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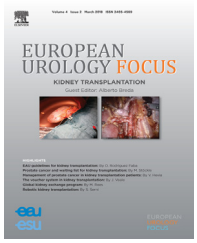

Prostate Cancer

Long-term Outcomes of Focal Cryotherapy for Low- to Intermediate-risk Prostate Cancer: Results and Matched Pair Analysis with Active Surveillance

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Abstract

Background: To date, only one trial compared focal therapy and active surveillance (AS) for low-risk prostate cancer (PCa). In addition, long-term outcomes of focal cryotherapy (FC) are lacking.
Objective: Our aim was to evaluate long-term outcomes of FC and compare them with AS.
Design, setting, and participants: We included two prospective series of 121 (FC) and 459 (AS) consecutive patients (2008–2018) for low- to intermediate-risk PCa.
Outcome measurements and statistical analysis: Study outcomes were radical therapy–free or androgen deprivation therapy (ADT)-free, any treatment-free, metastasis-free, and overall survival. A matched pair analysis was performed using seven covariates.
Results and limitations: The median FC follow-up was 85 mo (interquartile range 58–104); 92 (76%) men had International Society of Urological Pathology (ISUP) grade 1. Among matched variables, no significant differences were present except for cT stage and year of entry (both $p < 0.01$). Ten-year radical therapy–free or ADT-free, any treatment-free, metastasis-free, and overall survival were 51%, 40.2%, 93.9%, and 97%, respectively for FC. No differences were noted with AS (all $p > 0.05$), with the exception of time to radical therapy, time to radical therapy and ADT, and time to any treatment, all being shorter for AS (all $p < 0.01$). Freedom from radical treatment or ADT was higher for FC (AS 10 yr 39.3%; $p = 0.04$). Complications were relatively rare (26.5%) and mainly of low grade (Clavien >2, $n = 3$); three men developed incontinence ($p = 0.0814$), while both International Index of Erectile Function 5 and International Prostate Symptom Score scores increased ($p = 0.0287$ and $p = 0.0165$, respectively). Limitations include absence of randomization.
Conclusions: At an early long-term follow-up, FC in the context of mainly low-risk PCa is safe and increases time to radical therapy but does not provide meaningful oncological advantages compared with AS.
Patient summary: We compared focal cryotherapy with active surveillance mainly for low-risk prostate cancer. Focal cryotherapy, despite having fewer complications, did not yield meaningful advantages over active surveillance at 10 yr. Active surveillance should be preferred to focal cryotherapy for these patients.

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1. Introduction

Focal therapy (FT) is gaining interests among prostate cancer (PCa) practitioners [1–3], and the number of men treated is increasing despite it not being considered a standard of care [2].

Currently, among the main arguments hampering FT introduction in clinical practice are the absence of long-term results, which are important considering the relatively slow evolving course of intermediate-risk PCa [4], and the absence of randomized controlled trials (RCTs) against radical treatments [5,6].

However, another less considered but no less important aspect FT needs to prove is its superiority to expectant management. This holds true especially when considering that even radical treatment yields only moderate and no major advantages in terms of metastatic and cancer-specific and OS, respectively, compared with expectant management [4,7].

Although FT morbidity and variations of functional outcomes are minimal, by definition these treatment-related drawbacks must be expected to be higher than those for no treatment and need to be justified by advantages in terms of cancer control.

To date, only one RCT compared FT using vascular-targeted photodynamic therapy with active surveillance (AS), proving that FT reduces progression, PCa persistence at control biopsies, and need of radical treatment. However, this study provided short-term results only and focused on men with low-risk disease, excluding those with International Society of Urological Pathology (ISUP) grade >1 and a clinical stage of >T2a [8]. Furthermore, photodynamic therapy results may differ from those of other FT energies [1,2,6]. Taken together, these limitations hamper the possibility of generalizing these results to FT overall, while other comparisons between FT and AS are lacking.

Among different FT options, cryotherapy is currently one of the most frequently used ones [2]. Medium-term results have recently been described and showed promising cancer control with low morbidity [9–11]. Nonetheless, long-term follow-up has not been detailed well yet [2].

At our institution, we performed the first focal cryotherapy (FC) procedures >1 decade ago, and results are now mature enough to provide medium-term to relatively long-term outcomes [12,13].

Hence, we detailed FC outcomes and compared them with AS for low- to intermediate-risk localized PCa through a matched pair analysis to investigate whether FC yields any advantages in terms of radical treatment avoidance and, overall, oncological control at an early long-term follow-up.

