-treatment TUR-P, n (%) | 21 (14) |
| Total PSA nadir (ng/mL), Median (IQR) | 2.52 (1.59-4.51) |
| Time to PSA nadir (months), Median (IQR) | 3.0 (3.0-9.8) |
| PSA % reduction, Median (IQR) | |
| @ 3 months | 55 (39-72) |
| @ nadir | 62 (45-78) |

* *Exams performed before PI-RADS classification v1 was published.*
** *Results taking into consideration 126 patients with MRI suspicious for prostate cancer.*

### *Primary outcome - Failure free survival*

Patients were followed for a median time of 61 (IQR 48-82) months. Over all treated patients, the FFS at 2, 4, 5 and 7 years was of 75.6%, 53.6%, 42.1% and 27.3%, respectively. Survival from whole gland or systematic treatment at 2 and 4 years was of 78.9% and 53.9%, respectively.

Table 2 lists studied factors and their association with the need of additional treatment.

**Table 2.**
*Patients' characteristics according to necessity of salvage treatment and univariate analysis.*

| Characteristics | Failure free (n = 53) | Non-Failure free (n = 97) | Univariate P-value |
|---|---|---|---|
| Treatment, n (%) | | | 0.553 |
| Cryotherapy | 15 (28) | 22 (23) | |
| HIFU | 38 (72) | 75 (77) | |
| Age, Median (IQR) | 66 (61-2) | 69 (63-74) | 0.245 |
| Prostate volume (mL), Median (IQR) | 41.0 (35.0-47.0) | 40.0 (34.0-50.0) | 0.835 |
| Total PSA (ng/mL) | | | 0.580 |
| Initial tPSA < 10 ng/mL, n (%) | 35 (66) | 69 (71) | |
| Initial tPSA 10-20 ng/mL, n (%) | 18 (34) | 28 (29) | |
| cT stage, n (%) | | | 1.000 |
| cT1c | 40 (75) | 74 (76) | |
| cT2a-c | 13 (25) | 23 (24) | |
| Biopsy overall ISUP Grade, n (%) | | | 0.436 |
| 1 | 16 (30) | 21 (22) | |
| 2 | 35 (66) | 74 (76) | |
| 3 | 2 (4) | 2 (2) | |
| NCCN risk group, n (%) | | | 0.542 |
| Intermediate favorable | 43 (81) | 74 (76) | |
| Intermediate unfavorable | 10 (19) | 23 (24) | |
| Tumor per specific locations, n (%) | | | |
| Anterior zone | 8 (15) | 8 (8) | 0.268 |
| Apex | 11 (21) | 12 (12) | 0.235 |
| Base | 15 (28) | 36 (37) | 0.287 |
| Bilateral | 5 (9) | 6 (6) | 0.520 |
| Total PSA nadir (ng/mL), Median (IQR) | 1.89 (0.96-2.81) | 3.25 (1.93-5.68) | < 0.001 |
| Time to PSA nadir (months), Median (IQR) | 6 (3-12) | 3 (3-6) | < 0.001 |
| PSA % reduction, Median (IQR) | | | |
| @ 3 months | 66.1 (53.1-78.3) | 49.3 (26.9-63.4) | < 0.001 |
| @ nadir | 75.5 (61.6-84.7) | 55.8 (36.6-68.0) | < 0.001 |
| If PSA % reduction @ 3 months, n (%) | | | |
| > 30% | 38 (97) | 55 (72) | 0.002 |
| > 50% | 31 (79) | 36 (47) | < 0.001 |
| > 70% | 18 (34) | 13 (17) | < 0.00 |

Patients who needed additional treatment were more likely to have higher total PSA nadir (3.25 *vs* 1.89 ng/mL, p < 0.001), lower time to PSA nadir (3 *vs* 6 months, p < 0.001), lower total PSA reduction at 3 months (49.3% *vs* 66.1%, p < 0.001), lower total PSA reduction at nadir (55.8% *vs* 75.5%, p < 0.001). Other characteristics such has the treatment modality, age, prostate size, initial total PSA, cT stage, ISUP, NCCN risk group, tumor location and biopsy results by region did not differ between patients failing and not failing FT.

