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Brief Correspondence

Primary Whole-gland Cryoablation for Prostate Cancer: Biochemical Failure and Clinical Recurrence at 5.6 Years of Follow-up

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Abstract

We retrospectively evaluated complications and functional and oncologic outcomes of 94 consecutive men who underwent primary whole-gland cryoablation for localized prostate cancer (PCa) from 2002 to 2012. Kaplan-Meier and multivariable Cox regression analyses were performed using a landmark starting at 6 mo of follow-up. In total, 75% patients had D'Amico intermediate- (48%) or high- (27%) risk PCa. Median follow-up was 5.6 yr. Median time to prostate-specific antigen (PSA) nadir was 3.3 mo, and 70 patients reached PSA <0.2 ng/ml postcryoablation. The 90-d high-grade (Clavien Grade IIIa) complication rate was 3%, with no rectal fistulas reported. Continence and potency rates were 96% and 11%, respectively. The 5-yr biochemical failure-free survival (PSA nadir + 2 ng/ml) was 81% overall and 89% for low-, 78% for intermediate-, and 80% for high-risk PCa ($p = 0.46$). The median follow-up was 5.6 and 5.1 yr for patients without biochemical failure and with biochemical failure, respectively. The 5-yr clinical recurrence-free survival was 83% overall and 94% for low-, 84% for intermediate-, and 69% for high-risk PCa ($p = 0.046$). Failure to reach PSA nadir <0.2 ng/ml within 6 mo postcryoablation was an independent predictor for biochemical failure ($p = 0.006$) and clinical recurrence ($p = 0.03$). The 5-yr metastases-free survival was 95%. Main limitation is retrospective evaluation. Primary whole-gland cryoablation for PCa provides acceptable medium-term oncologic outcomes and could be an alternative for radiation therapy or radical prostatectomy.

Patient summary: Cryoablation is a safe, minimally-invasive procedure that uses cold temperatures delivered via probes through the skin to kill prostate cancer (PCa) cells. Whole-gland cryoablation may offer an alternative treatment option to surgery and radiotherapy. We found that patients had good cancer outcomes 5 yr after whole-gland cryoablation, and those with a prostate-specific antigen value ≥0.2 ng/ml within 6 mo after treatment were more likely to have PCa recurrence.

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Cryoablation is recommended as an alternative treatment for recurrent localized prostate cancer (PCa) [1]. Although biochemical failure (BF) outcomes postcryoablation have been reported, there is a lack of predictors for clinical recurrence (CR) [2,3]. Herein, we evaluated perioperative, 90-d complications, functional and oncologic outcomes, and identified predictors for BF and CR following whole-gland prostate cryoablation.

At our institution, cryoablation is offered as an alternative to standard treatment modalities. We reviewed the records of 94 consecutive men who underwent primary whole-gland cryoablation for clinically localized PCa from 2002 to 2012. Patients underwent transrectal ultrasonography (TRUS)-Doppler evaluation, followed by image targeting of suspicious hypoechoic lesions and systematic sextant prostate biopsy (Type EUB-6500; Hitachi Medical Systems America Inc.) [4–6]. Our study period started in 2002 when magnetic resonance imaging (MRI) was not available for image-fusion biopsy or staging. Nevertheless, detailed mapping of cancer location was recorded in three-dimensional schematic drawings, and TRUS images were electronically stored for surgical planning and follow-up [4–6].

Patients were grouped based on D'Amico PCa risk classification [7]. High-risk PCa patients underwent whole-body bone scan and computed tomography of abdomen and pelvis to rule out metastases. Neoadjuvant androgen deprivation therapy (ADT) was administered for 6 mo prior to cryoablation in 38 (40%) patients with large prostates to down-size large-volume prostates, which may pose a challenge for proper whole-gland cryoablation. No patients received adjuvant ADT. Although prostate size was not a selection criterion, the median (interquartile range [IQR]) and maximum prostate size at the time of cryoablation were 37 (27–47) ml and 60 ml, respectively.

