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Prostate Cancer Treated With Cryotherapy: A Subanalysis of Stratification by Risk Group, Race, Prostate Volume, and Neoadjuvant Hormone Therapy

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ABSTRACT

INTRODUCTION: Prostate cryoablation was developed with the intent of maximizing effectiveness while minimizing the morbidity of treating clinically localized prostate cancer. Our focus was to determine Kaplan-Meier (KM) biochemical recurrence-free survival (BRFS) estimates and how they might be affected by neoadjuvant hormone therapy, race, D'Amico risk group, and prostate volume.

METHODS: We retrospectively analyzed data from 190 patients receiving cryoablation for the primary treatment of T1 to T3 prostate cancer from 2003 to 2009. All patients underwent whole-gland prostate cryoablation by a single surgeon using the Cryocare CS System (HealthTronics; Austin, TX, USA). Patients received a prostate-specific antigen and digital rectal examination at 1, 3, 6, 9, 12, 18, 24, and 30 months after surgery. A PSA nadir of ≤ 0.1 ng/mL was used to define treatment success. KM BRFS curves were plotted overall and by subanalysis variable and compared using the log-rank test. Univariate Cox proportional hazard regression models were used to describe the effect of measured variables on risk of biochemical recurrence.

RESULTS: The mean follow-up was 27 months. A total of 153 patients (81%) reached the treatment goal of PSA nadir ≤ 0.1 ng/mL. Using a nadir + 2 ng/mL failure definition, BRFS rates were 94% and 85% for 1 year and 3 years, respectively. High D'Amico risk significantly predicted biochemical recurrence (hazard ratio [HR] = 3.65; P = .045). African American men had a nonsignificant trend toward increased risk (HR= 1.91; P = .12). BRFS did not differ when comparing men who did or did not receive hormone therapy (log-rank test: P = .57) or men with prostate size < 40 g vs ≥ 40 g (P = .72). The majority of complications were minor, with a rate of 12%.

CONCLUSIONS: Although neoadjuvant hormone therapy and prostate volume at the time of surgery were not statistically associated with BRFS, race approached significance and high D'Amico risk group was significant. Our short-term results justify the continuing use of cryosurgery for the management of localized prostate cancer.

KEYWORDS: Cryotherapy; Neoadjuvant Hormone Therapy; Prostate; Prostate Cancer; Prostate Cryoablation

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Abbreviations and Acronyms

ASTRO, American Society for Therapeutic Radiology and Oncology
BRFS, biochemical recurrence-free survival
CT, computed tomography
KM, Kaplan-Meier
PSA, prostate-specific antigen
RTOG, Radiation Therapy Oncology Group

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INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men in the United States. Current Surveillance Epidemiology and End Results data estimated that 217,730 men would be diagnosed with prostate cancer and 32,050 men would die of this disease in 2010 [1]. Traditionally, the treatment options for clinically localized prostate cancer included watchful waiting, radical prostatectomy, and radiation therapy. To date there are no randomized, prospective clinical trials comparing their efficacy.

Prostate cryoablation is based on the theory of using extremely cold temperatures to cause tissue necrosis or ablation. It was developed with the intent of maximizing effectiveness while minimizing the morbidity of treating clinically localized prostate cancer. Since 1996, when it was recognized as a therapeutic option by the American Urological Association, cryoablation has gained momentum in being an acceptable minimally invasive option for the treatment of localized prostate cancer.

Current third-generation cryotherapy entails using gases instead of liquids to produce the freezing. It also uses both active freezing and thawing cycles to produce better tissue ablation. Argon gas is used for the freezing and helium gas is used for the warming. Because this is a gas system, ultra-thin cryoprobes can be used through the Joule-Thompson effect, which describes the unique temperature change of a pressurized gas as it is forced through a valve that is becoming depressurized. The probes are placed in the perineum using a brachytherapy-type template without any incisions. These advancements in cryotherapy technology have reduced complications such as damage to the rectum, urethra, and external urinary sphincter.

The purpose of the present study was to examine patients who underwent primary third-generation whole-gland cryosurgical treatment of localized prostate cancer with respect to treatment outcome and morbidity profile. It has been theorized that the use of neoadjuvant hormone therapy decreases the size of the prostate gland, which facilitates cryosurgery by reducing complications. Optimal results are expected because large gland volumes prevent adequate freezing of the prostate. There is concern in freezing larger glands that there may be gaps in the lethal ice formation. Therefore, we also wanted to investigate how neoadjuvant hormone therapy and actual prostate gland size directly impact outcomes. To our knowledge, this has not been previously reported in the literature.