Kaplan Meier-analysis showed a significant difference for PSA reduction > 70% (log-rank test p = 0.002) (Figure 1a), but not for initial total PSA (log-rank test = 0.915) (Figure 1b), ISUP grade (log-rank test = 0.560) (Figure 1c) or NCCN sub-risk group (log-rank test = 0.676) (Figure 1d). Other variables not presented also haven't shown differences on the Kaplan-Meier analysis (treatment energy, age, prostate volume, clinical stage, csPCa locations and tumor location).

The additional selected treatment for the 97 (65%) patients who failed FT was radiotherapy + hormonal therapy in 37 (25%), radiotherapy in 6 (4%), radical prostatectomy in 16 (11%), hormonal therapy in 12 (8%), HIFU in 12 (8%), brachytherapy in 10 (7%) and cryotherapy in 4 (3%). Median time to additional treatment was of 45.5 (IQR 21.8-61.0) months. Reasons for further treatment are presented on Table 3.

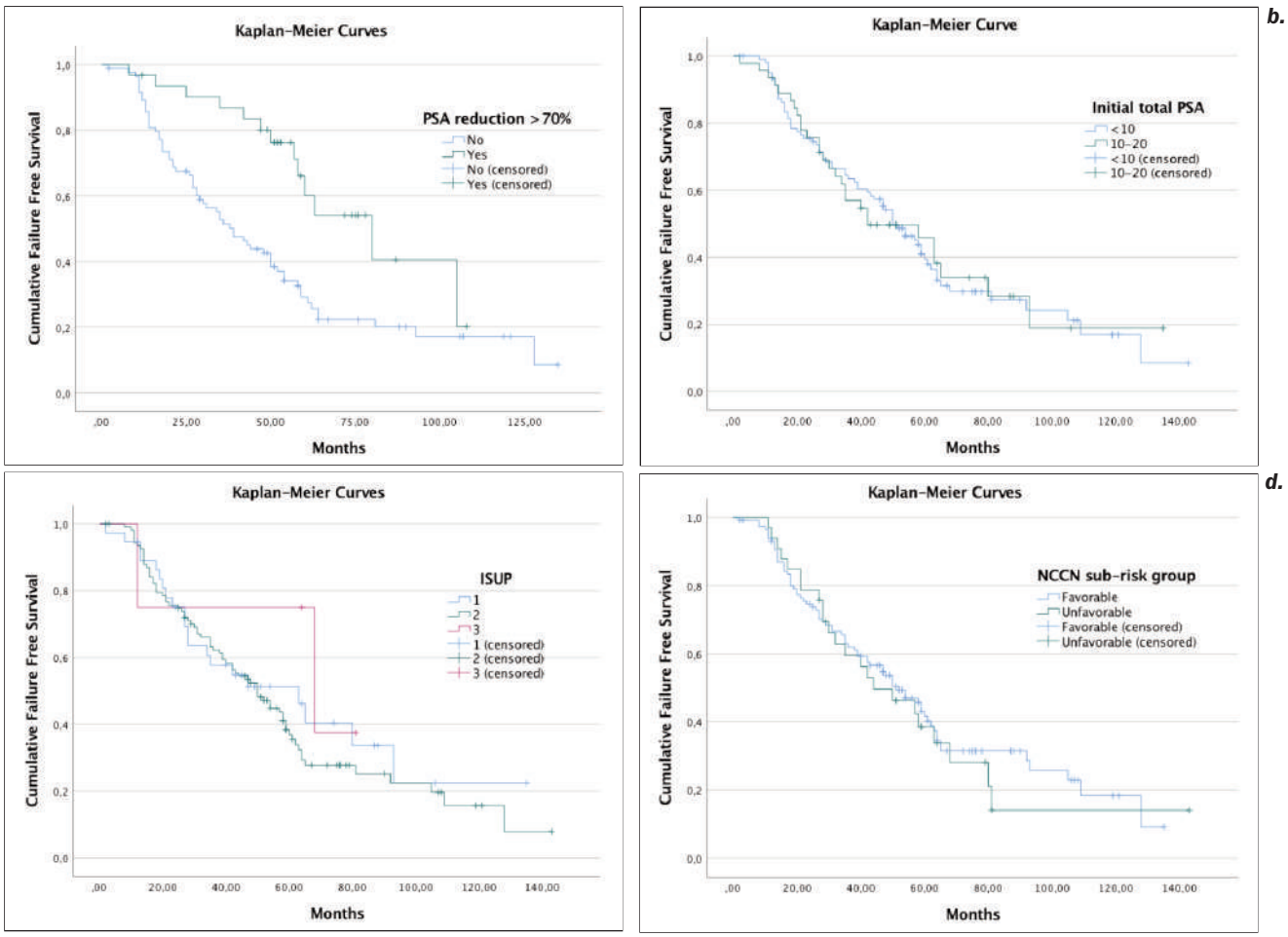
***Table 3.***
*Reasons for first additional treatment being performed.*