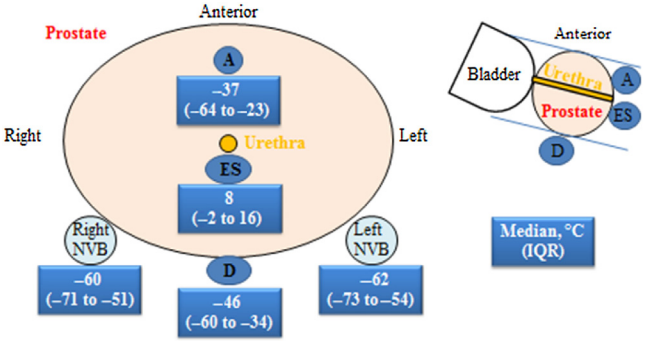


Fig. 1 – Thermocouple temperatures during whole-gland cryoablation of the prostate.
A = apex; D = Denonvilliers' fascia, ES: external rhabdoshphincter, IQR = inter quartile range, NVB = neurovascular bundles.

Table 1 – Demographics pre whole-gland cryoablation of the prostate[a]

Parameter	Median (IQR) or *n* (%)	Median (IQR) or *n* (%)	Median (IQR) or *n* (%)	*p* value
Follow-up time	All patients	≥6 mo	<6 mo	–
n	94	87	7	–
Age, yr	71 (66–75)	71 (66–75)	68 (60–78)	0.53
Prostate volume, ml	37 (27–47)	37 (27–50)	38 (24–40)	0.49
PSA, ng/ml	7.5 (5–11)	7.5 (5–11)	11 (4.6–24)	0.33
Clinical stage				
T1c	47 (50)	44 (51)	3 (43)	
T2a	35 (37)	31 (36)	4 (57)	
T2b	1 (1)	1 (1)	0 (0)	
T2c	4 (4)	4 (5)	0 (0)	0.79
T3a	6 (6)	6 (7)	0 (0)	
T3b	1 (1)	1 (1)	0 (0)	
Gleason score				
3 + 3	29 (31)	27 (31)	2 (29)	
3 + 4	24 (26)	23 (26)	1 (14)	
4 + 3	25 (27)	22 (25)	3 (43)	0.26
4 + 4	13 (14)	12 (14)	1 (14)	
4 + 5	3 (3)	3 (3)	0 (0)	
Biopsy cores, *n*	7 (6–8)	7 (6–8)	7 (7–8)	0.35
Cancer cores in biopsy, *n*	2 (2–4)	2 (2–4)	3 (2–3)	0.59
Maximum cancer core length, mm	6 (3–9)	6 (3–8.7)	3.5 (2–9)	0.38
Maximum cancer core, %	48 (20–65)	48 (20–68)	45 (25–60)	0.92
D'Amico risk group				
Low	24 (25)	22 (25)	2 (29)	
Intermediate	45 (48)	43 (49)	2 (29)	0.46
High	25 (27)	22 (25)	3 (43)	
Patients that received neoadjuvant ADT				
Low	10 (11)	9 (10)	1 (14)	
Intermediate	14 (15)	14 (16)	0 (0)	0.13
High	14 (15)	12 (14)	2 (29)	

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate specific antigen.
[a] Some cumulative percentages may not be 100% because of rounding.

Whole-gland cryoablation was performed by a free-hand technique under TRUS guidance using an argon/helium gas-based system (Endocare, HealthTonics Inc., Austin, TX, USA), with a double freeze-thaw cycle (Fig. 1) [5,6]. All patients maintained an 18F Foley catheter for 1 wk after cryoablation that was discontinued after a voiding trial. Follow-up with digital rectal examination (DRE), prostate-specific antigen (PSA), and TRUS imaging with Doppler was scheduled at 3, 6, and 12 mo after treatment and annually thereafter. Follow-up biopsy was offered to all patients at 12 and 24 mo or anytime if clinically indicated, including rising PSA, BF, or suspicious DRE or TRUS.

