

## ORIGINAL ARTICLE

# Treatment profile and complications associated with cryotherapy for localized prostate cancer: A population-based study

CB Roberts<sup>1</sup>, TL Jang<sup>2,3,4</sup>, Yu-Hsuan Shao<sup>2</sup>, S Kabadi<sup>5</sup>, DF Moore<sup>6</sup> and GL Lu-Yao<sup>2,4,7,8</sup>

<sup>1</sup>State University of New York Downstate Medical Center, Brooklyn, NY, USA; <sup>2</sup>Cancer Institute of New Jersey, New Brunswick, NJ, USA; <sup>3</sup>Division of Urology, Department of Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA; <sup>4</sup>The Dean and Betty Gallo Prostate Cancer Center, New Brunswick, NJ, USA; <sup>5</sup>Department of Epidemiology and Biostatistics, The School of Public Health, Drexel University, Philadelphia, PA, USA; <sup>6</sup>Department of Biostatistics, The School of Public Health, University of Medicine and Dentistry in New Jersey, Piscataway, NJ, USA; <sup>7</sup>Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA and <sup>8</sup>Department of Epidemiology, The School of Public Health, University of Medicine and Dentistry in New Jersey, Piscataway, NJ, USA

The aim of this study was to assess the treatment patterns and 3–12-month complication rates associated with receiving prostate cryotherapy in a population-based study. Men >65 years diagnosed with incident localized prostate cancer in Surveillance Epidemiology End Results (SEER)–Medicare-linked database from 2004 to 2005 were identified. A total of 21344 men were included in the study, of which 380 were treated initially with cryotherapy. Recipients of cryotherapy versus aggressive forms of prostate therapy (ie, radical prostatectomy or radiation therapy) were more likely to be older, have one co-morbidity, low income, live in the South and be diagnosed with indolent cancer. Complication rates increased from 3 to 12 months following cryotherapy. By the twelfth month, the rates for urinary incontinence, lower urinary tract obstruction, erectile dysfunction and bowel bleeding reached 9.8, 28.7, 20.1 and 3.3%, respectively. Diagnoses of hydronephrosis, urinary fistula or bowel fistula were not evident. The rates of corrective invasive procedures for lower urinary tract obstruction and erectile dysfunction were both <2.9% by the twelfth month. Overall, complications post-cryotherapy were modest; however, diagnoses for lower urinary tract obstruction and erectile dysfunction were common.

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## Introduction

As the introduction of PSA screening, an increasing number of men are being diagnosed with low-grade, low-stage and small-volume cancers that are potentially biologically indolent. Consequently, choosing whether and how to treat these tumors remains challenging. Men newly diagnosed with low-risk prostate cancer are frequently treated with standard therapies (ie, radical prostatectomy, external beam radiation therapy, brachytherapy, androgen deprivation therapy (ADT) or conservative management),<sup>1</sup> which are associated with high overall, cancer-specific and biochemical-recurrence free survival. However, radical prostatectomy, radiation therapy and ADT are accompanied by side effects

(eg, bladder and bowel dysfunction) that may impact negatively on health-related quality of life. Conversely, conservative management may induce anxiety and elevate stress levels.<sup>2</sup> As such, renewed interest has emerged in using minimally invasive approaches, such as cryotherapy, to treat men diagnosed with clinically, localized prostate cancer.

Cryotherapy has become more widespread in practice because of a better understanding of cryobiology,<sup>3</sup> introduction of third-generation cryoprobes and improvements in biopsy and imaging techniques, which have enhanced the ability to map the foci and location of tumors within the prostate and subsequently reduce morbidity while improving effectiveness.<sup>3–5</sup>

Although cryotherapy has been identified as a potential treatment option for men with clinically organ-confined disease by the American Urological Association,<sup>3</sup> there is no formal definition of cryotherapy eligible tumors and a lack of information regarding the actual recipients of cryotherapy. Moreover, morbidity associated with cryotherapy has been primarily reported from single hospital-based studies, typically in highly

Correspondence: Dr GL Lu-Yao, Medical Oncology, The Cancer Institute of New Jersey, 195 Little Albany Street, Room 5534; New Brunswick, NJ, USA.

E-mail: luyagr@umdnj.edu

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selected patients.<sup>6–14</sup> Thus, in a population-based study, we identify the risk profile of men with clinically localized prostate cancer initially treated with cryotherapy and characterize post treatment-related complications.

