BJUI
BJU INTERNATIONAL

Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry

John F. Ward and J. Stephen Jones*

*Department of Urology, University of Texas, M.D. Anderson Cancer Center, Houston, TX, and *Department of Regional Urology, Glickman Urological and Kidney Institute at Cleveland Clinic, Cleveland, OH, USA*

Accepted for publication 13 June 2011

Study Type – Therapy (cohort)
Level of Evidence 2b

What's known on the subject? and What does the study add?
Selective destruction of targeted prostate tissue is now technically feasible. Much has been theorized but little is known about the proper patient selection or treatment outcomes to determine if this organ preserving approach to prostate cancer has merit for further study and diffusion into wider practice.

Herein we present the largest retrospective registry report of men treated with sub-total prostate cryotherapy in order to begin to understand how this treatment is being applied despite the paucity of data.

OBJECTIVES

- To identify recent trends in focal cryotherapy from a prospectively maintained treatment registry.
- To describe treatment outcomes after uncontrolled application of focally ablative techniques within community practice.

MATERIALS AND METHODS

- We conducted an analysis of the COLD Registry to identify patients treated with partial gland prostate cryoablation between 1997 and 2007.
- Preoperative characteristics and postoperative cancer-specific and functional outcomes were assembled for analysis.

RESULTS

- The COLD Registry contained information for 5853 patients and focal cryotherapy was the codified procedure in 1160 patients (19.8%).
- A dramatic increase in focal treatments was observed, from 46 in 1999 to 567 in 2005 ($P < 0.01$).
- The biochemical recurrence-free rate (ASTRO definition) at 36 months was 75.7%.
- Prostate biopsy, performed in 164/1160 of patients (14.1%), was positive in 43 (26.3%) of those suspected of cancer recurrence, but in only 3.7% (43/1160) of treated patients.
- Urinary continence (defined as use of 0 pads) was 98.4%. Maintenance of spontaneous erections was 58.1%. Prolonged urinary retention (>30 days) occurred in six (1.1%) patients. Rectourethral fistula was observed in one (0.1%) patient.

CONCLUSIONS

- Focal cryoablation is increasingly used for selected patients with prostate cancer.
- Oncological efficacy in the present series appears similar to that of whole-gland cryoablation.
- The impact of focal cryoablation on urinary, sexual and bowel function appears to be less than that of radical therapies, although preservation of sexual function is not as high as might be expected.

KEYWORDS

focal therapy, prostate cancer, cryotherapy, outcomes, registry

INTRODUCTION

Whole-gland prostate cancer (PCa) treatments can damage the anatomical structures (bladder, erectile nerves, rhabdosphincter and rectum) that contribute to a high health-related quality of life. While the incidence of such damage has decreased as techniques to deliver both radiation and surgical extirpation have improved, morbidity remains significant in terms of both frequency and personal impact. Methods of avoiding or correcting iatrogenic dysfunction have not progressed significantly in the last 20 years, making this dysfunction a lifelong debilitation for many men treated for PCa. These morbidities, although tenable if required to avoid disease-specific mortality, are more objectionable if the costs are not justified by the disease risk. Although medical professionals continue to embrace the notion that many patients diagnosed with PCa may not need any treatment at all (active surveillance), patients are often reluctant to forgo treatment for any cancer diagnosis, and the use of active surveillance remains limited in current practice.

Organ-sparing therapy, most commonly termed 'focal therapy', has been suggested as a way to eliminate small-volume PCa,

this being the largest growing group of patients with newly diagnosed PCa. The hypothetical premise of focal therapy is that although clinically insignificant smaller tumours may coexist elsewhere in the prostate gland, a dominant tumour drives the biology of the disease; destroying the dominant tumour may, therefore, alter the natural history of the disease for the individual patient [1,2]. If focal therapy can destroy the dominant tumour in a way that limits the collateral damage to urinary, bowel and erectile functions associated with other PCa therapies, this form of therapy may be desirable for well selected patients who may be willing to accept potential oncological concessions in order to limit these risks.

