available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years

Duke Bahn [a,b], *Andre Luis de Castro Abreu* [a], *Inderbir S. Gill* [a], *Andrew J. Hung* [a], *Paul Silverman* [b], *Mitchell E. Gross* [a], *Gary Lieskovsky* [a], *Osamu Ukimura* [a,*]

[a] *Institute of Urology, Hillard and Roclyn Herzog Center for Prostate Cancer Focal Therapy, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [b] *Prostate Institute of America, Community Memorial Hospital, Ventura, CA, USA*

Article info

Article history:
Accepted March 5, 2012
Published online ahead of print on March 20, 2012

Keywords:
Prostatic neoplasms
Cryotherapy
Biopsy
Ultrasound
Prostate-specific antigen

Abstract

Background: Evolution of cryotherapy for prostate cancer is likely to result in parenchyma-sparing modifications adjacent to the urethra and neurovascular bundle. Results of initial series of focal therapy to minimize cryosurgery-related morbidity without compromising oncologic control have been encouraging, but limited in short-term outcomes.
Objective: To retrospectively report (1) median 3.7-yr follow-up experience of primary focal cryotherapy for clinically unilateral prostate cancer with oncologic and functional outcomes, and (2) matched-pair analysis with contemporaneous patients undergoing radical prostatectomy (RP).
Design, setting, and participants: Over 8.5 yr (September 2002 to March 2011), focal cryoablation (defined as ablation of one lobe) was performed in 73 carefully selected patients with biopsy-proven, clinically unilateral, low-intermediate risk prostate cancer. All patients underwent transrectal ultrasound (TRUS) and Doppler-guided sextant and targeted biopsies at entry.
Outcome measurements and statistical analysis: Post-therapy follow-up included measuring prostate-specific antigen (PSA) level every 3–6 mo; TRUS biopsies at 6–12 mo and yearly, as indicated; and validated symptom questionnaires. Matched-pair analysis compared oncologic outcomes of focal cryotherapy and RP (matched for age, PSA, clinical stage, and biopsy Gleason score).
Results and limitations: Complete follow-up was available in 70 patients (median follow-up: 3.7 yr; range: 1–8.5 yr). No patient died or developed metastases. Pre-cryotherapy mean PSA was 5.9 ng/ml and Gleason score was 6 ($n = 30$) or 7 ($n = 43$). Postcryotherapy mean PSA was 1.6 ng/ml (70% reduction compared to precryotherapy; $p < 0.001$). Of 48 patients undergoing postcryotherapy biopsy, 36 (75%) had negative biopsies; positive biopsy for cancer ($n = 12$) occurred in the untreated contralateral ($n = 11$) or treated ipsilateral lobe ($n = 1$). Complete continence (no pads) and potency sufficient for intercourse were documented in 100% and 86% of patients, respectively. Matched-pair comparison of focal cryotherapy and RP revealed similar oncologic outcome, defined as needing salvage treatment.
Conclusions: Primary focal cryoablation for low-intermediate risk unilateral cancer affords encouraging oncologic and functional outcomes over a median 3.7-yr follow-up. Close surveillance with follow-up whole-gland biopsies is mandatory.

* Corresponding author. Institute of Urology, Hillard and Roclyn Herzog Center for Prostate Cancer Focal Therapy, Keck School of Medicine, University of Southern California, 1441 Eastlake Ave., Ste. 7416, Los Angeles, CA 90089, USA. Tel. +1 323 865 3700; Fax: +1 323 865 0120.
E-mail address: ukimura@usc.edu (O. Ukimura).

0302-2838/$ – see back matter doi:10.1016/j.eururo.2012.03.006

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

1. Introduction

With prostate-specific antigen (PSA) testing widely used, more men are diagnosed with localized prostate cancer of lower volume and grade. Such cancers may not adversely affect the individual's overall survival, allowing conservative management with active surveillance as a treatment option [1]. Alternatively, if targeted focal therapy could cure or acceptably control such low-grade prostate cancer, it may become an appealing option for men who otherwise would be suitable candidates for active surveillance but who wish to use some form of therapy against their cancer [2]. According to Turpen and Rosser [3], "As defined by the International Task Force on Prostate Cancer and the Focal Lesion Paradigm, the goal of focal therapy for prostate cancer would be to 'selectively ablate(s) known disease and preserve(s) existing functions, with the overall objective of minimizing lifetime morbidity without compromising life expectancy.'"

Evolution of cryotherapy as a minimally invasive treatment option for men with clinically localized prostate cancer is likely to result in modifications of the established surgical technique, including parenchyma-sparing modifications adjacent to the urethra and neurovascular bundle. In 2008, the American Urologic Association released its best practices statement on cryosurgery for the treatment of localized prostate cancer [4]. The report outlined the long-term outcomes in 370 patients with prostate cancer who underwent whole-gland cryosurgery and showed that, according to Kaplan-Meier analysis, the biochemical disease-free survival rate at 10 yr was 80.6% and 74.2% for low- and moderate-risk groups, respectively [5]. In a randomized trial of whole-gland cryosurgery ($n = 122$) versus external radiation therapy ($n = 122$), more patients in the radiotherapy arm had a positive follow-up biopsy (28.9%) compared with patients in the cryosurgery arm (7.7%) at 36 mo [6]. Importantly, results of initial clinical series of cryosurgery as a focal treatment modality for prostate cancer to further minimize cryosurgery-related morbidity without compromising oncologic control have been encouraging [7–9]. We have previously reported short-term data of our initial experience ($n = 28$) with focal cryoablation [7]. At 70-mo follow-up, a 96% negative follow-up biopsy rate, 89% preservation of erectile function, and 100% continence rate were documented, with no rectal injury.