## Materials and methods

Data for this study were obtained from the 16 tumor registries participating in the National Cancer Institute's Surveillance Epidemiology End Results (SEER) program database linked to Medicare administrative claims. The SEER program monitors ~26% of the United States population and has complete ascertainment in 98% of cases.<sup>15</sup> Our study cohort consisted of men  $\geq 66$  years diagnosed with incident, localized prostate cancer (ICD-O-3 site code C619) while enrolled in Medicare between 2004 and 2005. All patients were initially treated with cryotherapy, a form of aggressive standard therapy (ie, radical prostatectomy or radiation therapy) or non-aggressive standard therapy (ADT or conservative management) within 1 year of being diagnosed with prostate cancer. Men with advanced prostate cancer (T3 or T4) ( $n = 2519$ ) or previous cancers ( $n = 4896$ ) were excluded. Additional exclusion criteria included patients whose diagnosis of prostate cancer was obtained from autopsy or death certificate ( $n = 745$ ), or tumor pathology not consistent with adenocarcinoma ( $n = 2167$ ). Given that TURP increases the risk of urinary complications, men with a history of TURP ( $n = 32$ ) or those who underwent TURP in combination with cryotherapy ( $n = 191$ ) were excluded.<sup>16</sup> Men with unknown Gleason score ( $n = 1120$ ), PSA level ( $n = 4589$ ), clinical stage ( $n = 1249$ ) or covariates ( $n = 52$ ) were also excluded. The final study cohort consisted of 21 344 men newly diagnosed with localized prostate cancer.

### Treatment

Cryotherapy and standard therapies were administered within 1 year following initial diagnosis of prostate cancer. Cryotherapy was identified from Medicare inpatient and outpatient claims using International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) procedure code 60.62, Current Procedural Terminology (CPT) code 55 873, Health Care Financing Administration Common Procedure Coding System (HCPCS) codes G0160 and G0161 and SEER data. Standard forms of therapy were identified from Medicare-billing codes and SEER data.

### Complications

ICD-9/CPT/HCPCS codes and Medicare claims data were used to ascertain the prevalence of diagnoses and invasive procedures reported for urinary, bowel and sexual function-related complications occurring 3, 6 and 12 months after cryotherapy. Patients with a Medicare claim of urinary, rectal or erectile dysfunction diagnoses or procedural-related complications before cryotherapy were excluded in order to identify the prevalence of post-treatment complications, which included lower urinary tract obstruction, erectile dysfunction, urinary incontinence, bowel bleeding, hydronephrosis, urinary fistula and bowel fistula. The medical codes for diagnoses and

procedures for the aforementioned complications are provided in Appendix A.

### Covariates

Demographic variables included age, race, marital status, income, geographic region, PSA, Gleason score, clinical stage, cancer-recurrence risk level and Charlson co-morbidity. Charlson co-morbidity score was derived from Medicare claims during the year before prostate cancer diagnosis by using a validated algorithm.<sup>17</sup> Risk level, a measure of disease progression and PSA failure, was defined based on the risk model defined by the National Comprehensive Cancer Network.<sup>17</sup> Low risk included clinical stage  $\leq T2a$ , PSA level  $\leq 10$  ng ml<sup>-1</sup>, Gleason score  $\leq 6$ ; intermediate risk included clinical stage T2b–T2c, PSA  $> 10$  and  $\leq 20$  ng ml, Gleason score = 7; and high risk included PSA  $> 20$  ng ml<sup>-1</sup> and Gleason score  $\geq 8$ .<sup>18</sup>

### Statistical analysis

Multivariate logistic regression was used to estimate odds ratios and 95% confidence intervals (CI) for the association between patient and tumor characteristics, and the selection of cryotherapy as opposed to aggressive or non-aggressive standard forms of therapy. Rates of urinary, bowel and sexual function-related diagnoses and corrective invasive procedures occurring 3, 6 and 12 months following cryotherapy are presented. All analyses were carried out using SAS statistical software (version 9.1, SAS Institute, Cary, NC, USA). The study was approved by the University of Medicine and Dentistry of New Jersey Institutional Review Board.

## Results

A total of 380 patients (1.8%) underwent cryotherapy as initial treatment for localized prostate cancer and had at least 1 year of follow-up after cryotherapy (Table 1). The majority of participants treated with cryotherapy, radical prostatectomy or radiation therapy were 66–74 years, 61.3%, 92.2 and 62.6%, respectively, whereas the majority of men given ADT or conservative management were  $\geq 75$  years, 68.8 and 54.4%, respectively. Most men treated with cryotherapy were diagnosed as having intermediate-risk disease (50%), followed by low-risk (33.7%) and high-risk (16.1%) disease. Of cryotherapy patients, 70.5% had no co-morbidities, 22.1% had one co-morbidity and 7.4% had at least two co-morbidities.