METHODS

The protocol for this retrospective study was approved by Eastern Virginia Medical School Institutional Review Board in Norfolk, VA. Data were obtained for patients treated from March 2003 to April 2009.

Patient Database

We analyzed the data from 225 patients who underwent third-generation prostate cryoablation for the primary treatment of T1 to T3 prostate cancer with intent to cure. All focal and salvage cryotherapy cases were excluded (n = 35). Thus, our data set consisted of 190 patients.

Procedures

Preoperative staging included serum prostate-specific antigen (PSA) level, digital rectal examination, prostate needle biopsy Gleason score, and transrectal ultrasonographic measurement of prostate volume. The metastatic workup included bone scans and computed tomography (CT) scans for high-risk patients.

All patients underwent whole-gland prostate cryoablation by a single surgeon (RG) using the Cryocare CS System (HealthTronics; Austin, TX, USA). Six temperature sensor probes (17-gauge) were used along with 6 to 8 cryoprobes (2.4 mm), depending on the prostate gland size. They were positioned in conjunction with a brachytherapy template. The temperature sensor probes were placed at the anterior gland, apex, external striated sphincter, Denonvillier's fascia, and the bilateral neurovascular bundles of the prostate. Argon gas was used for freezing and helium was used for thawing. The cryoablation was performed under 2 freeze-thaw cycles with the objective of attaining -20° to -40°C temperatures within the prostate tissue. The freeze was performed in an anterior to posterior direction to better visualize the ice ball as it advanced toward the anterior surface of the rectum. A urethral warmer was consistently used; it was removed 10-20 minutes after the procedure.

Postoperative Follow-up and Data Analysis

Patients received a PSA and digital rectal examination assessment at 1, 3, 6, 9, 12, 18, 24, and 30 months after surgery. Postcryoablation prostate biopsies were performed: (1) when a PSA value reached ≥ 0.5 ng/mL despite previously reaching a successful nadir, or (2) if biochemical failure occurred according to the Radiation Therapy Oncology Group (RTOG) - American Society for Therapeutic Radiology and Oncology (ASTRO) definition of nadir + 2 [2].

The patients were stratified into risk categories according to the D'Amico et al [3] criteria from 2003. *Low risk* included a PSA level < 10 ng/mL, Gleason score < 7, and Stage T_{2a} or less; *moderate risk* included PSA level 10 to 20 ng/mL or Gleason score 7 or Stage T_{2b} with other factors being low risk; *high risk* included PSA level > 20 ng/mL, Gleason score 8 to 10, Stage T_{2c}

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or higher, or any 2 increased risk factors.

Neoadjuvant hormone therapy was used in all patients who had a prostate gland size of > 40 g at the time of diagnosis or if the patient had high-risk disease. The hormone therapy was then discontinued in all patients immediately after the cryoablation except for those individuals with high-risk features. Patients at high risk were given 6-24 months of adjuvant therapy.

A PSA nadir of ≤ 0.1 ng/mL was used to define treatment success. Kaplan-Meier (KM) biochemical recurrence-free survival (BRFS) curves were plotted overall and by D'Amico risk group, race, presurgical hormone use, and prostate gland size. Survival curves were compared using the log-rank test. Univariate Cox proportional hazard regression models were used to describe the effect of age, race, risk group, hormone therapy, and prostate volume on risk of biochemical recurrence. Significance was defined as $P < .05$.

RESULTS

The baseline characteristics of patients who underwent cryotherapy are reported in Table 1. The mean follow-up period was 27 months. Posttreatment biopsies were performed in 15 patients (8%) for a rising PSA ≥ 0.5 ng/mL. Four of those patients (27%) had a positive biopsy that correlated with an eventual biochemical nadir + 2 ng/mL failure. The remaining 11 patients all had negative biopsies; however, the PSAs of 6 of the 11 patients continued to rise with eventual biochemical failure despite the negative biopsies. Adjuvant hormone therapy was continued in 17 patients (9%) postoperatively for high-risk disease, with the majority (76%) receiving therapy for > 6 months.