2. Patients and methods

2.1. Patients

2.1.1. FC—main cohort

We included consecutive patients diagnosed with localized PCa who underwent FC at Institut Mutualiste Montsouris, from 2008 to 2018. Treatment was performed in the context of a prospective registry as per guideline recommendations, after approval from the institutional review board and obtaining informed consent from patients [13].

All patients received FT using focal ablation, quadrant ablation, or hemiablation, depending on lesion localization. All cases were performed as first-line treatment. Cryotherapy was performed as previously described using transperineal needles (Galil Medical, Inc., and Cryocare; Varian Medical Systems, USA) [12]. Management of each patient (suitability and, eventually, management of recurrence) was discussed in a multidisciplinary meeting.

2.1.1.1. Inclusion. Institutional protocol generally comprised preoperative 1.5 or 3.0 T multiparametric magnetic resonance imaging (mpMRI) with FC being performed for low-/intermediate-risk PCa (defined as prostate-specific antigen [PSA] <20 ng/ml, ISUP ≤2, and clinical stage ≤T2c). A bone scan and cross-sectional abdominal imaging (mpMRI and/or computed tomography [CT] scan) were performed to rule out extraprostatic disease in intermediate-risk PCa. Biopsies were performed using a systematic (at least ten cores), saturation, or mpMRI targeted (at least ten systematic plus three targeted cores) approach depending on the period of inclusion, mpMRI findings, treating physician, and clinical case [13].

2.1.1.2. Follow-up. A standard control biopsy was performed at 1 year or earlier when indicated (continuing PSA rise or suspicious PSA persistence/imaging early after treatment). Similarly, mpMRI was generally performed 3–12 mo after treatment. PSA was obtained every 3 mo following the 1st year of treatment and every 6 mo in the following years, after the first control biopsy [13]. Whole gland treatment was generally recommended in case of upgrade to ISUP >2 on control biopsies, or PSA and/or imaging progression together with the diagnosis of ISUP 1 or 2 on control biopsies. Alternatively, focal retreatment was offered to patients in cases of unilateral ISUP 2 persistence/recurrence with no evidence of imaging progression or high volume (more than three cores) unilateral ISUP 1. Patients having small-volume ISUP 1 and not willing to undergo AS were also offered redo focal treatment (Supplementary material). In-field recurrence/persistence was defined as a positive control biopsy in the previously treated area, whereas out-of-field recurrence/persistence was defined conversely (contralateral or on a different sagittal area being categorized as apex, midgland, and base).

2.1.2. AS—control cohort

Patients were matched with men being enrolled in the AS program at St. Antonius Hospital, Utrecht, The Netherlands, from 2008 to 2018. Current AS patients are an updated subgroup of the Santeon consortium cohort, which consists of seven large nonacademic teaching hospitals in the Netherlands [14].

2.1.2.1. Inclusion. AS was performed in accordance with the protocol described in PRIAS [15,16].

Variations were allowed, and patients not fulfilling all these criteria who preferred conservative management were also treated with AS in selected cases [17].

2.1.2.2. Follow-up. The first repeat biopsies were usually performed at 1 and 4 yr. A PSA test was requested every 3 mo in the first 2 yr and every 6 mo thereafter. Variations to the PRIAS protocol on a per-patient basis were devised according to the treating physician.

AS was discontinued as per the PRIAS criteria in case of clinically significant PCa or PCa progression [16]. Nononcological reasons for discontinuing AS included psychological stress of the patient and competing diseases with a higher impact than PCa.

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2.2. Study aims

The study goal was to describe early long-term outcomes of FC and compare them with AS for low- to intermediate-risk localized PCa through a matched pair analysis.

The primary outcome was (salvage) treatment-free survival defined as absence of whole gland treatment or androgen deprivation therapy (ADT).

Secondary outcomes comprised: (1) any (salvage) treatment-free survival, including redo focal treatments; (2) metastasis-free survival; and (3) overall survival.

2.3. Variable categorization

Functional outcomes were recorded preoperatively, at 3 and 12 mo, including (1) erectile function through the International Index of Erectile Function 5 (IIEF-5) questionnaire, (2) continence through the self-reported function and International Continence Society (ICS) male short-form questionnaire, and (3) urinary function through the International Prostate Symptom Score (IPSS) questionnaire.

Peri- and postoperative complications were recorded by the treating physician according to the EAU recommendations and graded using the Clavien-Dindo system [18].

2.4. Statistical analysis

Comparisons were evaluated using the Wilcoxon-Mann-Whitney test for continuous and the chi-square or Fisher exact test for categorical variables, as appropriate.