In multivariate analyses, age, marital status, income, geographic region, Gleason score and Charlson co-morbidity score were significantly related to the selection of cryotherapy over aggressive therapies as initial treatment (Table 2). For instance, men  $\geq 75$  years were 1.58 (95% CI: 1.27, 1.95) times as likely to have cryotherapy than men 66–74 years. Income was inversely associated with the use of cryotherapy, such that men from low income were 1.46 (95% CI: 1.10, 1.93) times as likely to receive cryotherapy than men from higher income. Gleason score was the only tumor-related characteristic that was associated with cryotherapy use.

High-risk patients were less likely to be treated with cryotherapy than low-risk patients (odds ratios = 0.70;

**Table 1** Characteristics of patients treated with cryotherapy and standard forms of therapy for incident localized prostate cancer, SEER-Medicare

Characteristics	Cryotherapy (n = 380)	Aggressive standard therapies		Non-aggressive standard therapies	
		Radical prostatectomy (n = 3960)	Radiation therapy <sup>a</sup> (n = 10 757)	ADT (n = 3399)	Conservative management (n = 2848)
<b>Age (years)</b>					
66–74	61.3	92.2	62.6	31.2	45.6
75+	38.7	7.8	37.5	68.8	54.4
<b>Race</b>					
White	81.1	83.9	82.2	77.8	78.3
Black	12.1	8.0	10.4	13.6	14.7
Other	6.8	8.1	7.4	8.7	7.0
<b>Marital status<sup>b</sup></b>					
Married	66.8	81.8	75.0	56.4	57.3
Unmarried	22.1	14.5	19.6	23.0	24.0
Unspecified	11.1	3.7	5.3	20.7	18.8
<b>Income \$</b>	\$44 315	\$51 582	\$49 526	\$43 257	\$46 088
Median (IQR)	(\$33 090, \$57 677)	(\$39 208, \$70 418)	(\$36 371, \$66 651)	(\$31 507, \$59 650)	(\$33 294, 63 501)
<b>Region</b>					
South	32.4	12.4	17.4	20.5	18.1
North central	7.9	12.6	12.6	11.8	10.0
Northeast	10.0	10.4	26.5	17.8	15.2
West	49.7	64.7	43.5	49.9	56.7
<b>PSA (ng ml<sup>-1</sup>)</b>					
0–2.5	3.7	5.7	5.4	4.5	6.3
2.6–≤4.0	6.4	8.4	6.3	3.6	6.3
4.1–≤10	65.3	66.8	60.8	36.8	57.0
10.1–19.9	16.6	13.4	18.2	24.8	17.5
≥20	8.2	5.8	9.3	30.3	13.0
<b>Gleason score</b>					
2–6	46.1	36.8	48.5	32.7	64.3
7	44.2	49.8	36.7	37.3	24.8
8–10	9.7	13.4	14.9	30.0	10.9
<b>Clinical stage</b>					
T1	50.5	55.3	57.1	44.2	52.7
T2	49.5	44.7	42.9	55.8	47.3
<b>Risk<sup>c</sup></b>					
Low	33.7	28.1	34.6	17.7	46.6
Intermediate	50.3	54.0	44.2	36.0	34.4
High	16.1	18.0	21.3	46.3	19.0
<b>Charlson co-morbidity score</b>					
0	70.5	84.0	73.8	66.1	72.6
1	22.1	12.8	18.1	20.6	17.7
2+	7.4	3.2	8.1	13.3	9.8

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; SEER, Surveillance Epidemiology End Results.

$\chi^2$  test was used to assess the independence of patient demographic and clinical characteristics across treatment groups. All *P*-values were <0.001.

<sup>a</sup>Radiation therapy includes external beam radiation therapy and brachytherapy.

<sup>b</sup>Unmarried consists of men reported being separated, divorced or widowed.

<sup>c</sup>Patients were categorized into three risk groups on the basis of clinical classification, PSA level and Gleason score: low-risk (T1-T2a and PSA level <10 ng ml<sup>-1</sup> and Gleason score 2–6), intermediate-risk (T2b-T2c or 10 ≤ PSA ≤ 20 ng ml<sup>-1</sup> or Gleason score = 7) and high-risk (PSA level >20 ng ml<sup>-1</sup> or Gleason score 8–10).