A total of 153 patients (81%) reached the treatment goal of PSA nadir ≤ 0.1 ng/mL. Divided into risk categories, 42 of 54 (78%) of low-risk patients, 63 of 78 (81%) of moderate-risk patients, and 48 of 58 (83%) of high-risk patients had a PSA nadir ≤ 0.1 ng/mL. Of the 37 patients who did not reach the nadir, 11 (30%) had prostate glands ≥ 40 g at the time of surgery and 2 (5%) eventually had positive postcryoablation biopsy samples with seminal vesicle involvement but without prostate involvement. The other 24 patients (65%) had no identifiable risk factor for not reaching a PSA nadir ≤ 0.1 ng/mL. Seven of the 153 patients (5%) who reached the PSA nadir ≤ 0.1 ng/mL eventually failed at the nadir + 2 ng/mL definition, compared with 12 (32%) of the 37 patients who did not reach the PSA nadir.

All of the BRFS estimates were calculated with KM curves based on the RTOG-ASTRO nadir + 2 ng/mL definition of failure (Figures 1 through 5). Univariate Cox proportional hazard regression coefficients are reported in Table 2. Men with a high D'Amico risk had a more than 3 times greater chance of biochemical recurrence when compared with men at low risk. African-American men had a nearly 2-fold greater risk of biochemical recurrence when compared with men who were not African American, although this trend did not reach statistical significance. Age, prostate volume at the time of surgery, and neoadjuvant hormone therapy did not predict biochemical recurrence.

Table 1. Baseline Characteristics of Patients Undergoing Cryotherapy (N = 190).
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Characteristic	Value
Age, mean (SD), y	71.0 (7.0)
Race, n (% N)	
Caucasian	125 (66)
African American	57 (30)
Other	8 (4)
Hormone therapy, n (% N)	64 (34)
Prostate volume, mean (SD), g	33.8 (14.3)
Risk Stratification Group, n (% N)	
Low	54 (28)
Medium	78 (41)
High	58 (31)
Follow-up, mean (median), mo	27.4 (24.2)
Complication rate, n (% N)	12 (6)

Table 2. Univariate Cox Proportional Hazards (N = 190).
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Variable	Hazard Ratio	*P*
Age	NS	.51
Risk group		
Low	1.0	reference
Moderate	1.91	.34
High	3.65	.045
Race		
Caucasian + Other	1.0	reference
African American	1.91	.12
Hormone therapy (no versus yes)	NS	.57
Prostate volume (< 40 g versus ≥ 40 g)	NS	.72

Abbreviation: NS, nonsignificant

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Figure 1. Kaplan Meier Curve for Overall Biochemical Recurrence-Free Survival (BRFS).

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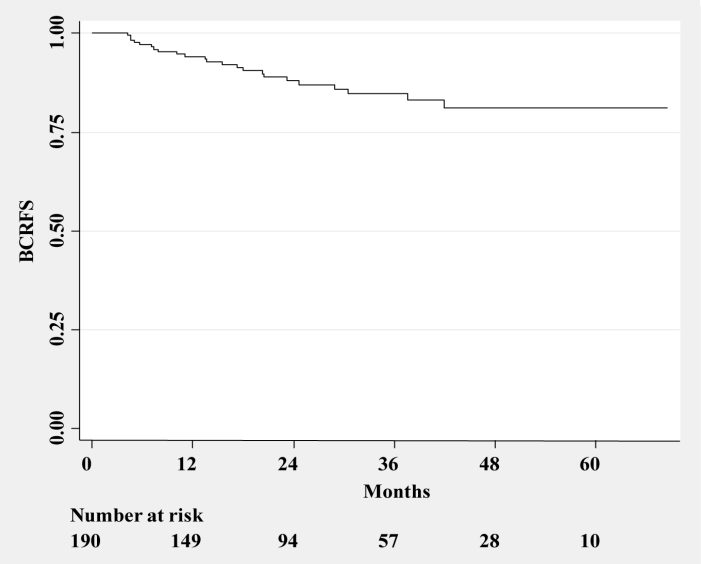

1-year BRFS: 94%
3-year BRFS: 85%

Figure 2. Kaplan Meier Curve for Overall Biochemical Recurrence-Free Survival (BRFS) Comparing Low, Medium, and High Risk Groups.