The concept of focal therapy for PCa follows the same treatment paradigm used for almost all other solid tumours, where careful study has shown that functional outcomes are improved by minimizing the excised or destroyed tissue with no resulting loss of oncological efficacy. The use of focal therapy to treat kidney and bladder malignancies is well established in the literature; however, additional research is needed to determine the clinical outcomes of focal therapy in the management of PCa, even though the multifocal nature of PCa is known to be similar to that of urothelial cancer. While the concept of organ preservation in PCa treatment is attractive to many patients, published data supporting such a hypothesis are sparse and almost completely anecdotal. To identify both recent trends in the treatment of PCa and clinical outcomes in patients with PCa treated with focal cryoablation, we retrospectively reviewed data from the COLD Registry.

MATERIALS AND METHODS

We queried the COLD Registry (http://www.coldregistry.com) to identify men who had undergone prostate cryoablation between 1999 and 2007 as a primary therapy for localized, histologically identified adenocarcinoma of the prostate.

The COLD Registry is a web-based database designed to address the specialized clinical data associated with prostate cryoablation. It is financially supported by Endocare Corp., a manufacturer of cryotherapy technology, which was recently acquired by Endo Pharmaceuticals. The database is maintained by an independent research company, Watermark Research Partners, Inc. (Watermark, Indianapolis, IN, USA) and an independent physician board oversees the database and takes all publication decisions. Physician participation in the COLD Registry is voluntary and uncompensated. The entire registry is approved by Liberty Institutional Review Board (IRB), and individually approved by local IRBs, based on participating institutional policies.

Watermark and the COLD Registry advisory board created standard clinical review forms that are completed by a physician or physician's employee for each patient treated with prostate cryoablation. Watermark completes random audits of 10% of participating sites annually to ensure that all data are as accurate and complete as possible. The data are wholly analysed by Watermark and presented independently of review or input from industry interests.

Patient data are entered into the COLD Registry under 'primary' or 'salvage' therapy and are further classified as 'whole-gland' or 'partial-gland' cryoablation. The COLD Registry advisory board does not provide participating physicians with standard selection criteria regarding the appropriate candidates for focal cryotherapy, therefore, the available data represent current community practice and prevailing selection criteria. The COLD Registry advisory board does not identify a standard volume of tissue for targeted destruction (treatment template), therefore, this dataset also represents the current state and heterogeneity of community organ-sparing techniques.

STATISTICS

On June 13, 2010 we searched the treatment records of 5853 patients with PCa treated with cryoablation between 1999 and 2007 (the last year for which verifiable data were available at that time). Our focal cryoablation cohort comprised men with localized PCa (cT1-T2) receiving primary cryotherapy that was categorized as 'partial-gland' ablation by the surgeon. Men receiving whole-gland cryoablation with 'nerve warming' were evaluated separately and are not included in the study cohort presented as 'focal cryoablation'. Outcomes for the focal cryoablation cohort are compared with men from the same database who underwent primary whole-gland cryoablation or salvage therapy after primary radiation therapy. For this cohort analysis, age, Gleason grade, clinical stage (according to the American Joint Committee on Cancer Staging Manual, 5th edition) and baseline PSA were assessed in relation to outcomes. Patients were risk stratified according to the definitions of D'Amico *et al.* [3] Patients who had received preoperative hormone therapy or TURP were excluded from the analysis.

Biochemical recurrence was defined, according to the ASTRO definition [4], as three consecutive increases in serum PSA level >6 months after focal cryoablation. The date of recurrence was considered to be the midpoint between the PSA nadir and the first PSA increase. This definition was used because it is commonly used to report results in which the prostate gland is left *in situ* which would allow simplified interpretation of the present results compared with those of the other therapies. Data were summarized using descriptive statistics. Comparisons between categorical variables were performed using the chi-squared test and Fisher exact test, when appropriate. The 5-year, biochemical recurrence-free survival rates were estimated using the Kaplan–Meier method. All statistical tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed independently at Watermark using commercial statistical software (MedCalc, Mariakerke, Belgium).