BF was defined as a PSA rise of ≥2 ng/ml above the nadir (Phoenix criteria). Other BF criteria were explored: PSA nadir + 1.2 ng/ml (Stuttgart criteria) and PSA ≥0.2 ng/ml (post-radical prostatectomy criteria) [2,8,9]. CR was defined as cancer on follow-up biopsy, evidence of recurrence by physical exam or imaging, salvage treatment, or initiation of ADT [8–10].

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Kaplan-Meier method was used to estimate survival curves. Log-rank test was used to compare risk groups. Multivariable cox regression included clinically important parameters and statistical significance on univariate analysis. Kaplan-Meier and multivariable Cox regression analyses were performed using a landmark starting at 6 mo of follow-up postcryoablation. Statistical significance was considered if p value was <0.05.

Table 1 shows patients' baseline characteristics. Furthermore, 90-d Clavien Grade I or II complications were 14% and 10%, respectively (Table 2). Three (3%) patients experienced urinary retention (Clavien Grade IIIa) requiring transurethral resection of the prostate. There were no rectal fistulas.

Oncologic outcomes are summarized in Tables 3, 4, and 5. Median (IQR) follow-up was 5.6 (3–7.9) yr (Table 3). According to PSA nadir + 2 ng/ml BF criteria, the median (IQR) follow-up was 5.6 (2.8–7.8) yr and 5.1 (3.5–7.5) yr for patients without BF and patients with BF, respectively. Median (IQR) time to PSA nadir was 3.3 (3–6.3) mo, and median nadir PSA was 0.1 (0.0–0.1) ng/ml. Seventy patients reached PSA <0.2 ng/ml. A total of 77 follow-up biopsies were performed in 45 patients with PCa found in nine patients (Table 3). Figure 2 shows PSA and PSA kinetics by CR and biopsy outcomes. Table 4 and Figures 3 and 4 show the estimated 5-yr BF-free survival and estimated 5-yr CR-free survival by different criteria. The 5-yr metastases-free survival was 95%. Two patients died, one from PCa originally diagnosed with intermediate-risk PCa. Multivariable analysis showed that failure to reach PSA nadir <0.2 ng/ml within

Table 2 – Summary of 90-d complications post whole-gland cryoablation of the prostate