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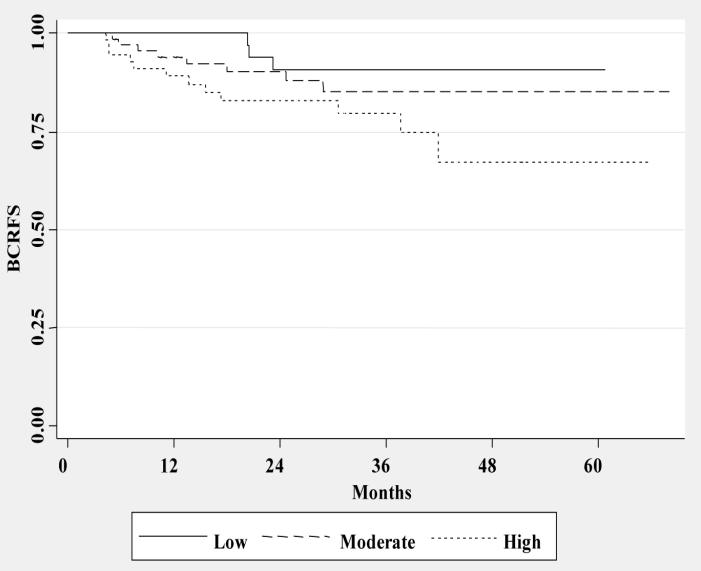

1-year BRFS: Low: 100%; Moderate: 94%; High: 89%
3-year BRFS: Low: 91%; Moderate: 85%; High: 80%
log-rank test: *P* = .07

Figure 3. Kaplan Meier Curve for Overall Biochemical Recurrence-Free Survival (BRFS) by Race.

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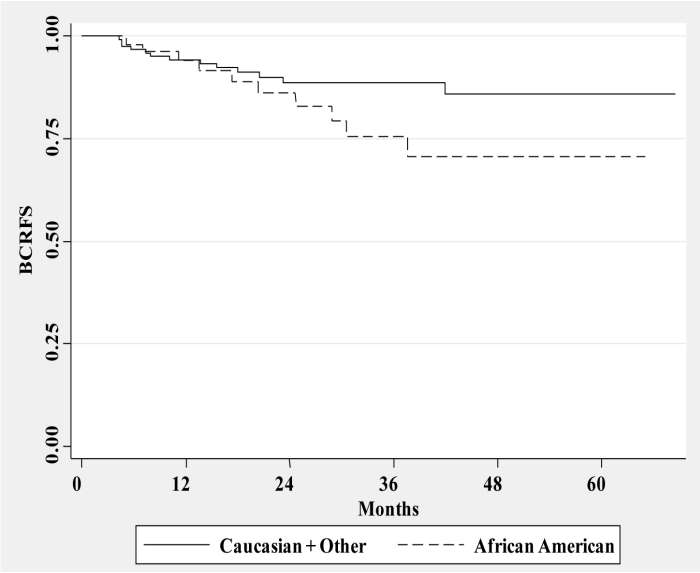

1 year cumulative BRFS: Caucasian + Other: 94%; African American: 94%; 3 year cumulative BRFS: Caucasian + Other: 89%; African American: 76%
log-rank test: *P* = .12

Figure 4. Kaplan Meier Curve for Overall Biochemical Recurrence-Free Survival (BRFS) With Hormone Therapy (HT) and Without Hormone Therapy (No HT).

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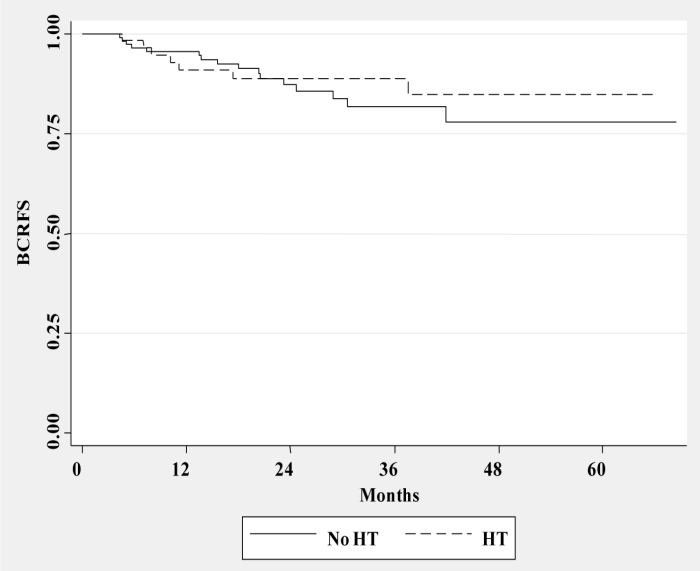

1 year cumulative BRFS: HT: 91%; no HT: 96%
3 year cumulative BRFS: HT: 82%; no HT: 82%
log-rank test: *P* = .57

Figure 5. Kaplan Meier Curve for Overall Biochemical Recurrence-Free Survival (BRFS) Comparing Prostate Volume Less Than 40 g Versus 40 g or More at the Time of Surgery.