In this paper, we report follow-up (median: 3.7 yr) experiences with focal cryosurgery in 73 carefully selected men with clinically unilateral low- to intermediate-risk prostate cancer, with an emphasis on our technique of sextant and targeted mapping biopsies and subsequent image-guided intervention.

2. Materials and methods

After obtaining institutional review board approval, retrospective analysis was performed of 73 men who had undergone focal cryoablation (from September 2002 to July 2010) for biopsy-proven, clinically unilateral, low-intermediate risk (PSA ≤20, Gleason score ≤7, clinical stage T1-T2b) prostate cancer (Fig. 1; Table 1). Focal cryoablation was defined as ablation of one lobe of the prostate. All patients gave preoperative consent after detailed discussion of limitations and benefits of focal cryoablation for the known clinically unilateral prostate cancer.

At study entry, all 73 patients (100%) underwent transrectal ultrasound (TRUS)–Doppler evaluation (Type EUB-6500; Hitachi Medical Systems America, Inc., Tarrytown, NJ, USA) followed by entry-staging biopsy. TRUS-suspicious regions were schematically represented on a worksheet, documenting lesion size, location, and vascularity (Fig. 2). Entry biopsies (median: 7; range: 6–9) were performed in a random, systematic, sextant template; additionally, one targeted biopsy was performed per TRUS-visible suspicious lesion (Table 1; Fig. 2). Exclusion criteria by entry biopsy included (1) clinically bilateral cancer, (2) Gleason score ≥8, and (3) biopsy-proven extraprostatic extension of cancer. Among the 93 potential candidates who were interested in focal cryotherapy and underwent the entry-staging biopsy in our institution, 20 patients (21.5%) met the exclusion criteria. Patients with PSA >10 ng/ml or Gleason score 7 disease underwent metastatic evaluation with abdominopelvic computed tomography and bone scintigraphy.

Any androgen deprivation therapy (ADT) and/or 5α-reductase inhibitors (5-ARI) that had been given by referring physicians at the outside institution was discontinued at study entry. During the entire follow-up period after focal cryoablation, no patients received any ADT and/or 5-ARI.

Focal cryoablation of the entire ipsilateral lobe was performed using an argon/helium gas-based system (Endocare, HeathTonics Inc., Austin, TX,

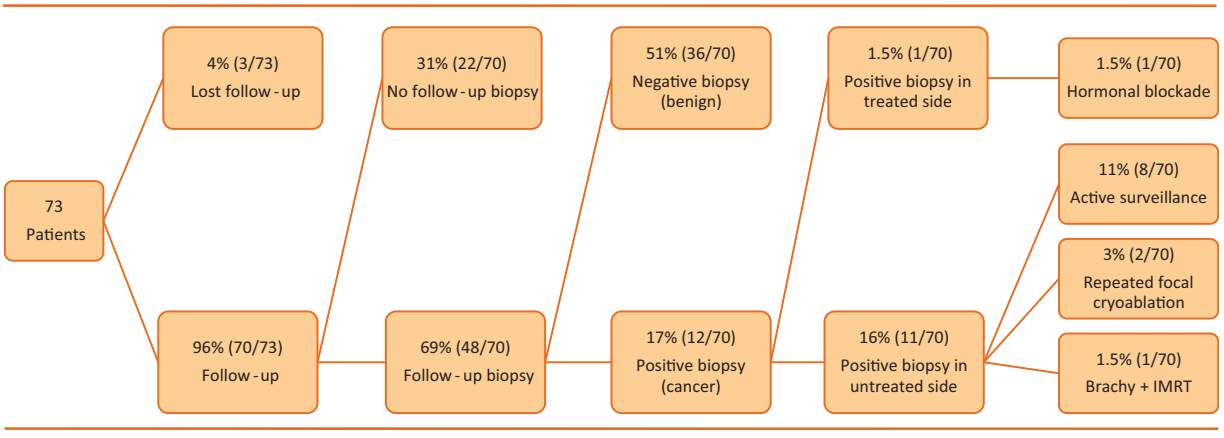


Fig. 1 – Schematic tree of study cohort. Brachy = brachytherapy; IMRT = intensity-modulated radiation therapy.

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

Table 1 – Demographics and intraoperative data of 73 patients

Variables	
Age, yr, median (range)	64 (47–79)
Pretreatment clinical stage, no. (%)	
T1c	41 (56)
T2a	31 (43)
T2b	1 (1)
US prostate volume, ml, median (range)	38 (15–114)
PSA, ng/ml, median (range)	5.4 (0.01–20)
PSA density, ng/ml per ml, median (range)	0.14 (0–0.54)
Gleason score in entry biopsy, no. (%)	
3 + 3	30 (41)
3 + 4	25 (34)
4 + 3	18 (25)
D'Amico risk criteria, no. (%)	
Low	24 (33)
Intermediate	49 (67)
TRUS-visible biopsy-proven index cancer, no. (%)	62 (85)
Total pretreatment biopsy cores, no.	≥13*
Entry staging biopsy (in all 73 patients)	
Entry biopsy cores, median (range)	7 (6–9)
Cores positive for cancer, median (range)	2 (1–4)
Ratio of positive to total cores (%)	135:512 (26.3)
Two adjacent sectors positive for cancer, no. (%)	30 (40)
Maximum cancer length in one core, mm, median (range)	4 (0.1–15.3)
Maximum cancer percentage of one core, median (range)	40 (4–95)
Cancer unilaterality, no. (%)	73 (100)
Urinary continence, no. (%)	73 (100)
IIEF-5** median (range)	22 (13–25)
Preoperative ability of sexual penetration†, proportion (%)	42/63 (66)
Score for preoperative ability of sexual penetration (1–5), no.	
(1) Almost never or never	12
(2) A few times (much less than half the time)	9
(3) Sometimes (about half the time)	5
(4) Most times (much more than half the time)	14
(5) Almost always or always	23
Intraoperative thermocouple reading at NVB on treated side	
≤−40 °C, no. (%)	62 (85)
−20 °C to −40 °C, no. (%)	11 (15)

US = ultrasound; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; IIEF-5 = International Index of Erectile Function; NVB = neurovascular bundle.