RESULTS

Our search of the COLD Registry identified 1160 patients for the focal cryoablation cohort. This subset represents 19.8% of the entire database and 22.1% of all primary cryotherapy procedures performed. Table 1 shows the clinical characteristics of the patients by type of cryotherapy received (focal, whole-gland, salvage). Patients who had undergone focal cryoablation were younger (mean age 67.8 years), had a lower clinical grade (74% with Gleason sum ≤6) and stage (87% ≤ cT2b), and were stratified to a lower risk group (12% high risk) than patients undergoing either whole-gland or salvage prostate cryoablation.

TABLE 1 Clinical characteristics of men within the COLD Registry undergoing focal, whole-gland and salvage prostate cryoablation during the same time period

	Focal cryoablation	Whole-gland cryoablation	Salvage cryoablation
No. of patients	**1160**	**4099**	**594**
Mean (SD) age, years	67.8 (7.80)	70.4 (21.8)	70.2 (6.8)
Mean (SD) follow-up, months	21.1 (19.7)	31.8 (30.5)	38.5 (39.5)
Gleason sum			
Data available, *n* (%)	1148 (99)	3982 (97)	564 (95)
≤6, *n* (%)	844 (74)	2383 (60)	249 (44)
7, *n* (%)	240 (21)	1046 (26)	168 (30)
≥8, *n* (%)	64 (6)	5531 (4)	147 (26)
Clinical stage			
Data available, *n* (%)	1160 (100)	4099 (100)	594 (100)
< T2b, *n* (%)	1013 (87)	2863 (70)	458 (77)
≥ T2b	147 (13)	1236 (30)	136 (23)
PSA (ng/mL) at baseline			
Data available, *n* (%)	1149 (99)	4011 (98)	590 (99)
<4, *n* (%)	211 (18)	618 (15)	187 (32)
4<10, *n* (%)	782 (68)	2374 (59)	254 (43)
10<20, *n* (%)	126 (11)	707 (18)	94 (16)
20+, *n* (%)	30 (3)	312 (8)	55 (9)
Risk category*			
Data available, *n* (%)	1157 (100)	4067 (99)	592 (100)
Low risk, *n* (%)	541 (47)	934 (23)	57 (10)
Intermediate risk, *n* (%)	473 (41)	1885 (46)	294 (50)
High risk, *n* (%)	143 (12)	1248 (31)	241 (41)

**Patients' risk is assigned to one of three categories using D'Amico risk definitions (low risk: Gleason score ≤6 AND ≤ clinical stage T2a AND PSA < 10 ng/mL; high risk: Gleason score 8 or higher and/or PSA >20 ng/mL and/or > T2b; intermediate risk anything else).*

We observed a significant increase (Fisher's exact test, $P < 0.001$) in the number of patients undergoing focal cryoablation from the beginning of the study to the end (Fig. 1). Focal cryoablation represented 2.1% (1/47) of all cryotherapy procedures within the COLD Registry in 1999. By 2007, the rate had risen to 38.2% (293/768) and continued to increase, despite an observed decrease in whole-gland treatments during the final 2 years of the study period. An analysis of the variations in patients within each risk group during this period found that the proportion of patients within each risk group had not changed (Fig. 2), despite the increased use of focal cryoablation. In other words, a trend towards using focal cryoablation only in patients with the lowest risk disease was not observed. The majority of patients treated with cryoablation had a low- or intermediate-risk disease profile.

The biochemical recurrence-free rate after focal cryoablation was 75.7%, 2 years after treatment (Table 2). When the focal cryoablation cohort's ability to achieve biochemical recurrence-free survival was compared with that of the whole-gland cryoablation cohort in the same time period, the results were similar (75.5% biochemical recurrence-free survival at 2 years after whole-gland cryoablation). Biochemical recurrence-free survival by risk group after both whole-gland and focal cryoablation is shown in Fig. 3. No significant difference in biochemical recurrence was observed between whole-gland- and focal cryoablation-treated patients for each risk category.