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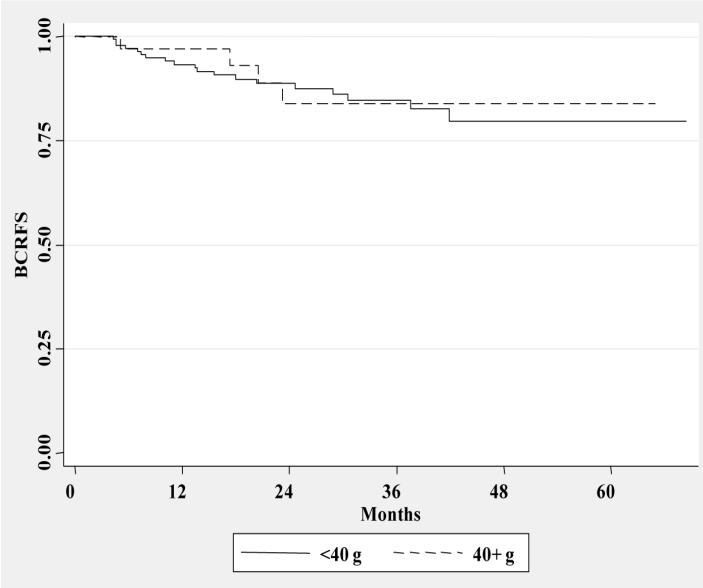

1 year cumulative BRFS: < 40 g: 93%; ≥ 40 g: 97%
3 year cumulative BRFS: < 40 g: 85%; ≥ 40 g: 84%
log-rank test: *P* = .72

Cryotherapy complications are reported in Table 3. The overall complication rate was 12% (23/190 patients). The rectourethral fistula occurred at 22 months after treatment. Of the patients with recurrent urinary tract infections, 1 had a cystoscopy performed that demonstrated a contained cavity within the space of the prostatic right lateral lobe. The infection and cavitation were managed by a suprapubic tube diversion and antibiotics, with subsequent resolution. All of the patients who reported moderate penile/perineal pain (2.6%) had resolved symptoms within 6 months. All of the patients with prolonged urinary retention eventually resolved their voiding difficulties, except for 1 patient who required a transurethral resection of the prostate at 6 months.

DISCUSSION

Even though cryoablation is recognized by the American Urological Association as a therapeutic option for the treatment of localized prostate cancer, there is still no clear definition of treatment success or biochemical failure. Much of the current literature debates this topic in the hopes of finding a consensus.

It is difficult to choose the PSA failure definition for cancer recurrence because any residual prostate cancer or benign prostate tissue can elevate PSA values. Shinohara et al [4] monitored the PSA nadir values after prostate cryotherapy in 110 patients and correlated them with biochemical or biopsy failure. They determined that a larger PSA nadir increased the chance for both biochemical and biopsy failure. A PSA nadir of ≤ 0.1 ng/mL was associated with a 21% biochemical failure and 7% biopsy failure rate. Koppie and associates [5] looked at how BRFS correlated with different PSA nadir definitions. Their biochemical recurrence was defined as 2 consecutive rises in PSA level after treatment. They reported that the best PSA nadir definition was ≤ 0.1 ng/mL, which corresponded to a BRFS of 95% at 1-year and 77% at 3-years after surgery. This was statistically significant (*P* = .0001) when compared with a PSA nadir between 0.1-0.4 ng/mL and ≥ 0.5 ng/mL. Therefore, our goal in the present study was to use a PSA nadir of ≤ 0.1 ng/mL.

There have been several other reported series in the literature using prostate cryotherapy, some involving 5-year or 10-year follow-up [6-13]. Results from these investigations are presented in Table 4. Most of the authors used a mix of second or third generation technology to report their results. There have been just a few reported series in the literature using strictly third-generation prostate cryotherapy. By using the RTOG-ASTRO nadir + 2 definition for biochemical failure in our study, the 1-year BRFS estimates were much improved. Our study is the only one in the literature using a PSA nadir of ≤ 0.1 ng/mL and the newer nadir + 2 ng/mL biochemical failure definition for strictly third-generation prostate cryotherapy.