To obtain an unbiased estimation of the treatment effect, we performed a matched pair analysis using propensity score, estimated using a multivariable logistic regression analysis with treatment type as the dependent variable. A priori selected variables were the following: age at treatment/AS inclusion, PSA, prostate volume, pretreatment biopsy ISUP grade and number of positive cores, digital rectal examination (DRE; clinical stage), and year of FT treatment/AS inclusion. The genetic matching method without replacement was used to achieve covariate balance and minimize bias related to data replacement or arbitrary caliper matching. Analyses were performed before and after matching.

Kaplan-Meier curves and log rank test were used to estimate survival probability and compare the two cohorts.

Statistics were conducted using Stata (Stata-Corp, College Station, TX, USA), R (R Foundation for Statistical Computing; http: //www.r-project.org/), and SAS (SAS Institute, Cary, NC, USA). All tests were two sided. All p values of ≤ 0.05 were considered significant.

3. Results

3.1. Focal cryotherapy

3.1.1. Baseline and follow-up features

We included 121 consecutive patients undergoing FC. Baseline features are displayed in Table 1. Preoperative mpMRI was performed in 86.8%. The median number of positive cores was 2 (interquartile range [IQR] 1–3), and the majority of patients had low-risk pathology (ISUP 1: 76%) and D'Amico score (65.3%).

The median follow-up time was 85 mo (IQR 58–104). At least one first control biopsy was performed in 96.6% and was negative in 57.1% at a median of 12 mo (IQR 10–15) from treatment (Table 2). The median number of control biopsies during follow-up was 1 (IQR 1–2), and PSA nadir was 2.63 ng/ml (IQR 1.55–3.95), achieved at a median of 3 mo from FT (IQR 3–9).

3.1.2. Oncological outcomes

Seventy-five patients (62%) had local PCa recurrence. Overall, the majority of men did not need any additional retreatments (55.4%), while of the 54 men undergoing salvage treatments, 14.8% underwent redo focal treatments, 63% whole gland treatment, and 22.2% ADT. The reasons for radical treatment or ADT are provided in Supplementary Table 1. Overall, 75 (62%) local recurrences occurred, of which 26 (34.6%) were in-field, 19 (25.3%) out-of-field, and 27 (36%) both in-field and out-of-field recurrence/persistence.

Systemic PCa spread was rare (4.1%), and no PCa-related deaths were recorded.

Five-year and 10-yr radical therapy–free or ADT-free survival and any treatment-free survival were 70.5% and 51% and 65% and 40.2%, respectively, for FC (Fig. 1). Metastasis-free and overall survival were 93.9% and 97%, respectively, at 10 yr. No PCa deaths were recorded.

3.1.3. Morbidity

Functional outcomes and complications are reported in Table 3. Thirty-five men experienced at least one complication. Three major complications were recorded (Clavien >2). After FT, three men had newly onset incontinence (ICS 1, n = 2; ICS 8, n = 1; p = 0.0814). Erectile function according to both the IIEF-5 and the IPSS increased after treatment (p = 0.0287 and p = 0.0165, respectively).

3.2. Matched pair analysis

3.2.1. Baseline and follow-up features

Baseline features of the AS cohort before and after matching are detailed in Table 1. Among the variables used for the matching no major differences were noticed, with the exception of an increased number of cT2 cases and later year of entry for the AS patients (both $p < 0.01$). The number of biopsy cores taken was higher in the FT group, and so were the number of preoperative mpMRI scans and percentage of saturation biopsies at entry (all $p < 0.01$).

Follow-up was longer following cryotherapy (p = 0.0027). In the AS matched group, fewer patients had a control biopsy and relatively more men had a positive biopsy ($p < 0.0001$; Table 2).

3.2.2. Oncological outcomes

Kaplan-Meier survival plots are shown in Figure 1. No significant differences were highlighted in all oncological endpoints and final pathological features in those who underwent radical prostatectomy (all $p > 0.05$), with the exception of time to radical therapy, or radical therapy and ADT, or any treatment, which were all shorter in the AS cohort ($p < 0.01$; Table 4), and freedom from radical therapy or ADT were higher for cryotherapy (AS 5 yr, 57.3%; AS 10 yr, 39.3%; p = 0.0444). Five-year and 10-yr treatment-free survival rates are available in the Supplementary

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Table 1 – Baseline features of the two cohorts before and after matching

