CRYOSURGERY FOR PROSTATE CANCER: A COMPREHENSIVE REVIEW

Einar Sverrisson, J. Stephen Jones and Julio M. Pow-Sang.

Department of Genito-Urinary Oncology. Moffitt Cancer Center.
1Department of Urology. Cleveland Clinic Foundation. USA

Summary.- OBJECTIVES: Cryosurgery for prostate cancer has evolved to become a reasonable treatment alternative for localized prostate cancer. The advent of third-generation machines and smaller cryoprobes together with better imaging modalities allows for precise treatment of the prostate in the primary, salvage and focal setting.

METHODS: A comprehensive review of the literature was performed from 1980 to January 2013 searching the Medline database. Information was extracted regarding oncologic and functional outcomes.

RESULTS: The outcomes of cryosurgery improved over time with intermediate biochemical disease free survival rates now comparable to other treatment modalities. Initially reported in the salvage setting after radiation therapy, the technology was subsequently expanded as primary treatment and more recently for focal therapy. With introduction of the third-generation cryosurgery system and better imaging modalities, the treatment related morbidities have decreased.

CONCLUSIONS: Oncologic and functional outcomes have improved and the procedure is increasing in use. Variable inclusion criteria and follow-up protocols still call for prospective studies to establish the efficacy of the procedure as compared to established local management options.

Keywords: Prostate cancer. Primary cryosurgery. Focal cryosurgery.

Resumen.- OBJETIVO: La criocirugía del cáncer de próstata ha evolucionado hasta convertirse en un tratamiento alternativo razonable para el cáncer de próstata localizado. La llegada de la tercera generación de máquinas y crio sondas más pequeñas junto con mejores técnicas de imagen permiten un tratamiento preciso de la próstata en el escenario principal, de rescate y focal.

MÉTODOS: Se llevó a cabo una revisión exhaustiva de la literatura desde 1980 a enero de 2013 buscando en la base de datos Medline. Se extrajo información con respecto a los resultados oncológicos y funcionales.

RESULTADOS: Los resultados de la criocirugía han mejorado con el tiempo, con tasas de supervivencia libre de enfermedad bioquímica ahora comparables con otras modalidades de tratamiento. Inicialmente descrita en el contexto de rescate tras la radioterapia, la tecnología...
INTRODUCTION

Prostate cancer (PC) is being detected at earlier, organ confined stages as compared to the recent past. Many of these cancers are clinically insignificant and can be initially managed by active surveillance. When the cancer is clinically significant, curative interventions with radical prostatectomy (RP) or radiation therapy (RT) are then considered. While not widely performed, primary cryosurgery (PCS) is a safe and acceptable additional primary treatment option for localized, clinically significant PC. With the realization that some cancers are either unifocal or in cases of multifocal lesions where only one of the lesions appears to be the clinically significant focus that will drive the biological potential of the cancer, focal therapy is a treatment alternative in the management of these very early cancers. Better imaging techniques and biopsy protocols are allowing for better selection of men who might benefit from this less invasive approach. Salvage cryosurgery (SCS) is another application for this technology in men with local recurrence of PC after primary RT or PCS.

Cryosurgery was initially primarily used as a salvage treatment option for patients who had failed radiation therapy, based on the limited alternatives available for this challenging clinical scenario. However, with emerging evidence of better intermediate oncological and functional outcomes, it has become an acceptable option for primary treatment of localized prostate cancer and more recently FCS. However, the comparison of outcomes is challenging due to variability in treatment protocols, including definition of biochemical failure, androgen deprivation, number of allowed treatments, and different follow-up schedules.

MECHANISM OF ACTION

By using hollow needles, argon and helium gases, freezing and thawing of the targeted tumor tissue can be achieved. Rapid freezing rate, low temperature threshold reached (-40°C), rapid thawing rate, and double freeze-thaw cycles have been shown to correlate with cancer cell destruction (1-6). When freezing is reached, the extracellular fluid begins to crystallize, resulting in hyperosmolar pressure of the surrounding extracellular fluid compartment and a subsequent water shift from the intracellular to the extracellular space occurs. Cellular dehydration and acidosis result in denaturing of cellular proteins. Cell metabolism begins to fail, resulting in apoptosis. During the thawing process, vasodilatation of the surrounding tissues leads to endothelial damage and formation of micro thrombi, with resulting tissue hypoxia. After two freeze cycles at freezing to temperatures targeted to achieve -40°C exposed tissue undergoes death (7).

PROCEDURE

Cryosurgery is performed under general or occasionally regional anesthesia. The patient is positioned in the dorsal lithotomy position. An ultrasound probe is introduced per rectum afixed to a supporting device and a urethral warmer introduced through the urethra into the bladder over a cystoscopically placed guidewire following probe
placement. The cryo-probes are percutaneously placed under ultrasound guidance into the prostate and temperature monitors placed into Denonvilliere’s, apex and external urinary sphincter. Two freeze-thaw cycles are delivered and at the completion of the procedure, the probes are removed and the urethral warmer is kept running for an 20 minutes to prevent urethral injury. The procedure takes approximately 60 minutes.

Some surgeons inject normal saline solution or other agents, including autologous blood, into the space between prostate and rectum to separate the structures in order to minimize freezing injury to the latter.