We chose to use the most recent RTOG-ASTRO definition for biochemical failure concerning external beam radiotherapy from the 2005 conference in Phoenix, Arizona: nadir + 2 ng/mL. This was a revision from the previous ASTRO definition

Table 3. Cyrotherapy Complications (N = 190).

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Complication	n	% N
Rectourethral fistula	1	0.5
Urethral sloughing	1	0.5
Persistent urinary tract infection	4	2.1
Penile/perineal pain	5	2.6
Prolonged retention (CIC)	6	3.2
Incontinence requiring pads	3	1.6
Myocardial infarction	1	0.5
Lower urinary tract symptoms	2	1.0

Abbreviation: CIC, clean intermittent catheterization

Table 4. Prostate Cryotherapy Series in the Literature.
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Series [Reference]	Year	N	Follow-up, Mo	Cryotherapy Generation	PSA Nadir, ng/mL	PSA Failure, ng/mL	% Biochemical Survival		
							Low Risk Group	Moderate Risk Group	High Risk Group
Long et al [8]	2001	975	60	2nd, 3rd		≥ 0.5 ≥ 1.0	60 76	61 71	36 45
Donnelly et al [9]	2002	76	60	2nd, 3rd		≥ 0.3 ≥ 1.0	60 75	77 89	48 76
Bahn et al [10]	2002	590	84	2nd, 3rd		≥ 0.5 ≥ 1.0 ASTRO	64 86 92	70 81 89	65 76 89
Ellis [14]	2002	75	3	3rd	≤ 0.4 (84%)				
Han et al [15]	2003	122	3 12	3rd	≤ 0.4 (81%)	> 0.4	86 78		77 71
Prepelica et al [11]	2005	65	72	2nd, 3rd		ASTRO			82
Cohen et al [13]	2008	370	150	2nd, 3rd		Nadir +2	80	74	46
Jones et al [12]	2008	1198	60	2nd, 3rd		ASTRO Nadir +2	85 91	73 79	75 62
Nederostek et al [current]	2011	190	12 36	3rd	≤ 0.1 (81%)	Nadir +2	100 91	94 85	89 80

ASTRO = 3 consecutive PSA increases.
Abbreviation: ASTRO, American Society for Therapeutic Radiology and Oncology

of 3 consecutive PSA increases after nadir. Even though the recommendations from the consensus conference clearly stated that this definition should only be used for external-beam radiotherapy and not for any other form of prostate cancer treatment including cryosurgery [2], it is the most comparable definition available in the current literature. Jones and associates [10] reported on the first analysis from the Cryo On-Line Data registry, a large central data set for patients undergoing whole-gland prostate cryoablation. They studied both the ASTRO definition of 3 consecutive PSA level increases and the newer RTOG-ASTRO nadir + 2 ng/mL definition. A total of 1,198 patients were reviewed and analyzed by risk category. They found that the RTOG-ASTRO nadir + 2 ng/mL definition gave the best results with 5-year BRFS estimates. Overall, our BRFS results were quite comparable.

In our investigation, we also looked at the effect of neoadjuvant hormone therapy and prostate gland size at the time of surgery on treatment outcomes. Interestingly, neither variable was statistically significant when looking at BRFS. In theory, initial postoperative PSA results could be biased by neoadjuvant hormone therapy, causing an artificially low result. Although it would be difficult to determine if this was true, it is reassuring to know that the 1-year and 3-year BRFS estimates did not differ between patients who did and did not receive neoadjuvant hormone therapy. The size of the prostate at the time of surgery could also influence the cryosurgery results by inhibiting the efficiency of the freeze cycle. If the prostate gland was too large, then the placement of the cryoprobes would not be adequate to freeze the entire gland. We chose a cutoff of 40 grams and found no difference in BFRS among the different groups.

Overall, only 19 of 190 (10%) patients had a biochemical recurrence. This low number of occurrences limited our statistical power for our subanalysis when comparing the various groups in our study. We observed interesting trends involving race and prostate gland size. However, we will require longer follow-up with increased failures to draw robust conclusions, particularly about the prognostic importance of hormone therapy and prostate gland size.

CONCLUSION

Our whole-gland prostate cryotherapy results are comparable to those from other series with regard to short-term cancer control. Biochemical recurrence was increased in men with high D'Amico risk. Men from the African-American race also showed a nonsignificant trend toward greater biochemical recurrence. Neoadjuvant hormone therapy and prostate gland size at the time of surgery did not significantly influence BRFS. These outcomes further justify the use of cryosurgery for the management of localized prostate cancer.

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Conflict of Interest: none declared.

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