	Unmatched					Matched				
	Cryotherapy		Active surveillance			Cryotherapy		Active surveillance		
	n/median	(%/IQR)	*n*/median	(%/IQR)	*p* value	*n*/median	(%/IQR)	*n*/median	(%/IQR)	*p* value
n	121		459			121		58		
Age (yr)	66	(62–71)	67	(63–72)	0.2924	66	(62–71)	67	(62–70)	0.7042
PSA (ng/ml)	6.42	(5.03–8.08)	7	(5.3–9.7)	**0.0395**	6.42	(5.03–8.08)	6.9	(5.2–8.6)	0.2366
cT stage					<**0.0001**					**0.0007**
cT1	101	(83.5)	173	(37.7)		101	(83.5)	35	(60.3)	
cT2	20	(16.5)	249	(54.2)		20	(16.5)	23	(39.7)	
cT3 [a]	0	(0.0)	37	(8.0)		0	(0.0)	0	0	
Prostate volume (cc)	42	(35–52)	49.6	(37–67)	**0.0007**	42	(35–52)	42	(39–53)	0.3514
PSA density	0.14	(0.11–0.21)	0.14	(0.10–0.21)	0.2323	0.14	(0.11–0.21)	0.18	(0.12–0.23)	0.1140
mpMRI					<**0.0001**					<**0.0001**
No	16	(13.2)	227	(49.5)		16	(13.2)	28	(48.3)	
Yes	105	(86.8)	232	(50.5)		105	(86.8)	30	(51.7)	
Negative	32	(30.5)	82	(35.3)		32	(30.5)	10	(33.3)	
Suspicious	73	(69.5)	150	(64.7)		73	(69.5)	20	(66.6)	
Entry biopsy										
Type					<**0.0001**					**0.0002**
Saturation	18	(17.5)	0	(0.0)		18	(17.5)	0	0	
Systematic	79	(76.7)	390	(85.0)		79	(76.7)	45	(77.6)	
Targeted only	0	(0.0)	12	(2.6)		0	(0.0)	1	(1.7)	
Targeted + systematic	6	(5.8)	57	(11.2)		6	(5.8)	12	(20.7)	
Number of biopsy cores										
Positive	2	(1–3)	2	(1–3)	0.3333	2	(1–3)	2	(1–3)	0.7668
1–3	103	(85.1)	397	(86.9)	0.6170	103	(85.1)	49	(84.5)	0.5160
>3	18	(14.9)	60	(13.1)		18	(14.9)	9	(15.5)	
Taken	12	(12–18)	10	(8–11)	<**0.0001**	12	(12–18)	10	(8–11)	<**0.0001**
ISUP					<**0.0001**					0.4522
1	92	(76.0)	421	(72.6)		92	(76.0)	47	(81.0)	
2	29	(24.0)	32	(7.0)		29	(24.0)	11	(19.0)	
3	0	0	5	(1.1)		0	0	0	0	
4	0	0	1	(0.2)		0	0	0	0	
5	0	0	0	0		0	0	0	0	
D'Amico risk class					**0.0021**					0.1906
Low	79	(65.3)	339	(73.9)		79	(65.3)	45	(77.6)	
Intermediate	40	(33.1)	91	(19.8)		40	(33.1)	13	(22.4)	
High	2	(1.6)	29	(6.3)		2	(1.6)	0		
Year of entry					<**0.0001**					<**0.0001**
2008–2011	56	(46.3)	117	(25.5)		56	(46.3)	15	(25.9)	
2012–2015	54	(44.6)	187	(40.7)		54	(44.6)	19	(32.7)	
2016–2018	11	(9.1)	155	(33.8)		11	(9.1)	24	(41.4)	

DRE = digital rectal examination; EAU = European Association of Urology; Entry = beginning of active surveillance program or year of FT; IQR = interquartile range; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.
Variables used for matching and relative p values before and after matching are underscored; significant *p* values are reported in bold; cT stage was evaluated through DRE as per EAU guidelines.
[a] cT3 disease was an exclusion criteria in both FT and AS protocols.

Table 2. Kaplan-Meier curves before matching are detailed in Supplementary Figure 1.

4. Discussion

In the current study, we report early long-term outcomes of FC for low- to intermediate-risk localized PCa and compare the results with those of patients undergoing AS using a matched pair analysis. To our knowledge, long-term follow-up of FC patients has scarcely been reported. Furthermore, no comparison with AS has been detailed yet using this energy source.

First, only slight improvement in the need of radical therapy or ADT was noted between FC and AS: at 10 yr, one out of two men requires whole gland or ADT treatment compared with six out of ten among those undergoing AS. Furthermore, this advantage becomes inconsistent if redo focal therapies are considered in the treatment definition. In this context, FC allowed a longer treatment-free window. Despite growing evidence, including cases from our group, detailing similar morbidity for radical salvage versus first-line surgery, this advantage seems to be marginal [19,20]. Overall, our data suggest that FC adds little or no oncological benefits in the context of mainly low-risk disease. The relatively high rate of disease-positive first control biopsies in the FC group further questions the rationale of actively treating these patients.