* Outside biopsies were performed as sextant protocol; however, since the report did not specify the total number of cores, the outside biopsy cores were counted as ≥6.

** 63 of 73 patients completed the IIEF-5.

† Definition of potency: patient reporting a score ≥3 for IIEF-5 question 2: "When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?"

USA). A double freeze-thaw cycle and a urethral warming device were used. Thermocouple sensors were inserted at five periprostatic locations: right/left neurovascular bundles (NVB), prostate apex, rhabdosphincter, and Denonvilliers' fascia between the prostate and rectum. If the cancer lesion abutted the posterior surface of the prostate, the Denonvilliers' fascia sensor was placed adjacent to the biopsy-proven cancer area. Our therapeutic goal was to achieve complete cryoablation of the ipsilateral lobe, which was documented in intraoperative TRUS monitoring, and to document a temperature of −40 °C or lower in the thermocouple sensor of the disease-side NVB or Denonvilliers' fascia sensor adjacent to the biopsy-proven cancer area.

Postcryotherapy follow-up included PSA monitoring every 3–6 mo, TRUS-Doppler imaging every 6 mo, and follow-up biopsies (sextant plus image-targeted biopsy) at 6–12 mo, then yearly or as otherwise indicated. Potency was defined as the ability to penetrate, quantified as a score ≥3 for the International Index of Erectile Function (IIEF)–5 question 2 with or without phosphodiesterase type 5 inhibitor (Table 1). Continence was defined as no use of pads.

A matched-pair analysis was performed to retrospectively compare oncologic outcomes of focal cryoablation and radical prostatectomy (RP). Patients were pair-matched for age, PSA level, clinical stage, and preoperative biopsy Gleason score. Thus, the cryoablation cohort comprised 68 men (2 men omitted by the computer during pair-matching) and the RP cohort comprised 68 matched-pair contemporaneous men who had undergone RP between January 2000 and September 2008 without any neoadjuvant or adjuvant therapy. RP patients were the most recent from a departmental RP database of 2802 men who had undergone the procedure between June 1980 and December 2009.

Pair-matched and all other statistical analyses were performed using SAS v.9.2 software (SAS Institute, Cary, NC, USA). The log-rank test was applied to survival analysis.

3. Results

Baseline characteristics are presented in Table 1. All 73 patients underwent TRUS-Doppler imaging and entry biopsies using a standardized approach (sextant plus targeted biopsies) (Fig. 2). Of the 73 patients, 20 were referred for elevated PSA without having undergone any prior biopsies by the referring physicians; 53 had biopsy-proven cancer and underwent restaging entry biopsy at our institution. Seventeen of the latter 53 patients (32%) had already received either short-term neoadjuvant ADT (n = 13; range: 3–9 mo) or 5-ARI (n = 4; range: 3–12 mo) before being referred to us. When comparing the outside pathology report to our entry-biopsy report for these 17 patients, the Gleason score was upwardly reassigned from ≤6 to 7 in 14 patients (26%), and downwardly reassigned in 3 patients (6%) from 8 to 6 (n = 1) or 7 (n = 2). The Gleason score remained unchanged between the outside pathology report and entry biopsy report in 36 patients (68%).

Sixty-two patients (85%) had TRUS-visible, targeted biopsy-proven cancer (Table 2). In the patients with a TRUS-visible cancer, the median number of positive biopsy cores was two (range: one to four), cancer core length was 5.5 mm (range: 0.5–15 mm). Twenty-one patients (34%) had a Gleason score 6 cancer on entry biopsy and 41 (66%) a had Gleason score 7 cancer (Table 2).

Table 2 – Comparison between transrectal ultrasound (TRUS)–visible and TRUS-invisible index lesion

Variables	Visible index lesion	Invisible index lesion	p
Lesions, no.	62	11	–
Maximum cancer core length, mm*, median (range)	5.5 (0.5–15)	1.3 (0.1–3)	0.0008
Percent cancer core length, median (range)	43 (15–95)	10 (5–55)	0.0004
Gleason score 6 vs 7	21 vs 41	9 vs 2	0.0053

* Index lesion was defined as biopsy-proven highest Gleason score or greatest cancer core length (percent) in biopsy specimen. Therefore, a lesion-targeted, biopsy-proven cancer was termed *TRUS-visible index lesion*, and a systematic biopsy-proven cancer was termed *TRUS-invisible index lesion*.