| Reason for treatment | Value (n = 150) |
|---|---|
| ISUP 1 infield persistence + PSA and/or image progression | 6 (4.0%) |
| ISUP 2 infield persistence | 3 (2.0%) |
| New ISUP 1 outfield | 5 (3.3%) |
| New ISUP ≥ 2 outfield | 20 (13.3%) |
| Infield progression to ISUP 2 | 1 (0.7%) |
| Infield progression to ISUP ≥ 3 | 13 (8.7%) |
| ISUP 2 infield recurrence | 14 (9.3%) |
| In & Outfield ISUP ≥ 2 | 27 (18.0%) |
| Biochemical recurrence +/- image progression | 6 (4.0%) |

### *Treatment complications*

Nineteen (13%) patients presented treatment related complications. One (1%) patient had a *Clavien-Dindo*

***Figure 1.***
*Kaplan-Meier analysis showing Failure Free Survival according to (a) PSA reduction > 70% at 3 months (log-rank test p = 0.002), (b) initial total PSA categories (log-rank test = 0.915), (c) ISUP grade (log-rank test = 0.560), and (d) NCCN sub-risk group (log-rank test = 0.676).*



grade I complication: hematuria needing hospitalization for continuous bladder irrigation. Twelve (8%) patients had *Clavien-Dindo* grade II complications: 11 (7%) urinary retentions, 6 (4%) acute bacterial prostatitis, 3 (2%) acute orchitis, 1 (1%) intense perineal pain. One (1%) patient had a *Clavien-Dindo* grade IIIb complication, a recto-cutaneous fistula needing colostomy. No deaths due to treatment were registered.

### *Biochemical recurrence after treatment*

A total of 88 (59%) patients presented biochemical recurrence according to the Phoenix criteria, with median time to PSA failure of 24.0 months. Patients with biochemical recurrence were younger than patients without biochemical recurrence (66 *vs* 70 years, p = 0.035). Other studied factors were not statistically different between patients with and without biochemical recurrence (Table 4).

### *Other follow-up data*

Nadir total PSA was reached at a median time of 3.0 (IQR 3.0-9.8) months.

MRI was performed at least once for 125 (83%) patients during the first 3 years; in 68 patients at 1 month and 79 at 1 year, being positive in 10 (15%) and 44 (56%) patients, respectively. Control biopsies were performed at least once for 122 (81%) patients during the first 3 years; in 96 cases during the first year. Presence of csPCa on biopsy after treatment was detected in 79 (53%) patients; in 31 (21%) cases with csPCa only on previous treated area and/or its borders, 20 (13%) with only outfield csPCa and 28 (19%) in both infield and outfield areas.

Systemic progression was found in 10 (7%) patients, with 4 (3%) presenting with pelvic lymph node disease and 6 (4%) with other metastatic progression.

Patients who developed metastatic disease were in 1 case a patient with initial total PSA of 12.1 ng/mL and high-volume ISUP 1 PCa, with total PSA of 16.4 ng/mL 3 months after HIFU, who had retroperitoneal metastasis on re-staging; and 5 cases of patients with initial total PSA > 10 ng/mL and csPCa, who had biochemical recurrence, underwent additional treatment, but had disease progression with metastasis detected 30-72 months after.