On the one hand, our analysis is in line with the results detailed by Azzouzi and associates [8], who also found reduced PCa progression and number of positive first

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Table 2 – Follow-up features of the two cohorts before and after matching

	Unmatched					Matched				
	Cryotherapy		Active surveillance			Cryotherapy		Active surveillance		
	n/median	(%/IQR)	*n*/median	(%/IQR)	*p* value	*n*/median	(%/IQR)	*n*/median	(%/IQR)	*p* value
Follow-up (mo)	85	(58–104)	62	(45–92)	<**0.0001**	85	(58–104)	54.5	(46–92)	**0.0027**
First control biopsy	115	(96.6)	269	(58.7)	<**0.0001**	115	(96.6)	35	(60.3)	<**0.0001**
Not performed	4	(3.4)	189	(41.3)	<**0.0001**	4	(3.4)	23	(39.6)	**0.0005**
Negative	68	(57.1)	73	(15.9)		68	(57.1)	6	(10.3)	
ISUP										
1	28	(59.6)	129	(67.5)		28	(59.6)	18	(64.3)	
2	15	(31.9)	41	(21.5)		15	(31.9)	7	(25.0)	
3	3	(6.4)	12	(6.3)		3	(6.4)	3	(10.7)	
4	1	(2.1)	5	(2.6)		1	(2.1)	0	(0.0)	
5	0	(0.0)	4	(2.1)		0	(0.0)	0	(0.0)	
Time from entry (mo)	12	(10–15)	13	(11–22)	**0.0118**	12	(10–15)	14	(11–26)	**0.0119**
No. of control biopsies	1	(1–2)	–	–	–	1	(1–2)	–	–	
PSA nadir (ng/ml)	2.63	(1.55–3.95)	–	–	–	2.63	(1.55–3.95)	–	–	
Time to nadir (mo)	3	(3–9)	–	–	–	3	(3–9)	–	–	

Entry = beginning of active surveillance program or year of focal therapy; IQR = interquartile range; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.
Significant *p* values are reported in bold.

control biopsies, and longer time to progression when randomizing men to either photodynamic therapy or AS. Nonetheless, while differences in progression timing and PCa rates on first control biopsy are noteworthy, the most meaningful endpoint is less marked in our cohort. Later onset of recurrences/progression after FT compared with AS together with a median RCT follow-up of 24 mo may only partially account for these differences, claiming the need for