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

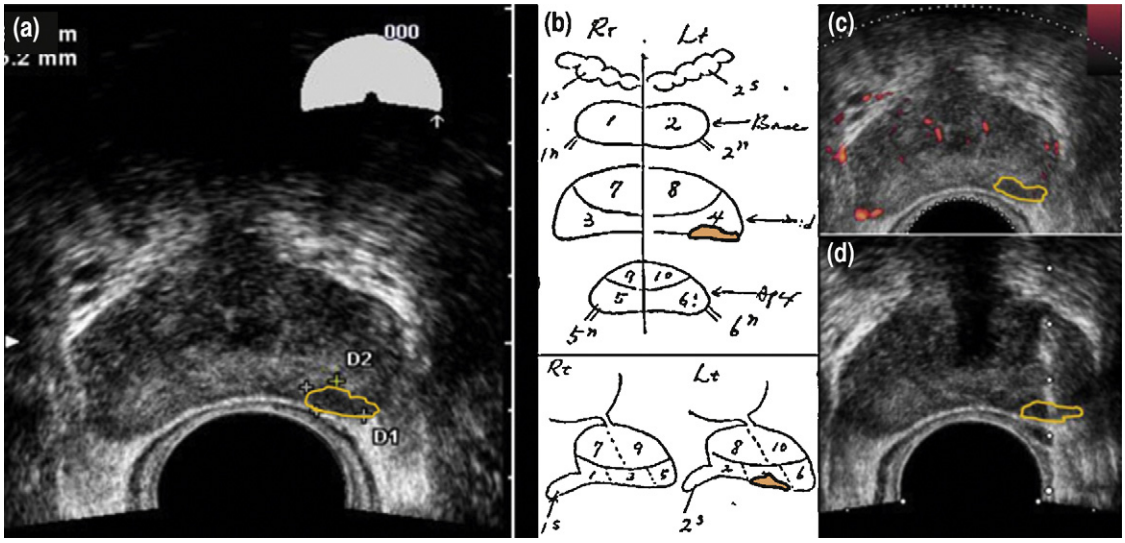


Fig. 2 – Three-dimensional mapping of cancer location by Gray scale and Doppler transrectal ultrasound (US) and documented prostate biopsy. The patient was a 51-yr-old male with prostate-specific antigen level: 4.71 ng/ml and clinical stage T1c with biopsy Gleason score 3 + 3 = 6 (low risk D'Amico criteria). (a) Gray-scale US and (c) power Doppler US demonstrated a suspicious hypoechoic lesion (12 × 3 × 9 mm) on the posterior lateral mid prostate. (d) The two cores of targeted biopsies (needle shown through the lesion) revealed a 2-mm core length in 10–20% of the Gleason score 6 (3 + 3) cancer. All acquired US images were stored in a hard drive and (d) schematic documentations of the US-visible lesion were recorded in the patient's medical record for future review.

Intraoperative thermocouple readings on the disease-side NVB were −40 °C or lower in 62 patients (85%) and −20 °C to −39 °C in 11 (15%). No patient sustained a rectal injury. All patients were discharged on the same day of surgery with a Foley catheter, which was removed 3–4 d postoperatively.

Median follow-up was 3.7 yr (range: 1–8.5 yr). Follow-up data from ≥1 yr were available in 70 patients; 3 patients were lost to follow-up (Fig. 1; Table 3). Follow-up times were 1–2 yr for 15 patients (21%), 2–4 yr for 25 (36%) patients, 4–6 yr for 15 (21%), and >6 yr for 15 (21%). No patient developed metastases or died. Of 48 patients consenting to at least one postcryotherapy biopsy, 12 had positive biopsies for cancer (1 ipsilateral [treated] lobe, 11 contralateral [untreated] lobe) (Table 4; Fig. 5). The ipsilateral positive biopsy (from the same lobe from which the entry biopsy was positive) occurred in an 81-yr-old patient who subsequently opted for ADT (Table 4). Of note, of the 11 patients with positive biopsy in the untreated (contralateral) lobe, 8 (73%) had low-grade, small-volume cancer on biopsy and chose active surveillance (Table 4).

Mean PSA and PSA kinetics for all evaluable patients with a negative (n = 36), positive (n = 12), or no postcryotherapy biopsy (n = 22) are presented in Figure 3. Compared to precryotherapy PSA level (mean: 5.9 ng/ml), postcryotherapy PSA level (mean: 1.6 ng/ml) decreased 70%, which was similar in patients with negative, positive, or no follow-up biopsy (Fig. 4).

All patients were continent after focal cryoablation. In preoperatively potent patients (n = 42), the median (range) total IIEF-5 scores of immediate preoperative, 1-yr postoperative, and 2-yr postoperative time points were 22 (13–25), 17 (5–24), and 19 (5–25), respectively. Postoperative sexual ability (penetration rate) was 74% at 1 yr, and 86% at 2.4 yr in men who were potent preoperatively (Table 3).

Table 3 – Oncologic and functional outcomes in 70 patients with >1-yr follow-up

Variables	
Follow-up biopsy	
Biopsy sets, no.	79
Biopsies per patient, no. (%)	
0	22 (31)
1	28 (40)
2	11 (16)
3	7 (10)
4	2 (3)
Timing of biopsy, mo	
6	26
12	28
24	17
36	8
Patients with ≥1 biopsy, no. (%)	48 (68.5)
Patients with positive cancer in follow-up biopsy, no (%)	12 (17)
Treated side (ipsilateral) lobe, no. (%)	1 (1.4)
Untreated side (contralateral) lobe, no. (%)	11 (16)
Death, no. (%)	0 (0)
Metastasis, no. (%)	0 (0)
Urinary continence, no. (%)	70 (100)
IIEF-5 at 1 yr, median (range)	17 (5–24)
Postoperative ability of sexual penetration at 1 yr, proportion (%)	31/42 (74)
Score for IIEF-5 question 2 (1–5), no.	
(1) Almost never or never	4
(2) A few times (much less than half the time)	6
(3) Sometimes (about half the time)	7
(4) Most times (much more than half the time)	13
(5) Almost always or always	11
IIEF-5 at 2 yr, median (range)	19 (5–25)
Time to recovery of potency, mo, median (range)*	7 (2–28)

IIEF-5 = International Index of Erectile Function.
* Of the preoperatively potent 42 patients, 31 had already reported a score ≥3 for IIEF-5 question 2 at postoperative year 1, and 5 had reported the recovery of potency after 1 yr (≤28 mo); consequently, the recovery rate of postoperative potency was 86% (36 of 42).