95% CI: 0.51, 0.96) (Table 3). The use of cryotherapy did not vary between men with intermediate or low-risk disease (odds ratios = 1.00; 95% CI: 0.80, 1.26).

Within 3 months after undergoing cryotherapy, 23.7% of men were diagnosed with or treated for lower urinary tract obstruction (Table 4). Erectile dysfunction, urinary incontinence and bowel bleeding were prevalent in 4.0, 3.8 and <2.9% of men, respectively. By 6 months, the rate

of erectile dysfunction was more than tripled and urinary incontinence doubled. At 12 months following cryotherapy, lower urinary tract obstruction, erectile dysfunction, urinary incontinence and bowel bleeding rose to 28.7, 20.1, 9.8 and 3.3% respectively. No man had a diagnosis or corrective invasive procedure within 12 months following cryotherapy for hydronephrosis, urinary fistula or bowel fistula.

**Table 2** Adjusted<sup>a</sup> ORs (95% CIs) for factors associated with the selection of cryotherapy instead of aggressive standard therapy<sup>b</sup> in men diagnosed with incident localized prostate cancer, SEER-Medicare

Characteristics	OR	95% CI	P-value
<b>Age (years)</b>			
75+	1.58	(1.27, 1.95)	<0.001
66–74		Referent	
<b>Race</b>			
Black/Other	0.99	(0.75, 1.29)	0.910
White		Referent	
<b>Marital status<sup>c</sup></b>			
Unmarried/Unspecified	1.66	(1.33, 2.07)	<0.001
Married		Referent	
<b>Income</b>			
Lowest tertile	1.46	(1.10, 1.93)	0.008
Middle tertile	1.35	(1.03, 1.77)	0.031
Highest tertile		Referent	
<b>Region</b>			
South	1.81	(1.42, 2.31)	<0.001
North central	0.55	(0.37, 0.81)	0.003
Northeast	0.45	(0.31, 0.64)	<0.001
West		Referent	
<b>PSA (ng ml<sup>-1</sup>)</b>			
0.1–≤10		Referent	
10.1–19.9	0.92	(0.69, 1.21)	0.544
≥20	0.95	(0.65, 1.40)	0.805
<b>Gleason score</b>			
2–6		Referent	
7	1.04	(0.84, 1.29)	0.732
8–10	0.60	(0.41, 0.86)	0.006
<b>Clinical stage</b>			
T2	1.22	(0.99, 1.50)	0.059
T1		Referent	
<b>Charlson co-morbidity score</b>			
0		Referent	
1	1.41	(1.10, 1.81)	0.008
2+	1.15	(0.77, 1.71)	0.498

Abbreviations: CI, confidence interval; OR, odds ratio; SEER, Surveillance Epidemiology End Results.

<sup>a</sup>Adjusted for patient and tumor characteristics included in the table.

<sup>b</sup>Aggressive standard therapies include radical prostatectomy, external beam radiation therapy and brachytherapy.

<sup>c</sup>Unmarried consists of men reported being separated, divorced or widowed.

Of the patients diagnosed with urinary incontinence, no one had a corrective invasive procedure, <11 men had a procedure to alleviate lower urinary tract obstruction or to ameliorate erectile dysfunction.

## Discussion

In this population-based study, we found that cryotherapy remains a novel strategy to treat men initially diagnosed with clinically localized prostate cancer. We observed that besides disease-risk level that several demographic characteristics are significantly associated with receiving cryotherapy. In addition, among men with no previous history of treatment-related complications,

**Table 3** The adjusted<sup>a</sup> association between the selection of cryotherapy instead of aggressive<sup>b</sup> standard therapies in men diagnosed with incident localized prostate cancer, SEER-Medicare

NCCN criterion <sup>c</sup>	OR	95% CI	P-value
High	0.70	(0.51, 0.96)	0.026
Intermediate	1.00	(0.80, 1.26)	0.986
Low		Referent	

Abbreviations: CI, confidence interval; NCCN, The National Comprehensive Cancer Network; OR, odds ratio; SEER, Surveillance Epidemiology End Results.

<sup>a</sup>Adjusted for age, race, marital status, income, region and Charlson co-morbidity score.

<sup>b</sup>Aggressive standard therapies include radical prostatectomy, external beam radiation therapy and brachytherapy.