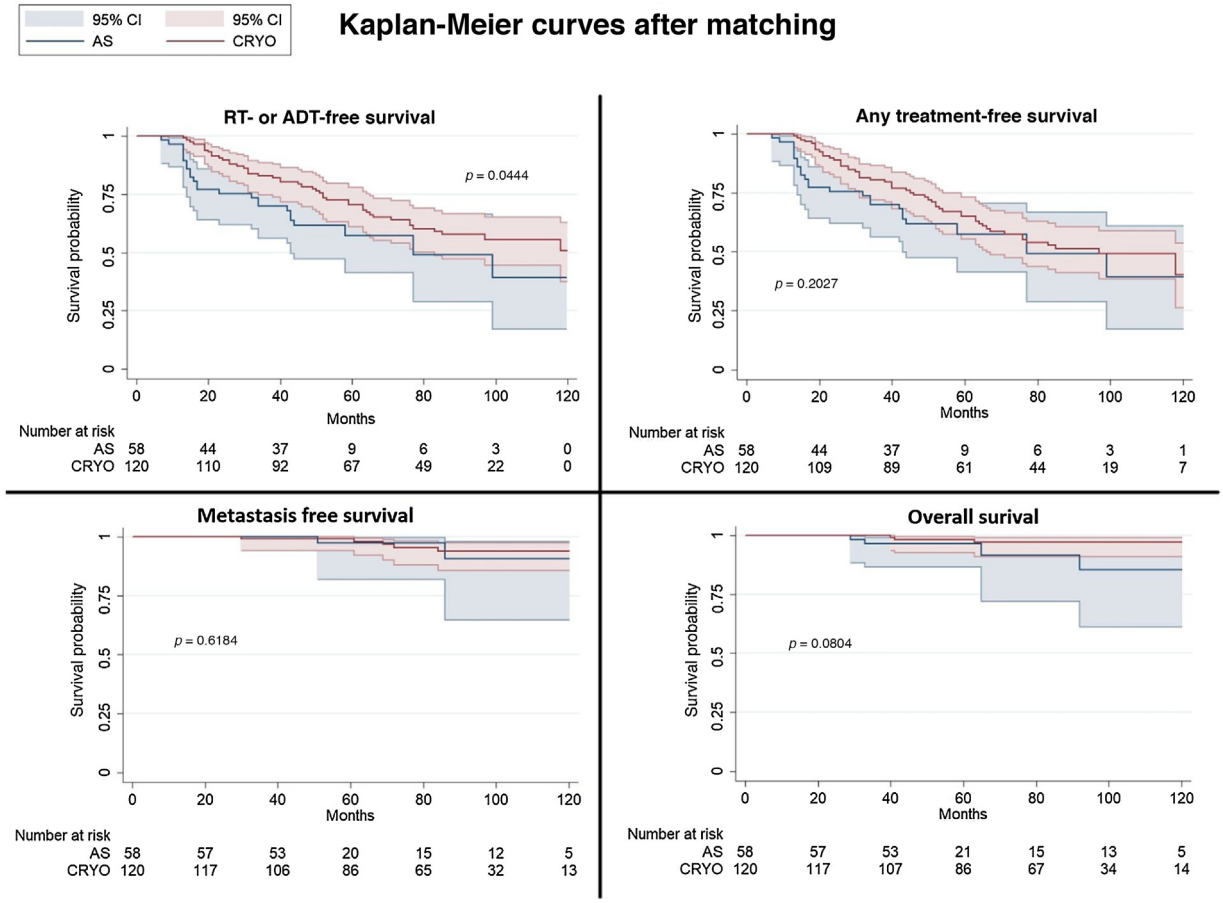

Fig. 1 – Kaplan-Meier plots of the two matched cohorts. Median treatment-free survival from RT or ADT was 71 (41–94) mo for cryotherapy and 43 (17–55) mo for active surveillance; median survival free from any treatment was 64 (40–93) mo for cryotherapy and 43 (17–55) mo for active surveillance. ADT = androgen deprivation therapy; AS = active surveillance; CI = confidence interval; CRYO = cryotherapy; RT = radiotherapy.

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Table 3 – Focal cryotherapy morbidity

	Median/*n*	(IQR/%)
Catheter (d)	2	(2–2)
Urethral slaughtering	0	(0.0)
Urinary retention	10	(8.3)
Urethral stenosis	1	(0.8)
Hematuria	6	(5.0)
Rectal fistula	1	(0.8)
UTI		
Epididymitis	7	(5.8)
Prostatitis	1	(0.8)
Men with complications	35	(26.5)
Clavien [a]		
1	16	(13.2)
2	13	(10.7)
3a	0	(0.0)
3b	2	(1.6)
4a	1	(0.8)
Functional outcomes [b]		
Baseline		
IIEF-5	10	(0–20)
IPSS	3	(0–9)
Continent	84	(100.0)
Incontinent	0	(0.0)

After FT [c]			*p* value*
IIEF-5	14.5	(5–18)	**0.0287**
IPSS	6	(3–9)	**0.0165**
Continent	81	(96.5)	0.0814
Incontinent	3	(3.5)	

FT = focal therapy; ICS = International Continence Society; IIEF-5 = International Index of Erectile Function 5; IPSS = International Prostate Symptom Score; IQR = interquartile range; UTI = urinary tract infection.
* Comparison of per patient pre- versus postcryotherapy scores.
[a] Per complication.
[b] Only patients having both baseline and post-FT data were included.
[c] When 12-mo results/questionnaires were not available, 3-mo results/questionnaires were used; among incontinent patients, two had an ICS questionnaire score of 1 and one had 8.

a trial update. Of note, no intermediate-risk disease was included in this RCT, although theoretically this should have resulted in increased progression during AS [21].

On the other hand, it is worth highlighting that our results do not mirror those of recent FC series detailing almost 90% radical treatment–free survival at 3 and 5 yr [9,11], even when including high-risk PCa together with a majority of intermediate-risk PCa. Shorter follow-up, increased use of transperineal template mapping biopsy as the upfront selection strategy, a smaller proportion of men undergoing at least one control biopsy, and more recent treatment period may only partly contribute to these marked differences, and longer-term results are awaited.

Second, stronger oncological endpoints, including systemic progression, PCa, and overall deaths were also comparable. This does not come as a surprise considering the natural history of disease, as in a low- to intermediate-risk PCa milieu, progression is a rare event even when higher proportions of intermediate-risk patients are included [4]. Considering long-term AS series results, a longer follow-up is unlikely to show any relevant differences in low-risk PCa [21]. Contrarily, further time may be needed to draw conclusions on intermediate-risk PCa, partially explaining the low rate of metastases and PCa-related deaths of the present and other recent series [9,11].