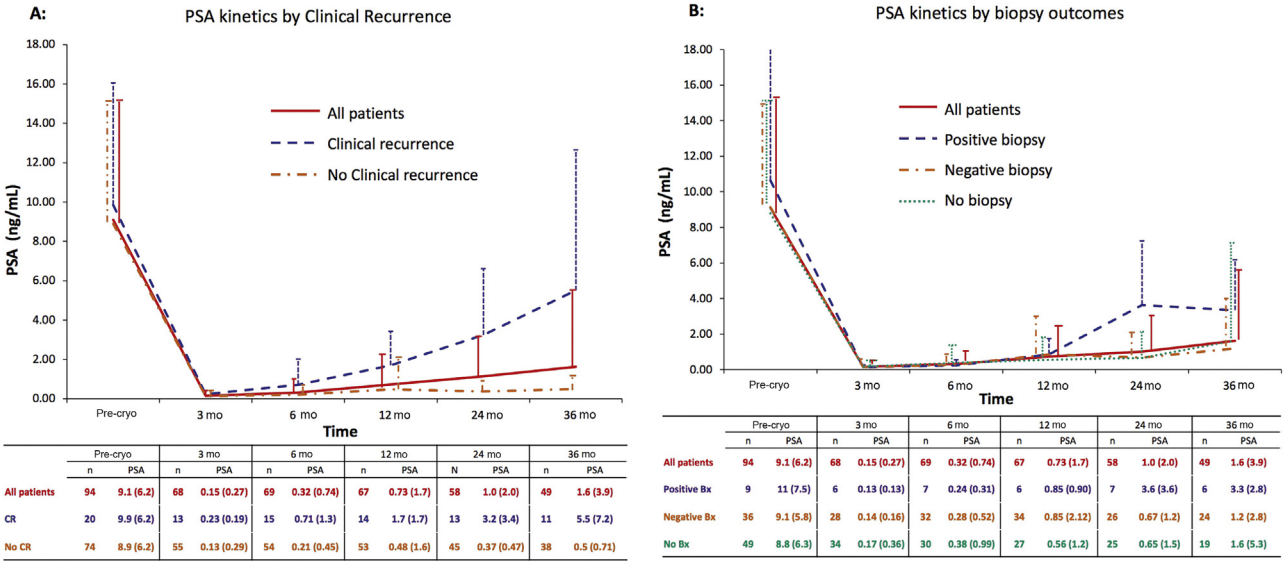
	Complication	Management
Clavien grade		
n	13 (14%)	
I		
1	Tissue sloughing	Expectant management
1	Urgency of urination	Symptomatic
2	Urinary retention	Prolonged Foley catheterization
II		
	Excruciating pain in the penis and scrotum	Analgesics
1	UTI	Antibiotics
1	Recurrent UTI/chronic prostatitis	Antibiotics
1	Urinary retention + UTI	Antibiotics + CIC
2	Urinary retention + UTI	Prolonged Foley catheterization + antibiotics
IIIa		
1	Urinary retention	TURP
2	Urinary retention + UTI	TURP + antibiotics

CIC = clean intermittent catheterization; TURP = transurethral resection of the prostate; UTI = urinary tract infection.
There were no rectal fistulas.
One patient developed late complication at 6 mo postcryoablation presenting with urinary retention due to bladder neck contracture and bilateral hydronephrosis secondary to bilateral ureteral strictures that required TURP, ureteral catheterization, and dilation.

Table 3 – Oncologic outcomes for whole-gland cryoablation of the prostate

Parameter	Median (IQR) or *n* (%)
Follow-up time, yr	5.6 (3.0–7.9)
PSA nadir value, ng/ml	0.1 (0.0–0.1)
Time to PSA nadir, mo	3.3 (3.0–6.3)
Patients who reached PSA <0.2 ng/ml, *n*	70
Follow-up biopsy sets, *n*	77
Follow-up biopsy sets per patient, *n*	
1	21
2	16
3	8
Patients with follow-up biopsy, *n*	45
Patients with cancer on follow-up biopsy, *n*	9[a]
Patients with recurrent disease[b], *n*	20
Patients with recurrent disease by baseline risk, *n*	
Low	2
Intermediate	9
High	9
Type of recurrent disease, *n*	
Cancer on follow-up biopsy	9
3 + 4	3
4 + 3	2
4 + 4	3
5 + 5	1
Local invasion	1
Salvage treatment	3 (EBRT *n* = 1, ADT *n* = 2)
Metastases[c]	7
5-yr metastases-free survival	95%
Patients died[d], *n*	2
Patients died from prostate cancer, *n*	1

ADT = androgen deprivation therapy; EBRT = external bean radiation therapy; IQR = interquartile range; PSA = prostate-specific antigen.
[a] Includes one patient with prostate cancer on cystoprostatectomy specimen.
[b] Recurrent disease was defined as follows: cancer on follow-up biopsy, any evidence of clinical recurrence (by physical exam or imaging), or initiation of salvage treatment or androgen deprivation therapy. Clinical recurrence was detected in 20 (21%) patients: positive prostate biopsy, 8; prostate cancer in cystoprostatectomy specimen, 1; metastasis, 7; local invasion, 1; salvage treatment, 1; initiation of ADT, 2.
[c] Of the seven patients with metastatic disease, three had high-risk and four intermediate-risk prostate cancer at entry. Two patients had bone metastases alone, two patients had lymph node metastases alone, and three patients had both bone and lymph node metastases.
[d] One patient died of penile cancer.