<sup>c</sup>Patients were categorized into three risk groups on the basis of clinical classification, PSA level and Gleason score: low-risk (T1-T2a and PSA level <10 ng ml<sup>-1</sup> and Gleason score 2–6), intermediate-risk (T2b-T2c or 10 ≤ PSA ≤ 20 ng ml<sup>-1</sup> or Gleason score = 7) and high-risk (PSA level >20 ng ml<sup>-1</sup> or Gleason score 8–10).

the rates of urinary incontinence, hydronephrosis, bowel bleeding, urinary fistula and bowel fistula post treatment were minimal. However, the rates of lower urinary tract obstruction and erectile dysfunction are common, but there is little need for ancillary corrective, invasive procedures.

Although men with high-risk disease were significantly less likely to receive cryotherapy than men with low-risk disease, nearly one in five men administered cryotherapy had high-risk disease (16.1%), indicating that in clinical practice cryotherapy is being used in patients with more aggressive cancers, (ie, men with PSA levels >20 ng ml<sup>-1</sup> or Gleason score 8–10). Albeit selection criteria for men undergoing prostate cryotherapy have yet to be definitively established, optimal candidates for this procedure generally include those with lower stage, lower-volume disease with PSA levels <20 ng ml<sup>-1</sup>.<sup>19</sup>

Interestingly, an inverse association between income and cryotherapy was observed. This may indicate that cryotherapy is becoming an attractive alternative for men with lesser means possibly in part because it is associated with shorter hospital stay, faster recovery time and is theoretically less costly than standard therapy.<sup>20</sup> Our findings support past studies, which have demonstrated that men with lower socioeconomic status were less likely to receive aggressive therapy in comparison with their richer counterparts.<sup>21</sup> For example, Cooperberg *et al.* recently reported that a greater percentage of men with an annual income of <\$20 000, \$20 000–\$30 000 or \$30 000–\$50 000 were treated with cryotherapy than men with an annual income ≥\$50 000.<sup>22</sup>

Of particular significance in our study, is the finding that the proportion of patients developing erectile dysfunction or urinary incontinence may increase over time, suggesting that the effects of cryotherapy may not only arise immediately after cryotherapy, but also remotely. For instance, from 6 to 12 months following treatment, the rates of erectile dysfunction increased from 13.2 to 20.1%, and urinary incontinence rose from 7.9 to 9.8%.

Complications occurring after cryotherapy have been widely studied in small single hospital-based studies. Reports of urinary incontinence ranged from 1.3 to 9.5%,<sup>7,9–12,14,23–25</sup> urinary strictures from 1.7 to 3.4%,<sup>10,12,14</sup> lower urinary tract obstruction/retention

**Table 4** Combined diagnoses and procedural related complications reported 3, 6 and 12 months after cryotherapy in men diagnosed with incident localized prostate cancer and no previous history of treatment. related morbidity, SEER-Medicare

Complication	3 months		6 months		12 months	
	n	%	n	%	n	%
Lower urinary tract obstruction <sup>a</sup>	78	23.7	90	27.4	94	28.7
Erectile dysfunction <sup>b</sup>	14	4	46	13.2	70	20.1
Urinary incontinence <sup>c</sup>	14	3.8	29	7.9	36	9.8
Bowel bleeding <sup>d</sup>	<11	<2.9	<11	<2.9	12	3.3
Hydronephrosis <sup>e</sup>	0	0	0	0	0	0
Urinary fistula <sup>f</sup>	0	0	0	0	0	0
Bowel fistula <sup>g</sup>	0	0	0	0	0	0

Abbreviation: SEER, Surveillance Epidemiology End Results.

<sup>a</sup>Lower urinary tract obstruction included medical claim of dilation, urethrotomy, urethroplasty, sphincterotomy, transurethral prostate resection/destruction, urethral stent or injection for stricture occurring. In all, 328 men had no previous history of urinary obstruction before cryotherapy.

<sup>b</sup>Erectile Dysfunction included medical claim for penile prosthesis or intracavernosal. In all, 349 men had no previous history of erectile dysfunction before cryotherapy.

<sup>c</sup>Urinary incontinence included a medical claim of urethra sphincter injection, artificial sphincter or incontinence repair (sling, urethroplasty) occurring. In all, 368 men had no previous history of urinary incontinence before cryotherapy.

<sup>d</sup>Bowel bleeding included hemorrhage or inflammation. In all, 359 men did not have bowel bleeding before cryotherapy.

<sup>e</sup>Hydronephrosis is distention of the renal pelvic and calices of the kidney with urine.