Third, we confirmed that FC yields a low complication rate and minimal influence on functional outcomes. In line with the results recently detailed by others [9–11], only one of four men experienced complications, being mainly of low grade; erectile function, urinary function, and continence were mostly unchanged or slightly worsened. On the one hand, although low, the impact of FC is likely higher than that of expectant management. On the other hand, even in the context of AS, PCa-related events, including anxiety, depression, erectile dysfunction, and others, and PCa-unrelated events are also likely to occur [8]. Absence of these data in our AS cohort hampers a direct comparison with FT.

Fourth, we provide a preliminary comparison of radical prostatectomy specimen following FT or AS, showing no relevant differences. As reported by our group and others, partial gland treatment may theoretically favor progression of insignificantly untreated PCa foci and/or increase aggressiveness of treatment-resistant PCa clones through a so-called “field effect” [6,20,22,23]. Although numbers are small, our findings are relevant as they argue against speculative evidence of FT worsening PCa features. On the contrary, locally aggressive and/or advanced disease after FC may rather be related to the same reasons as in AS patients, including PCa natural history and/or failures in patient selection. Importantly, men with adverse pathological features remain a minority.

From a clinical perspective, our findings suggest that FC should not be offered in men with low-risk PCa who are candidate for AS and should not be considered as a means of reducing the need of radical treatment in these patients. This mainly relates to the absence of meaningful advantages in terms of freedom from additional treatments and systemic progression together with an FT morbidity, which, despite being low, is likely higher than that of expectant management [8].

From a research perspective, we do not provide level 1 evidence, clinical trials are ongoing (NCT03531099), and AS in low-risk PCa may not be the optimal comparator for FT, given its excellent long-term outcomes [21]. FT protocols have evolved since the beginning of our experience; having overcome the safety phase, they are now focusing mainly on intermediate-risk disease, which is currently thought to be the optimal candidate [24]. However, we believe that our findings claim validation by larger prospective series and/or using other energy sources. Furthermore, potential advantages of FT over AS for intermediate-risk disease, and not only noninferiority to radical treatment, need to be highlighted urgently to decide whether to support FT or not. Finally, our preliminary data do not suggest an increased risk of worse radical prostatectomy pathology after FT compared with AS. Research efforts should be made to clarify whether the “field effect” induces clinically meaningful changes in the untreated prostate.

Our work does not come without limitations. First, low-risk PCa is not the ideal candidate for FT. Nonetheless, especially in the first years of our experience, these patients

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Table 4 – Oncological results of focal cryotherapy and active surveillance before and after matching

	Unmatched					Matched				
	Cryotherapy		Active surveillance			Cryotherapy		Active surveillance		
	n/median	(%/IQR)	*n*/median	(%/IQR)	*p* value	*n*/median	(%/IQR)	*n*/median	(%/IQR)	*p* value
Treatment after FC or during AS										
No	67	(55.4)	292	(63.9)	0.0885	67	(55.4)	34	(58.6)	0.0756
Focal	8	(6.6)	0	(0.0)		8	(6.6)	0	(0.0)	
Radical	34	(28.1)	164	(35.9)		34	(28.1)	24	(41.4)	
ADT	12	(9.9)	3	(0.7)		12	(9.9)	0	(0.0)	
Radical or ADT treatment	46	(38.0)	167	(36.4)	0.7403	46	(38.0)	24	(41.4)	0.6661
Time to treatment (mo)										
To any	42	(26–63)	24	(15–37)	**<0.0001**	42	(26–63)	17	(13.5–42.5)	**0.0011**
To radical	45	(26–64)	24	(15–37)	**<0.0001**	45	(26–64)	17	(13–42)	**0.0018**
To radical or ADT	42.5	(24–63)	24	(15–37)	**<0.0001**	42.5	(24–63)	17	(13.5–42.5)	**0.0018**
Radical treatment type and ADT										
Radiotherapy	10	(21.7)	71	(43.0)	**<0.0001**	10	(21.7)	7	(29.2)	**0.0002**
Radical prostatectomy	13	(28.3)	50	(30.3)		13	(28.3)	8	(33.3)	
HIFU	3	(65.2)	0	(0.0)		3	(65.2)	0	(0.0)	
Cryotherapy	4	(86.7)	0	(0.0)		4	(86.7)	0	(0.0)	
Brachytherapy	0	(0.0)	30	(18.2)		0	(0.0)	9	(37.5)	
ADT	12	(26.1)	3	(1.8)		12	(26.1)	0	(0.0)	
RT + ADT	1	(2.1)	9	(5.5)		1	(2.1)	0	(0.0)	
RP + ADT	2	(4.3)	0	(0.0)		2	(4.3)	0	(0.0)	
Brachytherapy + ADT	1	(2.1)	0	(0.0)		1	(2.1)	0	(0.0)	
Irreversible electroporation	0	(0.0)	2	(1.2)		0	(0.0)	0	(0.0)	
Systemic progression	5	(4.1)	12	(2.6)	0.5030	5	(4.1)	2	(3.4)	0.9497
Pelvic nodes	2	(1.6)	7	(1.5)		2	(1.6)	1	(1.7)	
Retroperitoneum or other sites	3	(2.5)	5	(1.1)		3	(2.5)	1	(1.7)	
Time (mo)	69	(61–72)	77.5	(50.0–95.5)	0.5266	69	(61–72)	68.5	(51–86)	0.8465
Deaths					0.1549					0.2216
Prostate cancer deaths	0	(0.0)	6	(1.3)		0	(0.0)	1	(1.7)	
Non–PCa-related deaths	3	(2.5)	26	(5.7)		3	(2.5)	3	(5.2)	
Time (mo)	41	(41–52)	38	(27–90)	0.8365	41	(41–52)	49	(31–78.5)	0.9999
Radical prostatectomy pathology										
ISUP					0.0864					0.2387
1	1	(6.7)	11	(22.9)		1	(6.7)	1	(14.3)	
2	8	(53.3)	26	(54.2)		8	(53.3)	5	(71.4)	
3	5	(33.3)	7	(14.6)		5	(33.3)	0	(0.0)	
4	0	(0.0)	4	(8.3)		0	(0.0)	1	(14.3)	
5	1	(6.7)	0	0		1	(6.7)	0	(0.0)	
pT				0	**0.0040**					0.2478
2	8	(53.3)	38	(79.2)		8	(53.3)	5	(71.4)	
3a	3	(20.0)	0	0		3	(20.0)	0	0	
3b	4	(26.7)	6	(12.5)		4	(26.7)	1	(14.3)	
4	0	(0.0)	4	(8.3)		0	(0.0)	1	(14.3)	
pN				0	0.1225					0.2210
0	4	(26.7)	8	(16.7)		4	(26.7)	0	(0.0)	
1	1	(6.7)	0	0		1	(6.7)	0	(0.0)	
x	10	(66.7)	40	(8.3)		10	(66.7)	7	(100.0)	