FIG. 1. Changes in total number of focal and whole-gland prostate cryoablation procedures per year.

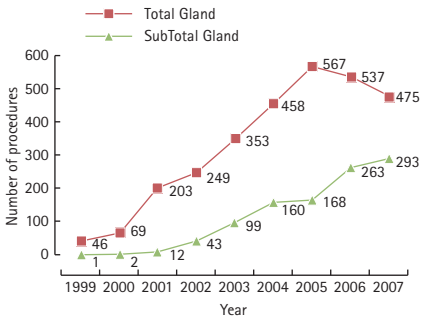
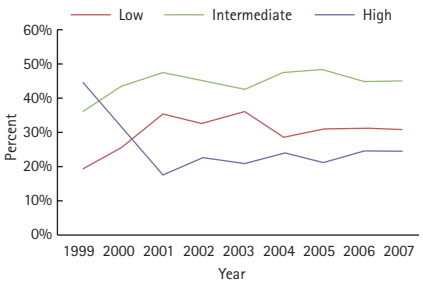
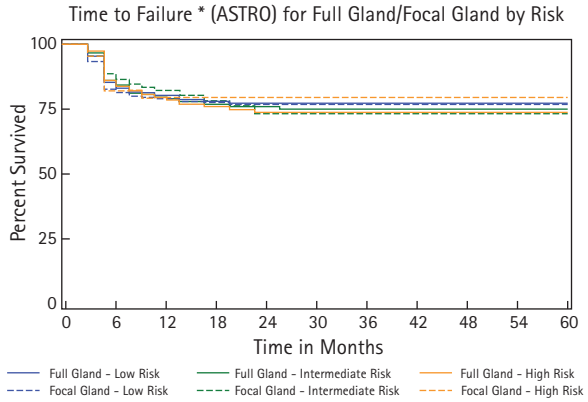


FIG. 2. Variation over time in risk group categorization at time of prostate cryoablation.



Prostate biopsy was performed after treatment because of increased post-treatment serum PSA level in 14.1% of the study cohort (Table 3). Surprisingly, the

FIG. 3.
Biochemical recurrence-free survival (ASTRO) after focal and whole-gland prostate cryoablation stratified by risk group.



Note: Percent Surviving is calculated from Kaplan-Meier product limit estimates.
Deaths are censored at the last recorded visit.
‡ Time to failure is defined as: 3 rises in PSA (≥ 6 months after surgery).
Failure occurs midpoint between NADIR and the first rise

Time in months:	0	6	12	18	24	30	36
Number left (Whole gland)							
low risk	593	442	350	273	230	230	230
intermediate risk	1097	817	632	483	405	303	303
high risk	760	554	420	320	255	255	255
Number left (Organ Preserving)							
low risk	338	234	166	111	92	92	92
intermediate risk	264	188	121	80	52	52	52
high risk	67	43	28	28	28	28	28

TABLE 2 Biochemical recurrence-free survival after focal cryoablation compared with matched patients undergoing whole-gland cryoablation during the same time period

	Biochemical recurrence-free survival	
Time from cryosurgery	Organ preservation prostate cryoablation, %	Whole-gland prostate cryoablation, %
6 months	84.2	83.3
12 months	80.7	78.7
24 months	75.7	75.5
36 months	75.7	75.1

TABLE 3 Comparison of biopsy results after focal cryoablation and whole-gland cryoablation

	Focal cryoablation, $n = 1160$	Whole-gland cryoablation, $n = 4099$
No. patients who underwent a biopsy after prostate cryoablation (%)	163 (14.1)	841 (20.6)
Positive biopsy of those who underwent biopsy (%)	43 (26.3)	125 (14.9)
Positive biopsy of entire cohort, %	3.7	3.0

biopsy rate in the focal cryoablation cohort was lower than that in the whole-gland cryoablation cohort (14.0% [163/1160 patients] vs 20.6% [841/4099 patients]; chi-squared test, $P < 0.001$). The overall positive biopsy rate for the focal cryoablation cohort was the same as that in the whole-gland cohort (3.7%, [3/1160 patients] vs 3% [125/4099 patients]; chi-squared test, $P = 0.26$), but with the low number of patients undergoing biopsy in each group, these findings are of limited value. The median (mean) Gleason score of the identified cancer in the 43 patients with a positive post-focal cryoablation biopsy was 6 (6.12).