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

Table 4 – Characteristics of patients who had positive follow-up biopsy

Patient		Precryotherapy (at entry)				Positive follow-up biopsy in untreated side								After positive follow-up biopsy		
	Age, yr	PSA at entry, ng/ml	Clinical stage at entry	Gleason score at entry biopsy	Risk category at entry	Time from cryosurgery, mo	PSA at positive biopsy, ng/ml	Indication of follow-up biopsy	Prior negative biopsy sets, no.	Gleason score of positive core	Positive cores, no.	Cancer core length, mm (%)	TRUS finding at biopsy	Management	Most recent PSA level	Further follow-up biopsy
1	64	5.6	T1c	3 + 3	Low	6	3.3	PSA	2	3 + 3	1	1.7 (10)	Invisible	AS††	4.3	Waiting
2	62	3.8	T2a	3 + 3	Low	20	2.3	Protocol	3	3 + 3	1	4.45 (35)	Invisible	AS††	0.6	NA
3	63	8.8	T1c	3 + 3	Low	6	4.9	PSA	1	3 + 3	1	1.5 (10)	Invisible	Re-Cryo†	0.8	NA
4	85	13.0	T1c	3 + 3	Inter	12	1.6	Protocol	1	3 + 3	1	4 (30)	Invisible	AS††	2.3	NA
5	76	9.7	T1c	4 + 3	Inter	47	2	Protocol	4	3 + 4	2	7 (50)	HEL	Brachy plus IMRT ‡	0.1	NA
6	63	7.7	T1c	3 + 3	Low	57	1	Protocol	3	4 + 3	2	7 (70)	Invisible	Re-Cryo†	0.1	NA
7	64	10.4	T1c	3 + 3	Inter	7	6.3	PSA	2	3 + 3	1	1 (5)	Invisible	AS ††	1.4	NA
8	73	2.5	T2a	3 + 4	Inter	6	0.9	Protocol	2	3 + 3	1	5.4 (30)	HEL	AS††	0.6	Negative
9	73	3.1	T2a	3 + 3	Low	15	1.3	Protocol	2	3 + 3	1	0.5 (5)	Invisible	AS††	1.36	Negative
10	70	3	T2a	3 + 3	Low	6	0.7	Protocol	1	3 + 3	1	1.3 (10)	Invisible	AS ††	1.02	NA
11	64	3.2	T2a	3 + 4	Inter	12	0.3	Protocol	2	3 + 3	1	1.5 (10)	Invisible	AS††	0.2	NA
Summary of 1–11: median (range)	64 (63–85)	5.6 (2.5–13)	T1c (*n* = 6) T2a (*n* = 5)	6 (*n* = 8) 7 (*n* = 3)	Low (*n* = 6) Inter (*n* = 5)	12 6–57	1.6 0.3–6.3	Protocol (*n* = 8) PSA (*n* = 3)	2 1–4	6 (*n* = 9) 7 (*n* = 2)	1 1–2	1.7 0.5–7	Visible (*n* = 2) Invisible (*n* = 9)	AS (*n* = 8) Treated (*n* = 3)	0.1–4.3	
Patient	Age, yr	Precryotherapy (at entry)				Positive follow-up biopsy in the treated side								After the positive follow-up biopsy		
12	81	2.3	T2a	3 + 4	Inter	30	9.7	PSA	3	4 + 4	1	2 (30)	Invisible	Hormone‡‡	0.1	NA

PSA = prostate-specific antigen; TRUS = transrectal ultrasound; NA = not applicable; AS = active surveillance; Re-cryo = repeat cryotherapy; Brachy = brachytherapy; IMRT = intensity-modulated radiation therapy; HEL = hypoechoic lesion in TRUS; Inter = intermediate.

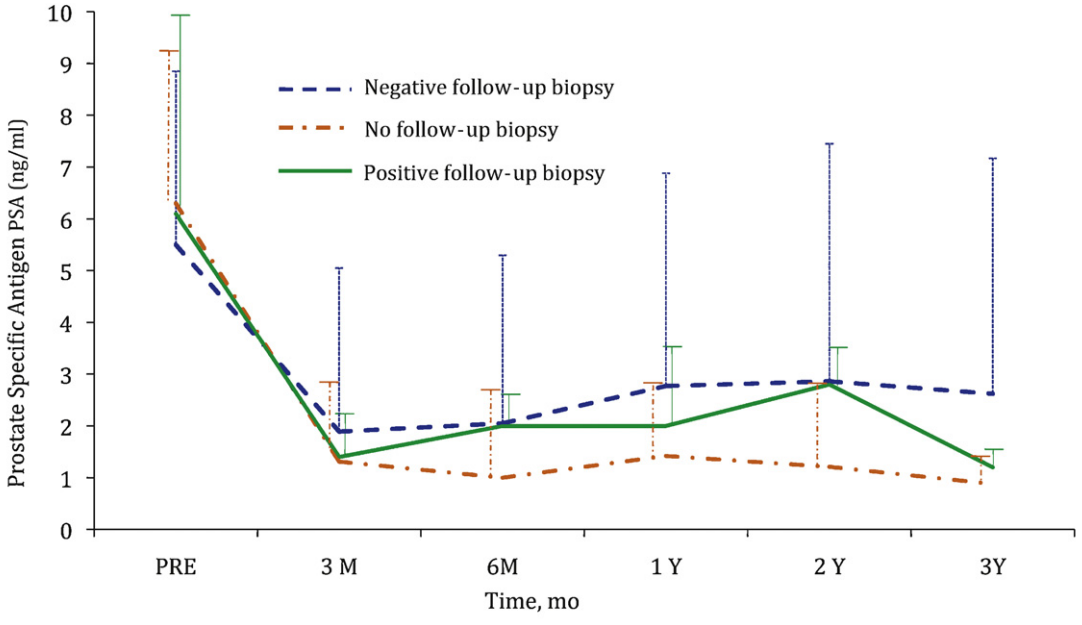
Detailed clinical courses after the positive follow-up biopsy:

† Two patients (No. 3 and 6) underwent repeat focal cryotherapy, and had well controlled PSA afterward.