<sup>f</sup>Bowel Fistula included medical claims of rectal repair, colostomy or ulcer.

<sup>g</sup>Urinary Fistula was defined as medical claims with repair of bowel-bladder fistula or closure of urethrostomy or urethrocutaneous fistula occurring.

from 13 to 23%,<sup>24,26–28</sup> bowel bleeding was 2.0%,<sup>12</sup> and erectile dysfunction from 47 to 94.9%.<sup>7,10,11,14</sup> Consistently, cryotherapy was found to be associated with a low rate of fistulas (<1%) several years after the procedure.<sup>7,10–14</sup>

In our cohort of men receiving prostate cryotherapy, no urinary or bowel fistulas or hydronephrosis were reported, and bowel bleeding was observed to be low at 12 months after cryotherapy. The 12-month rates of lower urinary tract obstruction and urinary incontinence in this study were greater than reported in previous studies. The higher complication rates found in this study may reflect differences in the definition of the complications, the use of population-based data as opposed to hospital-based data or publication bias. In particular, the higher rates of postoperative urinary incontinence may be indicative of the higher rates of mild to severe urinary symptoms in older men<sup>29,30</sup> that often is underreported,<sup>30,31</sup> and a larger prostate volume,<sup>32</sup> which interferes with urinary incontinence. Thus, the older men in this study may have some degree of pre-existing urinary dysfunction or larger prostate, which may augment their risk of urinary incontinence post cryotherapy. The rate of erectile dysfunction in this study was lower than previous estimates and may be attributed to our study population consisting of men 66 years of age or older. Older men may not be as concerned about reporting and treating erectile dysfunction as younger men. In addition, some cases of erectile dysfunction may not have been identified because we lacked validated instruments to assess erectile dysfunction such as the International Index of Erectile Function,<sup>33</sup> the Quality of Erection Questionnaire<sup>34</sup> or the Sexual Health Inventory

for Men.<sup>35</sup> It is also feasible that the rate of erectile dysfunction may have been underestimated during the study period because some patients may have used devices or agents (eg, vacuum erection device, internal penile pump, phosphodiesterase type 5 inhibitors) to rectify their erectile dysfunction.

The postoperative complication rates may also vary across studies because of differences in tumor characteristics (eg, gland size), rates of complications pre-cryotherapy (eg, impotency), duration of follow-up, definition of complications, inclusion of men with a history of TURP, use of previous treatments (eg, external beam radiation therapy) and the generation of the cryotherapy device(s).

An advantage of this study is that updated data pertaining to cryotherapy were used. Previous studies reported outcomes when cryotechnology and imaging were evolving.<sup>7,9–14,23</sup> As thereafter, further technological advancements in the field have been achieved, such as the use of argon gas instead liquid nitrogen, which has enabled cryotherapy to be delivered in a more precise, safer and efficacious manner.<sup>3,36</sup> Consequently, our findings provide valuable insight into the prevalence of morbidity associated with this treatment in a technologically more advanced era.

Certain limitations of our study warrant mention. Although our findings likely reflect clinical practice in the United States because the SEER database covers 26% of the United States population, we were unable to explore the influence of other pertinent risk factors, such as gland volume and configurations. Additionally, given that the data for this study were extracted from administrative claims data, we were unable to evaluate erectile dysfunction and urinary complications using validated instruments of quality of life.<sup>33–35</sup> Thus, the rates of these complications may be underestimated. Further, because of the inherent limitations of using administrative claims data, we were unable to decipher the generation of the cryotherapy devices that were performed on patients. However, given that the procedures occurred within a narrow window of time from 2004 to 2005, variation in the generation of the cryotherapy devices used was most likely minimized.

The results from this study may not be generalizable to younger men because Medicare consists of men 65 years and older. We also could not distinguish between whole-gland cryotherapy and focal cryotherapy, as current procedural codes do not exist to allow for this differentiation. Finally, the use of administrative claims to estimate treatment-related complications may result in an underestimation of the true complication prevalence.

In summary, our findings provide an estimate of contemporary post-treatment complications associated with cryotherapy. The results from this study suggest that among men diagnosed with localized prostate cancer that morbidity post cryotherapy is modest; lower urinary tract obstruction and erectile dysfunction remain common following cryotherapy; complications can manifest even 1 year after treatment; and a small proportion of men may require invasive corrective procedures to address these complications. Patients should be fully informed of the complications presented herein, as well as the lack of well-controlled or randomized studies supporting its efficacy.