	Pre-cryo		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	PSA	n	PSA	n	PSA	n	PSA	N	PSA	n	PSA
All patients	94	9.1 (6.2)	68	0.15 (0.27)	69	0.32 (0.74)	67	0.73 (1.7)	58	1.0 (2.0)	49	1.6 (3.9)
CR	20	9.9 (6.2)	13	0.23 (0.19)	15	0.71 (1.3)	14	1.7 (1.7)	13	3.2 (3.4)	11	5.5 (7.2)
No CR	74	8.9 (6.2)	55	0.13 (0.29)	54	0.21 (0.45)	53	0.48 (1.6)	45	0.37 (0.47)	38	0.5 (0.71)

	Pre-cryo		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	PSA	n	PSA	n	PSA	n	PSA	n	PSA	n	PSA
All patients	94	9.1 (6.2)	68	0.15 (0.27)	69	0.32 (0.74)	67	0.73 (1.7)	58	1.0 (2.0)	49	1.6 (3.9)
Positive Bx	9	11 (7.5)	6	0.13 (0.13)	7	0.24 (0.31)	6	0.85 (0.90)	7	3.6 (3.6)	6	3.3 (2.8)
Negative Bx	36	9.1 (5.8)	28	0.14 (0.16)	32	0.28 (0.52)	34	0.85 (2.12)	26	0.67 (1.2)	24	1.2 (2.8)
No Bx	49	8.8 (6.3)	34	0.17 (0.36)	30	0.38 (0.99)	27	0.56 (1.2)	25	0.65 (1.5)	19	1.6 (5.3)

Fig. 2 – Prostate-specific antigen (PSA) kinetics in follow-up of primary whole-gland cryoablation of the prostate by: (A) Clinical recurrence; (B) Biopsy outcomes. PSA values are shown as mean (standard deviation).
Bx = biopsy; Cryo = cryoablation; CR = clinical recurrence; PSA = prostate-specific antigen.

Table 4 – Biochemical failure and clinical recurrence outcomes post whole-gland cryoablation of the prostate

Criteria	Estimated 5-yr biochemical failure-free survival			Estimated 5-yr clinical recurrence-free survival[a]
	PSA ≥0.2 ng/ml, %	PSA nadir + 1.2 ng/ml (Stuttgart), %	PSA nadir + 2 ng/ml (Phoenix), %	Clinical recurrence, %
All patients	47	78	81	83
Low-risk PCa	56	90	89	94
Intermediate-risk PCa	47	79	78	84
High-risk PCa	33	65	80	69

PCa = prostate cancer; PSA = prostate-specific antigen.
[a] Clinical recurrence was defined as follows: cancer on follow-up biopsy, any evidence of clinical recurrence (by physical exam or imaging), any salvage treatment or initiation of androgen deprivation therapy.

6 mo postcryoablation was as an independent predictor for BF ($p = 0.006$) and CR ($p = 0.03$; Table 5).

Functional outcomes were assessed within 2 yr of follow-up using the best score on patients' self-reported questionnaires. Continence (use of no pads) and potency (patient reporting a score ≥3 on International Index of Erectile Function-5 question 2) were reported in 96% and 11% patients, respectively (Table 6). While whole-gland cryoablation has been associated with high rates of impotence [3], focal cryoablation is associated with potency in 86% of patients, with zero incontinence, and encouraging oncologic outcomes [6]. These may be improved by better patient selection with the use of multiparametric MRI.

There is a lack of consensus on the definition of BF postcryoablation. We used the Phoenix criteria, which is used for patients with clinically localized PCa, with or without short-term neoadjuvant ADT [8]. Our data are in agreement with prior reports from the Cryo On-line Database registry [2,3] and randomized controlled trials [10].