Three (2%) patients died during follow-up, both due to reasons unrelated to PCa.

***Table 4.***
*Patients' characteristics according to biochemical recurrence free survival and univariate analysis.*

| Characteristics | Biochemical recurrence free (n = 62) | Biochemical recurrence (n = 88) | Univariate P-value |
|---|---|---|---|
| Treatment, n (%) | | | 0.702 |
| Cryotherapy | 14 (23) | 23 (26) | |
| HIFU | 48 (77) | 65 (74) | |
| Age, Median (IQR) | 70 (64-73) | 66 (61-71) | 0.035 |
| Prostate volume (mL), Median (IQR) | 40.5 (32.75-48.25) | 40 (35-49.25) | 0.782 |
| Total PSA (ng/mL) | | | 1.000 |
| Initial tPSA < 10 ng/mL, n (%) | 43 (69) | 61 (69) | |
| Initial tPSA 10-20 ng/mL, n (%) | 19 (31) | 27 (31) | |
| cT stage, n (%) | | | 0.442 |
| cT1c | 45 (73) | 69 (78) | |
| cT2a-c | 17 (27) | 19 (22) | |
| Biopsy overall ISUP Grade, n (%) | | | 0.699 |
| 1 | 17 (27) | 20 (23) | |
| 2 | 44 (71) | 65 (74) | |
| 3 | 1 (2) | 3 (3) | |
| NCCN risk group, n (%) | | | 0.165 |
| Intermediate favorable | 52 (84) | 65 (74) | |
| Intermediate unfavorable | 10 (16) | 23 (26) | |
| Tumor per specific locations, n (%) | | | |
| Anterior zone | 8 (13) | 8 (9) | 0.592 |
| Apex | 9 (15) | 14 (16) | 0.824 |
| Base | 16 (26) | 35 (40) | 0.083 |
| Bilateral | 3 (5) | 8 (9) | 0.365 |
| Total PSA nadir (ng/mL), Median (IQR) | 2.28 (1.02-4.19) | 2.73 (1.80-4.65) | 0.085 |
| Time to PSA nadir (months), Median (IQR) | 5 (3-11) | 3 (3-8) | 0.580 |
| PSA % reduction, Median (IQR) | | | |
| @ 3 months | 57.14 (43.24-76.28) | 55.43 (37.56-68.70) | 0.517 |
| @ nadir | 64.16 (46.97-79.06) | 62.16 (42.58-77.13) | 0.522 |

## Discussion

This study represents our experience as one of the first centers treating patients with intermediate-risk PCa with FTs, and shows our experience since the beginning of this practice. As such, during this time period treatment instruments have evolved, patient selection criteria have been refined, and knowledge has improved.

We report the oncological outcomes of 150 consecutive patients with intermediate-risk localized PCa treated with either cryotherapy (25%) or HIFU (75%). 144 patients were followed longer than 24 months, with a median follow-up time of 61 (IQR 48-82) months. Although a big proportion of patients (65%) were submitted to additional treatments (with 71 in 97 of those cases being treated with whole-gland or systemic treatment), the median time of FFS was of 45.5 (IQR 21.8-61.0) months, which means that FT resulted in a substantial delay to radical treatment for a big proportion of patients. The safety profile of the treatment was good, with only 1 patient having a complication *Clavien-Dindo* ≥ 3. Only 10 (7%) of patients presented disease progression, with 6 (4%) as metastatic disease, and there were no deaths related to PCa.

It has the limitations of being a single center retrospective study, capturing patients during a long timeframe, in which treatment instruments, diagnostic methods, and disease comprehension has evolved. We also note that the first cases included account to 2009 when FT treatments were undergoing their first discovery period. In addition, since some patients referred to us for treatments come from other big distances their follow-up is sometimes changed to a local physician after an initial time of stable disease, leading to some early censoring of patients who have good outcomes. These 2 factors may tilt our results to seem worse than current practice.