The morbidity of primary focal cryoablation, whole-gland cryoablation and salvage cryoablation during this study period is presented in Table 4. Rectourethral fistula was extremely rare and had occurred in only 1/1160 patients in the focal cryoablation cohort compared with 0.4% of patients in the whole-gland cohort. For the focal and whole-gland cohorts, complete urinary continence after cryoablation was very high (98.4% and 96.9%, respectively). Temporary urinary retention after cryoablation was a rare event that had occurred in 1.1% of the focal and 1.6% of the whole-gland cryoablation cohort. Patients who had reported the ability to have sexual intercourse before focal cryoablation were more likely to have maintained this ability after treatment (58.1%) than patients in the whole-gland cohort (32.3%).

DISCUSSION

There was a >1000 fold increase in the use of focal cryoablation during the study period, despite the paucity of literature on its oncological efficacy or associated morbidity. The present study, which presents prospectively maintained patients treated with the intent to preserve a portion of the prostate from cryoablation, is the largest report with the longest follow-up currently available. A selection criterion for choosing between organ-sparing cryotherapy and other options is not available in the registry. Nevertheless, in the present review we found that focal cryoablation offered men selected for this treatment an oncological efficacy similar to whole-gland cryotherapy over the same time period, with improved urinary continence, preservation of erectile function and decreased urinary retention. Rectourethral fistula was extremely rare, with only one case reported.

We now have a basis upon which we can move this treatment approach forward to better examine patient selection, treatment templates, efficacy and perioperative morbidity in a larger prospective and cooperative fashion.

The movement towards a preservation approach to a cancerous organ is a familiar one in oncology. At one time, if cancer was found in any solid organ, the entire organ was removed. Efforts for the past 20 years have been focused on more sensitive and

specific means of identifying even a small focus of PCa within the gland, which was then enough to justify radical therapy using surgery or radiation in most practices. However, the concept of empiric radical therapy has failed the test of time for most solid cancers, and organ preservation has become the standard management for breast, renal, lung and colon cancers [5,6].

In urology, this same concept has led to widespread use of organ-sparing techniques for kidney and non-muscle-invasive bladder cancer. For bladder cancer, a 'field change' phenomenon has tempered the use of focal cryoablation in patients with high grade cancer and has mandated the development of adjunctive intravesical therapies. However, it must be recognized that the majority of PCa is not considered to be as lethal as high grade bladder cancer, so the fear of incurability should logically be less stifling to the creative advance of treatments that preserve organ function.

TABLE 4 Comparison of treatment-associated morbidity at 12 months

Morbidity by procedure type (*number of patients in whom sufficient pre- and post-procedure information was available for analysis*)	No. of patients (%)
Urinary Incontinence	
Focal (507)	8 (1.6)
Whole-gland (2099)	65 (3.1)
Salvage (299)	33 (12.3)
New-onset erectile dysfunction	
Focal (291)	122 (41.9)
Whole-gland (639)	432 (67.6)
Salvage (60)	36 (60.0)
Rectourethral fistula	
Focal (1160)	1 (0.1)
Whole-gland (4099)	18 (0.4)
Salvage (594)	9 (1.5)
Urinary retention (>30 days)	
Focal (518)	6 (1.2)
Whole-gland (2177)	34 (1.6)
Salvage (282)	12 (4.3)

In 1990, most urologists believed that men diagnosed with PCa had clinically significant disease that required radical therapy. With the introduction of serum PSA testing and widespread PCa screening, the promise of altering the dismal prognosis of this disease and offering a cure, with earlier diagnosis at a lower stage, has been more frequent. Thus, the face of this disease has changed. Since 1997, there has been a 100% increase in incidence of PCa from 90 000 to 180 000 cases per year, during which time the number of men with metastases at presentation declined 30% from 35 000 to 29 000 cases per year [7,8]; however, comparatively younger men with apparently early-stage, low grade, small-volume disease accounted for the majority of the overall increase in incidence.