Post-cryoablation biopsy rates range from 28% to 72% of patients, with an estimated positive biopsy rate of 7.7–23.5% [3,10]. The rate of post-cryoablation biopsy is influenced by PCa risk, biopsy protocol (mandatory vs for-cause), patient compliance, and follow-up time. A previous study reported that 72% patients underwent mandatory biopsy at 36 mo post-treatment, with 7.7% showing recurrent PCa [10]. It is noteworthy that in our study, patients with negative biopsy postcryoablation had similar PSA kinetics as those with no follow-up biopsy (Fig. 2B).

Predictors for CR post whole-prostate cryoablation still need to be explored [2,3]. After a comprehensive exploratory univariate analysis, various clinically relevant (ie, D'Amico risk stratification) and statistically significant parameters (ie, PSA nadir) were selected for multivariable analysis, demonstrating that failure to reach PSA nadir <0.2 ng/ml within 6 mo post whole-gland cryoablation is an independent predictor for both BF and CR. It is noteworthy that high-risk PCa was a predictor for CR on univariate analyses ($p = 0.03$) and trended towards statistical significance ($p = 0.06$) on multivariable analysis.

This study is limited by its retrospective nature. Patients were selected by TRUS and biopsy rather than with MRI and MRI/TRUS fusion biopsy, which could add accuracy to staging and potentially provide better outcomes [11]. Similarly, MRI was not part of the follow-up protocol