## Conflict of interest

The authors declare no conflict of interest.

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## Disclaimer

This study utilizes the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The content of the information does not necessarily reflect the position or the policy of the Government or the employers, and no official endorsement should be inferred.

## References

- Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004; **22**: 2141–2149.
- Dale W, Bilir P, Han M, Meltzer D. The role of anxiety in prostate carcinoma: a structured review of the literature. *Cancer* 2005; **104**: 467–478.
- Babaian RJ, Donnelly B, Bahn D, Baust JG, Dineen M, Ellis D *et al*. Best practice statement on cryosurgery for the treatment of localized prostate cancer. *J Urol* 2008; **180**: 1993–2004.
- Saliken JC, Donnelly BJ, Rewcastle JC. The evolution and state of modern technology for prostate cryosurgery. *Urology* 2002; **60**: 26–33.
- Sartor AO, Hricak H, Wheeler TM, Coleman J, Penson DF, Carroll PR *et al*. Evaluating localized prostate cancer and identifying candidates for focal therapy. *Urology* 2008; **72**: S12–S24.
- Malcolm JB, Fabrizio MD, Barone BB, Given RS, Lance DF, Lynch JW *et al*. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. *J Urol* 2010; **183**: 1822–1828.
- Coogan CL, McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. *J Urol* 1995; **154**: 1813–1817.
- Ellis DS, Manny Jr TB, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. *Urology* 2007; **70**: 9–15.
- Donnelly BJ, Saliken JC, Ernst DS, Ali-Ridha N, Brasher PM, Robinson JW *et al*. Prospective trial of cryosurgical ablation of the prostate: five-year results. *Urology* 2002; **60**: 645–649.
- Aus G, Pileblad E, Hugosson J. Cryosurgical ablation of the prostate: 5-year follow-up of a prospective study. *Eur Urol* 2002; **42**: 133–138.
- Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology* 2002; **60**: 3–11.
- Cohen JK. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. *Urology* 1996; **48**: 178–180.
- Prepelica KL, Okeke Z, Murphy A, Katz AE. Cryosurgical ablation of the prostate: high risk patient outcomes. *Cancer* 2005; **103**: 1625–1630.
- Long JP, Fallick ML, LaRock DR, Rand W. Preliminary outcomes following cryosurgical ablation of the prostate in patients with clinically localized prostate carcinoma. *J Urol* 1998; **159**: 477–484.
- Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002; **40**: IV-3–IV-18.
- Shinohara K, Connolly JA, Presti Jr JC, Carroll PR. Cryosurgical treatment of localized prostate cancer (stages T1 to T4): preliminary results. *J Urol* 1999; **15**: 115–121.
- Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. Dec 2000; **53**: 1258–1267.
- National Comprehensive Cancer Network 2010 Available at: <http://www.nccn.org>. Accessed (March 15, 2010).
- Finley DS, Pouliot F, Miller DC, Belldgrun AS. Primary and salvage cryotherapy for prostate cancer. *Urol Clin North Am* 2010; **37**: 67–82.
- Ritch CR, Katz AE. Prostate cryotherapy: current status. *Curr Opin Urol* 2009; **19**: 177–181.
- Kane CJ, Lubeck DP, Knight SJ, Spitalny M, Downs TM, Grossfeld GD *et al*. Impact of patient educational level on treatment for patients with prostate cancer: data from CaPSURE. *Urology* 2003; **62**: 1035–1039.
- Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol* 2010; **28**: 1117–1123.
- Wong WS, Chinn DO, Chinn M, Chinn J, Tom WL. Cryosurgery as a treatment for prostate carcinoma: results and complications. *Cancer* 1997; **9**: 963–974.
- Long JP, Bahn D, Lee F, Shinohara K, Chinn Do, Macaluso Jr JN. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. *Urology* 2001; **57**: 518–523.
- Kimura M, Mouraviev V, Tsivian M, Moreira DM, Mayes JM, Polascik TJ. Analysis of urinary function using validated instruments and uroflowmetry after primary and salvage prostate cryoablation. *Urology* 2010; **76**: 1258–1265.
- Long JP. Is there a role for cryoablation of the prostate in the management of localized prostate carcinoma? *Hematol Oncol Clin North Am* 1996; **10**: 675–690.
- Shinohara K, Rhee B, Presti Jr JC, Carroll PR. Cryosurgical ablation of prostate cancer: patterns of cancer recurrence. *J Urol* 1997; **158**: 2206–2210.
- Wake RW, Hollabaugh Jr RS, Bond KH. Cryosurgical ablation of the prostate for localized adenocarcinoma: a preliminary experience. *J Urol* 1996; **155**: 1663–1666.
- Markland AD, Goode PS, Redden DT. Prevalence of urinary incontinence in men: results from the national health and nutrition examination survey. *J Urol* 2010; **84**: 1022–1027.
- Diokno AC, Estanol MVC, Ibrahim A, Balasubramaniam M. Prevalence of urinary incontinence in community dwelling men: a cross sectional nationwide epidemiological survey. *Int Urol Nephrol* 2007; **39**: 129–136.
- Dugan E, Roberts CP, Cohens SJ, , Preisser JS, , Davis CC, Bland DR *et al*. Why older community-dwelling adults do not discuss urinary incontinence with their primary care physicians. *J Am Geriatr* 2001; **49**: 462–465.
- Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999; **53**: 581–589.