Although the prognosis for PCa is now very different from what it was 20 years ago, the aggressiveness of our treatment has not changed commensurately; when treatment is deemed necessary or desired, physicians continue to depend on radical therapies for all men. Recently, both medical professionals and the lay population have expressed concern about over-treating PCa, and the assumption that immediate radical treatment is needed has been challenged [9,10].. However, the active monitoring and delayed intervention approach is not without concerns; consistently, in studies where active surveillance criteria have been retrospectively applied to patients who chose radical prostatectomy at diagnosis, a substantial proportion of men who might have been considered potential active surveillance candidates have had aggressive tumour features [11–13]. Most notably, these studies consistently report that more than 50% of cancers in these patients are upgraded to Gleason grade 7 or higher tumours. Thus, there is concern that treatment delays caused by active surveillance may be associated with an impaired chance of curability [13,14]. This concern is further compounded by the lack of reliable triggers for intervention including PSA kinetics [15,16].

Reports from a prospective active surveillance study in Toronto, Canada, showed that 26% (117/450) of patients who had been treated initially with active surveillance and who subsequently had undergone definitive therapy (surgery or radiation) experienced a 50% rate of biochemical recurrence during a median follow-up period of 6.8 years; this rate is substantially higher than that predicted using preoperative nomograms and the highest risk inclusion criteria that still defined eligibility for that trial [17–19]. Conversion to radical therapy during active surveillance has been reported for 14–39% of patients with PCa [20–23]. Given these reports, the short-term benefits of active surveillance may not outweigh the long-term consequences for a substantial number of patients and, although the authors strongly advocate its use, active surveillance remains an exceedingly uncommon option for patients with small-volume PCa in the USA.

Limiting cancer treatment to just the malignancy and immediate surrounding tissue within the preserved primary organ is a transition that is familiar to patients and physicians; however, the prostate is not anatomically amenable to partial extirpation of the peripheral zone. With the advent of directly applied, precisely controlled ablative technology (cryoablation, high-intensity focused ultrasound, photodynamic therapy and laser-induced interstitial therapy), the concept of organ-sparing therapy went from improbable to plausible, and the explosion of its use in this dataset shows its appeal to the urology community.

Cryoablation became the *de facto* energy source of choice in the USA because it was the only technology approved both by the Food and Drug Administration for the destruction of soft tissue and by Medicare for the treatment of PCa. Cryotherapy also has the advantage of having a long history of effective tumour treatment in different parts of the body, including treatment of the

entire prostate gland. The rocky early start that prostate cryoablation experienced has been mitigated largely by major technical advances in the procedure, such as improved urethral warmer design and third-generation technologies based on the Joule–Thompson effect, and cryoablation has been shown to be effective and safe when used to treat the entire prostate gland [24,25].

The concept of managing PCa as chronic disease, using targeted destruction of identifiable disease, and possibly using chemopreventive agents to inhibit the formation of new carcinomas, is being accepted increasingly in preference to the alternative treatment options for patients with newly diagnosed PCa, who prefer some treatment to no treatment or to radical treatment.

The biology of index lesion targeting becomes central to the concept of successful focal therapy [26]. The multifocality of PCa may not affect its clinical course, as >80% of secondary satellite lesions are low grade and <0.5 cm^3 (the threshold believed by numerous authorities to be associated with clinical disease progression). The presence and volume of these secondary cancer foci have been found to be unrelated to biochemical recurrence after radical prostatectomy, although it should be acknowledged that these low-risk areas are removed if surgery is performed, so their ultimate risk is not established [27,28].