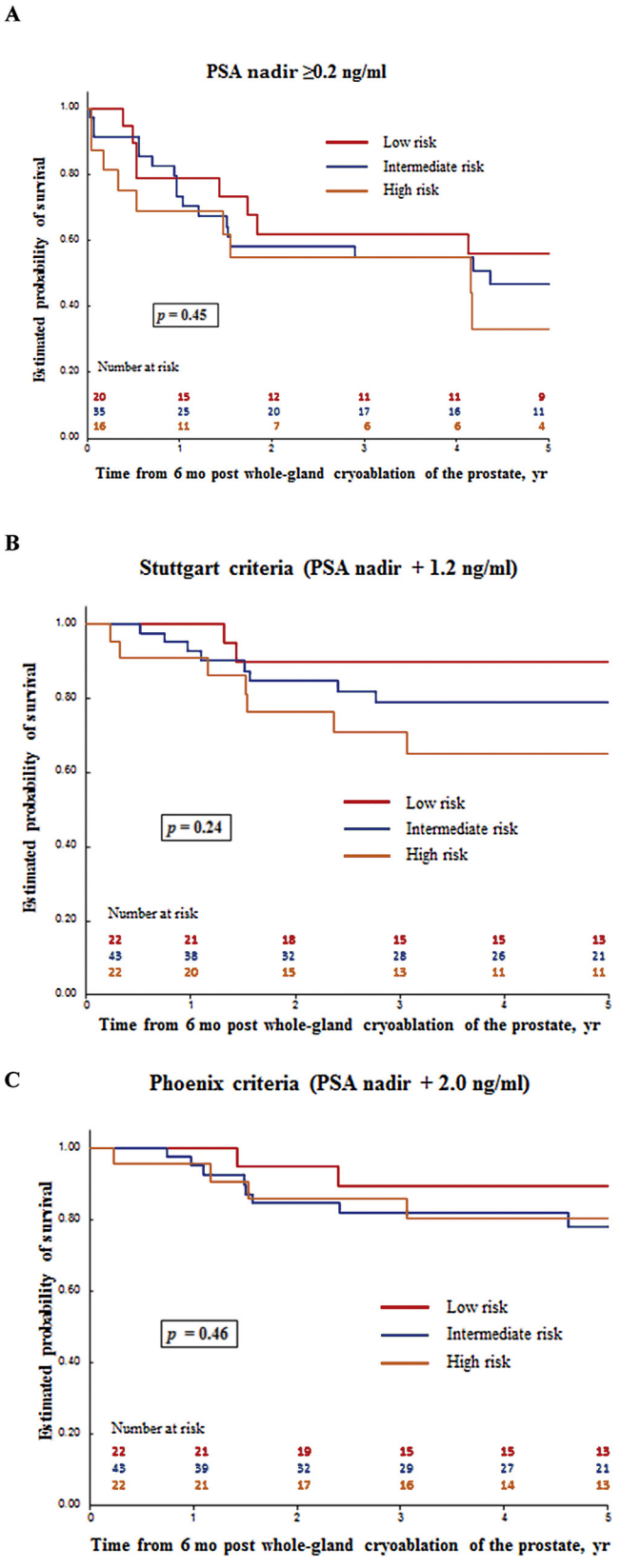


Fig. 3 – Biochemical failure-free survival for prostate cancer after primary whole-gland cryoablation of the prostate accordingly to different definitions. (A) Prostate-specific antigen (PSA) ≥ 0.2 ng/ml; (B) PSA nadir + 1.2 ng/ml; (C) PSA nadir + 2.0 ng/ml.