†† Of the eight patients who chose to undergo active surveillance due to small cancer foci in the positive follow-up biopsy, one had elevated PSA, none had foci suspicious in imaging, and two had another staging follow-up biopsy, which were negative for cancer during their active surveillance.

‡ Patient 5, who had Gleason 7 cancer in the positive follow-up biopsy, underwent brachytherapy and IMRT.

‡‡ The PSA level of Patient 12, who had hormone therapy, decreased to 0.1 ng/ml in 1 yr.



	Preoperative-CRYO		3		6		12		24		36	
	n	PSA	*n*	PSA	*n*	PSA	*n*	PSA	*n*	PSA	*n*	PSA
All patients	70	5.9 (3.9)	53	1.7 (2.6)	57	1.8 (2.6)	52	2.4 (3.4)	45	2.6 (3.9)	31	2.1 (3.8)
Negative Bx	36	5.5 (3.3)	32	1.9 (3.1)	34	2 (3.2)	32	2.7 (4.1)	28	2.8 (4.5)	21	2.6 (4.5)
No Bx	22	6.3 (4.9)	13	1.3 (1)	12	1 (0.7)	9	1.4 (1.8)	7	1.2 (0.9)	2	0.9 (0.4)
Positive Bx	12	6.1 (3.6)	8	1.4 (1.6)	11	2 (1.9)	11	2 (1.8)	10	2.8 (3)	8	1.2 (0.8)

Fig. 3 – Prostate-specific antigen (PSA) kinetics in follow-up of focal cryoablation. Mean (standard deviation) PSA values were similar for all assessable subjects followed with a negative biopsy (*n* = 36), a positive biopsy (*n* = 12), or no biopsy (*n* = 22). Bx = biopsy, Cryo = cryoablation.

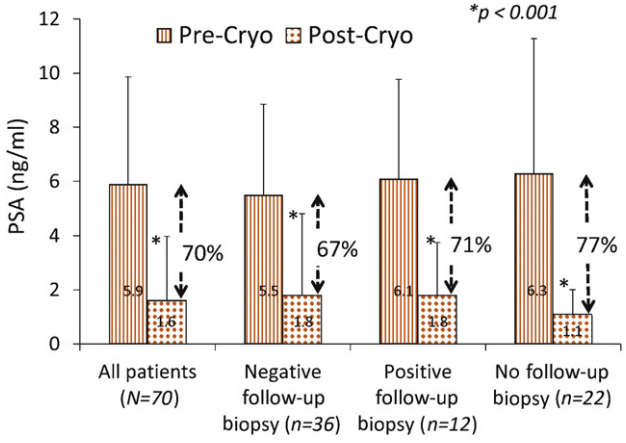


Fig. 4 – Change in mean prostate-specific antigen (PSA) levels (plus or minus standard deviation) from pre- to postfocal cryoablation. In 71 men, mean postcryotherapy PSA was 1.6 ng/ml (70% reduction compared to preoperative value; $p < 0.001$). There was no statistical difference in PSA reduction from pre- to postcryoablation among the subsets of patients with negative follow-up biopsy (*n* = 36), no follow-up biopsy (*n* = 22), or positive follow-up biopsy (*n* = 12). Cryo = cryoablation.

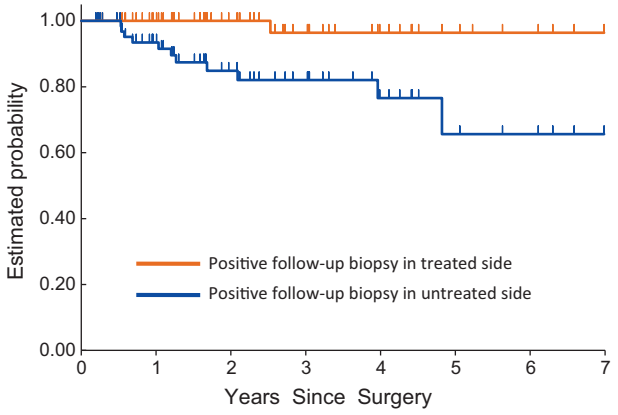


Fig. 5 – Analysis of estimated probability of biopsy-proven prostate cancer in either treated or untreated side by follow-up biopsy.

3.1. *Matched-pair analysis*

There was no statistical difference in the relative risk for need of salvage treatment between focal cryoablation and RP ($p = 0.55$) (Fig. 6; Table 5).

4. Discussion

Focal cryotherapy is associated with encouraging short-term outcomes [7–10]. To our knowledge, we present the longest oncologic and functional follow-up (median: 3.7 yr; range: 1–8.5 yr) after focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer. Additionally, in a retrospective matched-pair cohort, oncologic outcomes after focal cryosurgery versus RP were similar in comparison of need for salvage therapy ($p = 0.55$) (Fig. 6).