In the present paper, we do not suggest that focal therapy has a proven role in the care of patients with PCa, but it must be conceded that the data that support any treatment option, including active surveillance, are inadequate. The data presented in the present paper represent the largest single series to date to report on cancer-specific and quality-of-life outcomes for patients treated with cryoablation with the intent to provide organ preservation.

A major limitation of these data is the lack of defined criteria for treating the patient with focal cryoablation and not having specified ablative templates. Despite this limitation, the data suggest urologists are prudently selecting most patients for focal cryoablation and individualizing the treatment to the patient; the cancer-specific outcomes of biochemical recurrence and biopsy-proven recurrence are similar to disease-specific outcomes for men treated with whole-gland cryoablation. For focal cryoablation to be implemented successfully, it must not only deliver effective cancer control but must also deliver improved urinary continence and sexual function. These data show minimal impact on urinary function, but also show clearly that maintenance of sexual function is certainly not assured after focal cryoablation. Additional study is needed on the differences between treatment templates and ablative energies to determine optimum protocols for PCa treatment.

The present study is also limited by the use of the ASTRO definition of biochemical recurrence; a definition developed for patients treated primarily with radical radiation therapy. Although this definition was not developed for patients treated by other methods, it has been widely applied outside of the radiation-treated patient with PCa. We would, however, expect the kinetics of serum PSA after focal therapy using any ablative energy to be different from those observed after radical therapy, thus the use of serum PSA as a surrogate marker for cancer treatment after focal cryoablation remains unknown.

Another limitation is the dependence on participants in the COLD Registry to provide appropriate treatment and outcome details, a problem common to multi-site treatment registries. The duration of follow-up is not long enough to determine whether the natural course of the disease was altered through targeted cryoablation, but the present study does provide a study cohort large enough to evaluate short-term oncological efficacy, which serves to encourage continued exploration of this potentially paradigm-shifting therapy. Finally, the financial sponsorship of the COLD Registry must be considered, as should the measures taken to mitigate its effects on any analyses using this data.

In conclusion, organ-sparing therapy has slowly become the standard therapy for most solid tumours, but its role in treating PCa has been limited by high rates of multifocality and anatomical challenges. We are not insinuating that focal cryoablation is proven to play a role in the successful treatment of PCa, however, the COLD Registry data show not only that focal cryoablation is used widely in the urological community but also that it provides promising short-term outcomes for well selected patients with PCa. Morbidity was low, although >40% of patients experienced impotence, and 26% of patients that underwent biopsy for rising PSA levels after therapy had persistent cancer. We emphasize that additional study is needed to determine the proper indications and techniques for using focal cryoablation to treat PCa as well as the expected outcomes of such treatment; to this end, the data in the COLD Registry offer the largest and most substantial collection of information on the use of focal cryotherapy for PCa treatment.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Kristi M. Speights, Associate Scientific Editor, M.D. Anderson Cancer Center for her outstanding editorial contributions.

The M.D. Anderson Cancer Center is supported by a Core grant (CA16672). The COLD Registry is supported by an unrestricted educational grant from Healthtronics, Austin, TX, USA.

CONFLICT OF INTEREST

John F. Ward received an unrestricted Research Grant from Healthtronics. J. Stephen Jones is a Speaker for Healthtronics.

REFERENCES

1 **Hall GS, Kramer CE, Epstein JI.** Evaluation of radical prostatectomy specimens. A comparative analysis of sampling methods. *Am J Surg Pathol* 1992; **16**: 315–24
2 **Andreoiu M, Cheng L.** Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. *Hum Pathol* 2010; **41**: 781–93
3 **D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH.** Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol* 2003; **21**: 2163–72

4 Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997; **37**: 1035–41

5 **Brkovic D, Riedasch G, Staehler G.** [Status of organ preserving surgery in renal cell carcinoma]. *Urologe A* 1997; **36**: 103–8