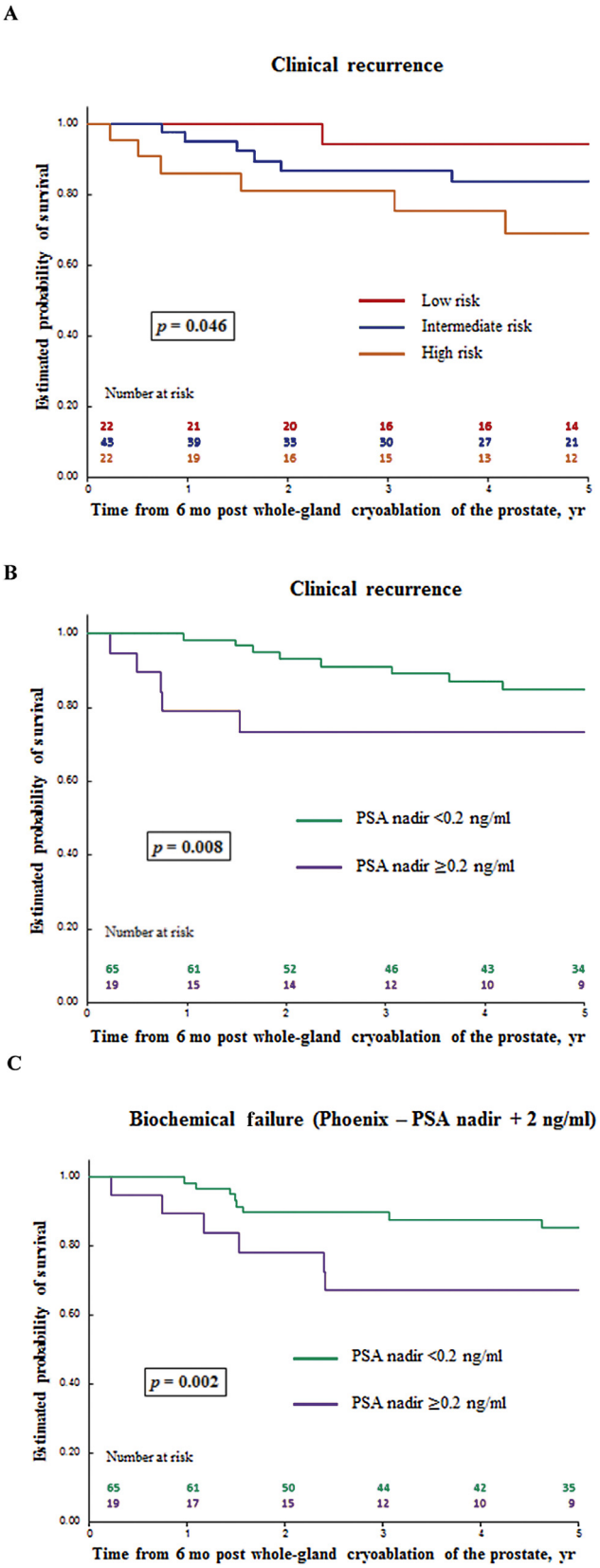


Fig. 4 – Biochemical failure-free survival and clinical recurrence-free survival for prostate cancer after primary whole-gland cryoablation of the prostate. (A) Clinical recurrence-free survival by prostate cancer risk. (B) and (C) Clinical recurrence-free survival and biochemical failure-free survival by PSA nadir value.
PSA = prostate-specific antigen.

Table 5 – Univariate and multivariate analysis for detecting predictors for biochemical failure and clinical recurrence post whole-gland cryoablation for prostate cancer

	Biochemical failure (PSA nadir + 2 ng/mL, Phoenix)				Clinical recurrence[b]			
	Univariate		Multivariate		Univariate		Multivariate	
	HR, 95% CI	*p* value	HR, 95% CI	*p* value	HR, 95% CI	*p* value	HR, 95% CI	*p* value
Risk classification								
Intermediate vs low	2.19, 0.61–7.89	0.24	1.96, 0.54–7.12	0.31	2.7, 0.58–12.6	0.21	2.48, 0.53–11.6	0.25
High vs low	2.07, 0.52–8.28	0.30	1.59, 0.39–6.46	0.92	5.38, 1.16–24.9	0.03	4.48, 0.96–21.0	0.06
Failed to reach PSA <0.2 ng/ml[a]	3.75, 1.52–9.29	0.004	3.63, 1.45–9.05	0.006	3.24, 1.30–8.09	0.01	2.83, 1.12–7.11	0.03

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] Within 6 mo of follow-up.
[b] Clinical recurrence was defined as follows: cancer on follow up biopsy, any evidence of clinical recurrence (by physical exam or image), any salvage treatment or initiation of androgen deprivation therapy.

Table 6 – Functional outcomes post whole-gland cryoablation of the prostate

Parameter	*n* (%)
Potency	
Potent men pre-cryoablation	34 (36)
Score for IIEF-5 question 2 (1–5) pre-cryoablation, *n*	
1–2	60
3	7
4	6
5	21
Score for IIEF-5 question 2 (1–5) postcryoablation, *n*	
1–2	90
3	1
4	1
5	2
Maintain potency postcryoablation	4 (11)
Continence	
Continent men pre-cryoablation	92 (98)
Retained continence postcryoablation [a]	88 (96)

IIEF = International Index of Erectile Function.
Functional outcomes were assessed, within 2 yr of follow up, using the best score on patients' self-reported questionnaires.
Definition of continence: use of no pads.
[a] Of the four patients that did not retain continence, three (75%) patients used only one pad per day.
Definition of potency: patient reporting a score 3 or more for IIEF-5 question 2: "When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?"
(1) Almost never or never
(2) A few times (much less than half the time)
(3) Sometimes (about half the time)
(4) Most times (much more than half the time)
(5) Almost always or always.

either, which may have identified recurrences earlier. Nevertheless, our data show that whole-gland prostate cryoablation is safe and provides acceptable medium-term oncologic outcomes that are comparable to other treatment modalities. Failure to reach PSA nadir <0.2 ng/ml within 6 mo postcryoablation is a predictor for BF and, more importantly, for CR.

Author contributions: Andre Luis de Castro Abreu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Oishi, Gill, de Castro Abreu.
Acquisition of data: Oishi, Nassiri, Shin, Bove.
Analysis and interpretation of data: Oishi, de Castro Abreu, Cacciamani.
Drafting of the manuscript: Oishi, Ashrafi, Lin-Brande, Nassiri.
Critical revision of the manuscript for important intellectual content: Ashrafi, Ukimara, Bahn, de Castro Abreu.
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Supervision: Gill, de Castro Abreu.
Other: None.

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