With the debate on FT for intermediate-risk disease still ongoing (9, 10), we believe gathering to be important in counseling patients who search for non~radical treatment options; or wish to change from active surveillance to active treatment due to desire to act and fear of progression, which are reasons as common as common as disease progression (11, 12).

Regarding oncological safety, groups as the *Imperial College London* have reported on their experience. On a propensi-

ty-score matched study (13) comparing oncological outcomes between patients who underwent FT or radical prostatectomy at their center, they report a FFS (95% CI) at 3, 5 and 8 years of 86% (81-91%), 82% (77-88%) and 79% (73-86%) for radical prostatectomy and of 91% (87-95%), 86% (81-92%) and 83% (76-90%) after FT (p = 0.12). Their report shows similar oncological outcomes between both modalities. However, this was a retrospective study and the groups compared after matching included 38.2% and 37.0% patients with ISUP 1 PCa.

Recently, *Reddy et al.* (14) published the largest reported cohort on FT: a multi-center study including 1379 men undergoing HIFU for localized PCa treatment, with 66% in the intermediate-risk group. They reported an overall FFS rate of 69% at 7 years. Of note is that in their protocol, a second HIFU treatment regardless of timing is allowed and was performed in 252 patients, placing the re-treatment free survival at 7 years at 43%.

For intermediate-risk patients, they report a FFS of 83% at 5 years, and 68% at 7 years. In this study, no patients developed metastasis or died due to PCa, and 7 (0.5%) patients had complications with *Clavien-Dindo* score > 2 (14). Their nominal FFS was higher than in our current report since the 2 year time-frame. However, we note that the authors allowed for a second FT without considering a treatment failure, and their retreatment-free survival at 7 years was of 49% and the whole-gland or systemic treatment survival at 7 years was of 78%, which is also above our reported values. Complications were in line with our current study, with serious events being rare.

In a multi-center study including 703 men with low or intermediate-risk PCa receiving FT, % PSA reduction was found to be an independent predictor of any additional treatment, with FFS at 5 years of approximately 70%, 50% and 20%, for % PSA reductions of 0%, 50%, and close to 100%, respectively (15). The same association was found in our study, with this factor seeming a possible measure that can help setting up an adequate follow-up strategy and counseling patients on risk of disease recurrence.

Although here we do not report on functional outcomes, many groups have reported good results with FT, with 94-100% pad-free rate regarding urinary incontinence and 47-86% erectile function (16).

With FT on the rise in both recognition and availability (17, 18), our current and other's reports (19) show that clinicians have been treating patients with higher risks both on and off trial, as some patients express a desire to undergo FT outside of those criteria, searching for a chance of benefit (avoiding or delaying complications) when treatment is advised but there is no immediate threat to life, as is the case of localized intermediate-risk PCa.

While urological guidelines (1, 6) still consider FT as experimental treatments, the *German Society of Urology* (20) has published in 2022 a list of recommendations considering FT an option for patients with unilateral low-risk PCa who decline "*standard therapies*" and active surveillance, but reminding of the available data being insufficient to access FT oncological effectiveness. Other publication has reported on a Delphi-method consensus meetings of 47 FT experts recommending allowing treatment of low and intermediate-risk PCa with volume up to 3 mL in 1 hemi-gland, if total PSA lower than 10 ng/mL (21).

The oncological and functional reported outcomes for FT in PCa have also been reported in at least 72 studies, with 8 different energy modalities and including 5827 patients (19). However, those are mostly from single-arm stage 2 studies. To add to the current data, we would like next years to bring us results on randomized controlled trials for FT versus radical treatment and active surveillance, with populations of mainly intermediate-risk PCa patients. Those trials will need to prove both efficacy and safety of FT.

## Conclusions

This series adds information on the outcomes of FT in the treatment of localized intermediate-risk PCa. The oncological control and survival without whole-gland or systemic treatment were satisfactory. In those who needed additional treatment, FT delayed its need in a reasonable amount of time, with a very good side-effect profile.

With a low percentage of metastatic disease and no PCa related deaths, this study advocates for allowing FT as a treatment option in selected cases of intermediate-risk disease.

Randomized controlled trials comparing FT with active surveillance and radical treatments are needed to further establish the role of those treatments.

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