6 **Macmillan RD, Purushotham AD, George WD.** Local recurrence after breast-conserving surgery for breast cancer. *Br J Surg* 1996; **83**: 149–55

7 **Jemal A, Siegel R, Xu J, Ward E.** Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277–300

8 **Cooperberg MR, Broering JM, Kantoff PW, Carroll PR.** Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol* 2007; **178**: S14–9

9 **Klotz L.** Active surveillance versus radical treatment for favorable-risk localized prostate cancer. *Curr Treat Options Oncol* 2006; **7**: 355–62

10 **Stattin P, Holmberg E, Bratt O, Adolfsson J, Johansson JE, Hugosson J.** Surveillance and deferred treatment for localized prostate cancer. Population based study in the National Prostate Cancer Register of Sweden. *J Urol* 2008; **180**: 2423–9; discussion 2429–30

11 **Thaxton CS, Loeb S, Roehl KA, Kan D, Catalona WJ.** Treatment outcomes of radical prostatectomy in potential candidates for 3 published active surveillance protocols. *Urology* 2010; **75**: 414–8

12 **Smaldone MC, Cowan JE, Carroll PR, Davies BJ.** Eligibility for active surveillance and pathological outcomes for men undergoing radical prostatectomy in a large, community based cohort. *J Urol* 2010; **183**: 138–43

13 **Ploussard G, Salomon L, Xylinas E *et al*.** Pathological findings and prostate specific antigen outcomes after radical prostatectomy in men eligible for active surveillance–does the risk of misclassification vary according to biopsy criteria? *J Urol* 2010; **183**: 539–44

14 **van den Bergh RC, Steyerberg EW, Khatami A *et al*.** Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; **116**: 1281–90

15 **Ross AE, Loeb S, Landis P *et al*.** Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol* 2010; **28**: 2810–6

16 **Whitson JM, Carroll PR.** Active surveillance for early-stage prostate cancer: defining the triggers for intervention. *J Clin Oncol* 2010; **28**: 2807–9

17 **Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A.** Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010; **28**: 126–31

18 **Stephenson AJ, Scardino PT, Eastham JA *et al*.** Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst* 2006; **98**: 715–7

19 **Kattan MW, Zelefsky MJ, Kupelian PA, Scardino PT, Fuks Z, Leibel SA.** Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol* 2000; **18**: 3352–9

20 **Hardie C, Parker C, Norman A *et al*.** Early outcomes of active surveillance for localized prostate cancer. *BJU Int* 2005; **95**: 956–60

21 **van den Bergh RC, Vasarainen H, van der Poel HG *et al*.** Short-term outcomes of the prospective multicentre 'Prostate Cancer Research International: Active Surveillance' study. *BJU Int* 2010; **105**: 956–62

22 **Krakowsky Y, Loblaw A, Klotz L.** Prostate cancer death of men treated with initial active surveillance: clinical and biochemical characteristics. *J Urol* 2010; **184**: 131–5

23 **Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J.** PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *Int J Cancer* 2007; **120**: 170–4

24 **Jones JS, Rewcastle JC, Donnelly BJ, Lugnani FM, Pisters LL, Katz AE.** Whole Gland Primary Prostate Cryoablation: initial results from the Cryo On-Line Data Registry. *J Urol* 2008; **180**: 554–8

25 **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

26 **Ahmed HU.** The index lesion and the origin of prostate cancer. *N Engl J Med* 2009; **361**: 1704–6

27 **Nelson BA, Shappell SB, Chang SS *et al*.** Tumour volume is an independent predictor of prostate-specific antigen recurrence in patients undergoing radical prostatectomy for clinically localized prostate cancer. *BJU Int* 2006; **97**: 1169–72

28 **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

Correspondence: John F. Ward, Department of Urology, University of Texas, M. D. Anderson Cancer Center, PO Box 301439, Houston, TX 77230-1439, USA.
e-mail: jfward@mdanderson.org

Abbreviations: **PCa**, prostate cancer; **IRB**, Institutional Review Board.