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

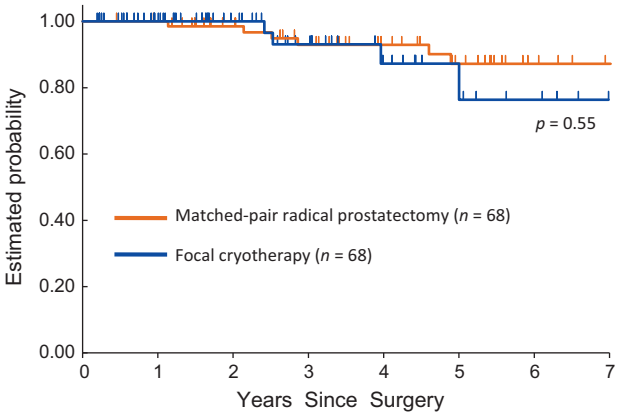


Fig. 6 – Pair-matched analysis with salvage-therapy-free survival curve in patients who underwent primary focal cryotherapy versus radical prostatectomy showed no statistical difference.

Appropriate patient selection and standardized follow-up protocols remain controversial issues in focal therapy for prostate cancer [2,11]. In our opinion, image visibility of prostate cancer is important for enhancing patient selection for cancer control, since image mapping of cancer lesions allows precise therapeutic targeting by image guidance. We believe the encouraging oncologic outcomes of our study were a result of accurate TRUS-based sextant and targeted biopsies and mapping, since the TRUS-visible biopsy-proven lesions were often located in the treated lobe in our selected cohort. Thus, in our series, 85% of patients (62 of 73) had a TRUS-visible index lesion that was spatially mapped, targeted, and biopsied to document cancer location and extent. As shown in Table 2, TRUS-visible, targeted-biopsy-proven index lesions had significantly higher Gleason scores and greater cancer involvement than TRUS-invisible index lesions. As such, our data suggest that TRUS visibility of a lesion may correlate with clinically important cancer, which, in turn, can facilitate more precise targeting during focal therapy. Real-time thermal monitoring of the ice-ball periphery ensured that lethal temperatures (−40 °C or lower) encompassed the ipsilateral lobe completely. Only one patient (1.4%) had positive local follow-up biopsy in the diseased lobe. We believe that despite successful achievement of lethal temperature on thermocouple reading, a positive biopsy in the treated side may still occur at the intervening mid portion between two adjacent cryoprobes, where cytocidal temperature might not be achieved due to insufficient fusion of the two ice balls.

Image-guided spatial localization of cancer is important not only for patient selection, but also for follow-up monitoring. Since entry biopsy targeted TRUS-visible cancer in 85% of patients, follow-up biopsies must include targeted biopsy from the areas where the targeted biopsy-proven cancer was documented. Follow-up biopsies in the treated side confirmed no clinical evidence of cancer in 98% of patients (47 of 48). Ohori et al. reported that the index lesion typically accounts for 80% of the tumor bulk, with the remaining 20% comprising smaller secondary lesions [12]. Similarly, Villers et al. reported that 80% of incidental carcinomas were <0.5 ml [13]. In this series, our follow-up systematic biopsies from the untreated, contralateral, previously negative lobe revealed newly diagnosed cancers in 11 patients (23%): Gleason score 6 in 55% (6 of 11), 7(3 + 4) in 18% (2 of 11), and 7(4 + 3) in 9% (1 of 11) patients. However, 8 of 11 patients elected to undergo active surveillance for this biopsy-detected, low-grade, small-volume cancer in the untreated lobe. Consequently, only 4 (5.7%) of 70 patients undergoing primary focal cryotherapy underwent salvage treatment in this study. The statistical analysis revealed no difference in relative risk between the primary focal cryotherapy and RP series. Six patients (8.8%) in the RP series underwent salvage therapy.

Given the potential for cancer multifocality and/or bilaterality, as well as potential underdiagnosis at the entry biopsy, follow-up biopsies of the untreated lobe are mandatory, because the untreated prostate lobe should be monitored similarly, as in active surveillance protocols. Following focal cryoablation, current PSA criteria have a limited role in predicting local recurrence in the treated lobe, or progression in the untreated lobe, and/or underdiagnosis at entry in the untreated lobe. It is noteworthy that in our series, even patients with biopsy-proven recurrence had well controlled PSA levels (range: 0–1.5 ng/ml). In other words, our mandatory postcryotherapy biopsies revealed cancer before a significant PSA rise. Interestingly, percent decrease of PSA from precryotherapy (mean: 5.9 ng/ml) to postcryotherapy (mean: 1.6 ng/ml) was 70%. Since untreated tissue remained in the contralateral lobe, this 70% PSA

Table 5 – Characteristics in matched-pair analysis

	Focal cryoablation	Radical prostatectomy*	*p* value
Patients, no.	68	68	–
Age, yr, median (range)	64 (47–80)	64 (49–78)	0.46
PSA, ng/ml, median (range)	5.5 (0.01–20)	5.3 (1–19.5)	0.62
PSA, ng/ml, no. (%)			
<4	23 (34)	23 (34)	
≥4–10	37 (54)	37 (54)	1
>10–20	8 (12)	8 (12)	
Gleason score, no. (%)			
6	28 (41)	28 (41)	
3 + 4	24 (35)	28 (41)	1
4 + 3	16 (24)	12 (18)	
Clinical stage, no. (%)			
T1c	41 (61)	41 (61)	1
T2a	27 (39)	27 (39)	
Pathologic stage, no. (%)			
T2a		11 (16)	
T2b		1 (1.5)	
T2c	–	37 (54.5)	–
T3a		15 (22)	
T3b		4 (6)	
Positive margins, no. (%)	–	9 (13)	–
Follow-up time, yr, median (range)	3.7 (1–8)	4.1 (0.5–10.5)	–

PSA = prostate-specific antigen.
* Matched one-to-one for age, PSA level, clinical stage, and biopsy Gleason score from database of 1268 patients who underwent radical prostatectomy from January 2000 to September 2008 without any adjuvant or neoadjuvant therapy.