- 33 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): A multi-dimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–830.
- 34 Rhoden EL, Telöken C, Sogari PR, Vargas Souto CA. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. *Int J Impotence Res* 2002; **14**: 242–250.
- 35 Wei J, Dunn R, Litwin M, Sandler H, Sanda M. Development and Validation of the Expanded Prostate Cancer Index Composite (EPIC) for Comprehensive Assessment of Health-Related Quality of Life in Men with Prostate Cancer. *Urology* 2000; **56**: 899–905.
- 36 De La Taille A, Benson MC, Bagiella E, Burchardt M, Shabsigh A, Olsson CA *et al*. Cryoablation for clinically localized prostate cancer using an argon-based system: complication rates and biochemical recurrence. *BJU Int* 2000; **85**: 281–286.

**Appendix A** Definitions of complications following cryotherapy

Complications	Medical codes		
	Diagnoses	Procedures	
	ICD-9-CM	ICD-9-CM	CPT/HCPCS
<i>Erectile</i>			
Impotence, dysfunction	607.84		
Penile prosthesis		64.94, 64.95, 64.96, 64.97	54400, 54401, 54402, 54405, 54407, 4408, 54409, 54410, 54411, 54415, 54416, 54417, C1007, C1813, C2622, C3500, C8514, C8516, C8534, L7900
Intracavernosal injection			54231, 54235, J0270, J0275, J2440, J2760
<i>Lower urinary tract obstruction</i>			
Stricture, obstruction, retention	596.0, 598x, 599.6, 788.2x		
Dilation, urethrotomy, urethroplasty, sphincterotomy		57.85, 57.91, 57.92, 58.0, 58.1, 58.3x, 58.44, 58.46, 58.47, 58.5, 58.6, 58.99, 60.95, 60.2x	52275, 52276, 52281, 52510, 53010, 53400, 53405, 53410, 53415, 53420, 53425, 53600, 53601, 53605, 53620, 53621
Transurethral prostate resection/destruction			52601, 52612, 52614, 52620, 52630, 53850, 53852
Urethral stent			2282
Injection for stricture			52283
<i>Urinary incontinence</i>			
Incontinence, sphincter, deficiency	788.3x, 599.82		
Urethra, sphincter injection		59.72	51715
Artificial sphincter		58.93	53445, 53447
Incontinence repair (sling, urethroplasty)		59.3, 59.4, 59.5, 59.6, 59.71, 59.79	53440, 51840, 51841, 53442, 53443
<i>Urinary fistula</i>			
Urethral fistula	596.1, 596.2, 599.1	57.83, 57.84, 58.43	44660, 44661, 53520
Intestinovesical fistula	5991		
Vesical fistula NEC	5961		
Repair of a bowel-bladder fistula or closure of urethrostomy	5962	5783, 5784, 5843	44660, 44661, 53520
<i>Bowel fistula</i>			
Fistula, ulcer	569.41, 569.81	48.73, 48.93	45800, 45805, 45820, 45825
Rectal repair, colostomy		46.1x, 48.31, 48.32, 48.33	45562, 45563
<i>Hydronephrosis</i>			
Distention of the renal pelvic and calices of the kidney with urine	591		
<i>Bowel bleeding</i>			
Hemorrhage, inflammation	558.1, 569.3, 578.9		

Abbreviations: CPT, current procedural terminology; HCPCS, Health Care Financing Administration Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification.  
Medical codes regarding diagnoses and corrective invasive procedures for complications occurring after cryotherapy as initial treatment for prostate cancer.