ADT = androgen deprivation therapy; AS = active surveillance; FC = focal cryotherapy; HIFU = high-intensity focused ultrasound; IQR = interquartile range; ISUP = International Society of Urological Pathology; PCa = prostate cancer; RP = radical prostatectomy; RT = radiotherapy.
Significant *p* values are reported in bold.

were still offered radical treatment as per guideline recommendation at the time. In this context, FT was thought to be a valid alternative. Second, the PCa staging workup changed markedly from 10 yr ago and preoperative mpMRI targeted biopsies were rarely performed. Nonetheless, the majority of men had preoperative mpMRI and/or thorough preoperative evaluation, as per the more recent recommendation. Third, despite using a matched pair algorithm, some features remained unbalanced among the groups, namely, year of entry and clinical stage, evaluated through DRE. However, some lead-time selection bias is inevitable for every series providing long-term results. In addition, given the similarity of all other matched variables and the low inter-rater agreement of DRE, these differences likely have a minimal impact only.

Fourth, pathological results of postcryotherapy radical prostatectomy may not be applicable to other energy sources as they relate to different biological and physical cell- and gland-induced damage. Fifth, although our cohorts are prospective registries, study hypothesis and outcome analysis were retrospective, with patients' data collection not being specifically designed for the present work. As

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such, some potentially relevant points, including quality of life and functional outcomes in the AS cohort, were not addressed. Finally, focal therapy was not available as an option for men in the AS cohort; if some men with less aggressive disease had undertaken this option instead of radical therapies, differences among the groups would have likely been even less significant.

5. Conclusions

At an early long-term follow-up, FC in the context of mainly low-risk PCa is safe and may allow a longer window free from radical treatment or ADT when compared with AS. However, despite favoring a slightly reduced need of radical therapy or ADT, it does not provide meaningful oncological advantages. Metastasis and PCa deaths are rare, but more than one in two men needs additional PCa treatment. Further studies are needed to confirm our findings in the context of other energy sources including a higher number of patients and to specifically investigate FT versus AS in intermediate-risk disease.

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Study concept and design: Marra, Soeterik, Sanchez-Salas.
Acquisition of data: Marra, Sanchez-Salas, Oreggia, Filippini.
Analysis and interpretation of data: Marra, Soeterik, Filippini, Sanchez-Salas.
Drafting of the manuscript: Marra, Soeterik, Sanchez-Salas.
Critical revision of the manuscript for important intellectual content: All authors.
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***Ethics statement*:** All included patients undergoing focal therapy provided written informed consent. Need for written informed consent was waived for the patients undergoing AS by the local institutional review board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2021.04.008.

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