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006

decrease after hemiablation seems a reasonable benchmark to indicate successful ablation of the index lesion, based on prior data that the index cancer accounts for 80% of entire cancer volume in a given patient [12]. However, since a clear limitation of our study was that not every patient underwent 3-mo follow-up with PSA after cryotherapy, further study is necessary to better define PSA kinetics after prostate hemicryoablation.

A major limitation of our study includes the fact that 22 patients (31%) refused follow-up biopsy, typically because of their negligible posttreatment PSA level (<1 ng/ml). Importantly, imaging such as TRUS is operator dependent and may not visualize all clinically significant cancer. Additionally, complete cancer kill in the treated lobe is difficult to prove without RP surgery and submission of the entire gland. Performance of follow-up biopsy in treated and untreated lobes in 100% of patients may increase the cancer detection during follow-up. However, the clinical implication of increasing the number of follow-up biopsies is unknown, because it may simply reveal small foci of low-grade cancer, which may be clinically irrelevant. Further study is necessary to define the ideal strategy of where and when to perform follow-up biopsy. One study suggests that only imaging-suspicious lesions be targeted [10]. Since multiparametric magnetic resonance (MR) imaging may be better for maximizing visualization of clinically significant cancer [14], further studies may involve this modality.

New technologies, such as computer- and/or robotic-assisted biopsy and intervention platforms, can potentially record the three-dimensional (3D) coordinates and trajectories of biopsies and enhance 3D cancer mapping for future rebiopsy or targeted intervention [15]. Emerging technologies of TRUS with contrast-enhanced ultrasound and MR-TRUS fusion will likely play an essential role in image mapping of prostate cancer in the near future [16,17].

5. Conclusions

Median 3.7-yr follow-up outcomes of primary focal cryotherapy in selected patients with clinically unilateral, low-intermediate risk prostate cancer are encouraging. Detailed cancer mapping with systematic and lesion-targeted biopsies, followed by cryohemiablation with precise image monitoring, were central to our approach. Careful patient selection, an integrated imaging-oriented strategy, and meticulous follow-up are essential prerequisites for any focal therapy protocol.

Author contributions: Osamu Ukimura 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: Bahn, Gill, Ukimura.
Acquisition of data: Abreu, Hung, Silverman, Ukimura.
Analysis and interpretation of data: Bahn, Abreu, Gill, Ukimura.
Drafting of the manuscript: Ukimura.
Critical revision of the manuscript for important intellectual content: Lieskovsky, Gross, Gill.
Statistical analysis: Abreu, Hung, Silverman, Ukimura.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Gill.
Other (specify): None.

Financial disclosures: Osamu Ukimura certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

[1] Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer. A decision analysis. JAMA 2010;304:2373–80.
[2] Eggener SE, Scardino PT, Carroll PR, et al. International Task Force on Prostate Cancer and the Focal Lesion Paradigm. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 2007;178:2260–7.
[3] Turpen R, Rosser CJ. Focal therapy for prostate cancer: revolution or evolution? BMC Urology 2009;9:2.
[4] Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol 2008;180:1993–2004.
[5] Cohen JK, Miller Jr RJ, Ahmed S, Lotz MJ, Baust J. Ten-year biochemical disease control for patients with prostate cancer treated with cryosurgery as primary therapy. Urology 2008;71:515–8.
[6] Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer 2010;116:323–30.
[7] Bahn DK, Silverman P, Lee Sr F, Badalament R, Bahn ED, Rewcastle JC. Focal prostate cryoablation: initial results show cancer control and potency preservation. J Endourol 2006;20:688–92.
[8] Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The "male lumpectomy": focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol 2008;26:500–5.
[9] Truesdale MD, Cheetham PJ, Hruby GW, et al. An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: recommendations for follow up. Cancer J 2010;16:544–9.
[10] Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011;185:1246–55.
[11] Bostwick DG, Waters DJ, Farley ER, et al. Group consensus reports from the Consensus Conference on Focal Treatment of Prostatic Carcinoma, Celebration, Florida, February 24, 2006. Urology 2007;70(Suppl):42–4.
[12] Ohori M, Eastham JA, Koh H, et al. Is focal therapy reasonable in patients with early stage prostate cancer (CAP)? An analysis of radical prostatectomy (RP) specimens. J Urol 2006;175(Suppl):507.
[13] Villers A, McNeal JE, Freiha FS, Stamey TA. Multiple cancers in the prostate. Morphologic features of clinically recognized versus incidental tumors. Cancer 1992;70:2313–8.
[14] Hoeks SM, Barentsz JO, Hambrock T, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. Radiology 2011;261:46–66.

[15] Ukimura O, Hung A, Gill IS. Innovations in prostate biopsy strategies for active surveillance and focal therapy. Curr Opin Urol 2011;21: 115–20.

[16] Pinto PA, Chung PH, Ratinehad AR, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol 2011; 186:1281–5.

[17] Ukimura O, Desai M, Palmer S, et al. Accuracy of 3D elastic registration system of prostate biopsy location by real-time 3D TRUS guidance with MR/TRUS image fusion. J Urol 2012;187: 1080–6.

Please cite this article in press as: Bahn D, et al. Focal Cryotherapy for Clinically Unilateral, Low-Intermediate Risk Prostate Cancer in 73 Men with a Median Follow-Up of 3.7 Years. Eur Urol (2012), doi:10.1016/j.eururo.2012.03.006