**PRIMARY CRYOSURGERY**

Primary cryosurgery is a treatment option for men with localized PC (T1c-T3) of any grade. Most of the studies focusing on PCS are retrospective in nature with a median follow-up ranging from 3-60 months. Although long-term survival data are lacking for PCS, 60-90% biochemical disease-free survival (bDFS) at 5 to 10 years has been reported (8-13). Many authors also report 5 to 10 years bDFS stratified according to the D’Amico risk classification and ranging from 60-90% for low risk, 60-80% for intermediate risk and 45-70% for high risk patients (8-12).

In 2008, Cohen et al published 10-year outcome data on 204 patients treated with PCS for localized PC. At a median follow-up of 12.6 years, they reported bDFS (Phoenix criteria) rates of 80.6%, 74.2%, and 45.5% for low, moderate, and high risk patients, respectively. Biopsies were recommended at 3 to 6 months postoperatively and again in 2 to 5 years. The 10-year negative biopsy rate (76.96%) was favorable and the average number of post-treatment biopsies per patient was two. Thirty-one (15.2%) patients underwent 2 treatments and one received 3 treatments for biopsy proven recurrence. Their results suggested that patient’s age, pre-operative and nadir PSA levels were associated with treatment failure (9).

In 2008, Jones and colleagues reported the initial results from the largest database available, the COLD (Cryo On-Line Data) base. This is a secure online database, consisting of case report forms designed to collect perioperative information on patients treated with cryosurgery for PC. A total of 1,198 men treated with PCS by 27 physicians were identified. At a median follow-up of 24 months, using the ASTRO (American Society for Therapeutic Radiology and Oncology) criteria for biochemical failure, the 5-year overall bDFS was 77.1% and when stratified according to the D’Amico’s risk classification, low risk, intermediate risk and high risk were 85%, 73% and 75%, respectively. They also reported bDFS rates using the Phoenix criteria (nadir+2ng/ml) and the 5-year rates were slightly different as expected (91%, 79% and 62% for low, intermediate and high risk patients respectively). A total of 336 (28%) patients underwent post-treatment biopsy and of those with biochemical recurrence, 38% (49 of 129) had positive biopsy compared to 14.5% (30 of 207) of those who underwent biopsy in the absence of biochemical failure. The urinary incontinence rate was low and only 2.9% required pads. Of the 354 men who were potent prior to treatment, 25.2% had returned to intercourse but only 8.8% did not require any pharmacological or device assistance (11).

More recently, Dhar et al used the same database to study older patients (> age of 75 years) treated with PCS. They stratified 860 patients according to the D’Amico risk classification and used both the ASTRO and the Phoenix criteria to define biochemical failure. At a median follow-up of 16 months, the 5-year bDFS were comparable to the Jones data. The 5-year rates were 82.4%, 78.3%, 77.6% (ASTRO), and 74.9%, 61.4%, and 58% (Phoenix) for low, moderate and high risk, respectively (14).

Polascik et al treated 50 men with PCS, with the majority consisting of low risk (72%) by D’Amico risk stratification. Thirteen (26%) men received neoadjuvant hormonal therapy due to enlarged prostate (>40 cm3). Using a PSA level of 0.5 ng/ml or greater to define failure, forty-five (90%) patients had no evidence of recurrence at a median follow-up of 18 months. Two (4%) of the 5 men who failed treatment underwent a biopsy which demonstrated persistent tumor and they were subsequently treated with salvage cryotherapy or RT. The PSA levels in two patients normalized but one’s continued to rise. Of the 6 men who were potent preoperatively, 3 (50%) responded to 5-phosphodiesterase inhibitors and the urinary continence rate was excellent (47 of 49 were completely continent and 2 required 1-2 pads per day) (15).

More recent trials have demonstrated similar oncological and functional outcomes. Lian and colleagues treated 102 men with T1c-T2c PC and reported a bDFS of 92.2% (failure defined as a PSA level >0.5 ng/ml) at a median follow-up of 30 months (range 9-56). The rates of urinary incontinence and impotence were 4% and 64.1%, respectively (16) (Tables I and II).

Although PCS is an acceptable treatment option for localized PC, recent randomized trial comparing PCS and external beam radiation therapy
for locally advanced PC showed unfavorable outcomes for PCS. Chin et al randomized 64 patients with locally advanced PC (T2c-T3b) to either PCS (33) or EBRT (31). All patients received 6 months of hormone (luteinizing hormone-releasing hormone (LHRH) agonist) therapy (3 months prior and 3 months after the treatment) and the patients in the EBRT group received 66 Gy in 33 fractions. At a median follow up of 37 months, the biochemical failure rate (ASTRO definition) was significantly higher in the PCS group. The 4-year bDFS for the PCS and EBRT groups were 13% versus 47%, respectively. However,

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow up (months)</th>
<th>Cryogen System</th>
<th>BR</th>
<th>bDFS (%)</th>
<th>OS (%)</th>
<th>Biopsy positive (%)</th>
<th>ADT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(38)Ko (3 years), n=33</td>
<td>61</td>
<td>3rd</td>
<td>ASTRO</td>
<td>90.9 HR</td>
<td>88</td>
<td>none</td>
<td>100</td>
</tr>
<tr>
<td>(16)Lian, n=102</td>
<td>30</td>
<td>3rd</td>
<td>&gt;0.5</td>
<td>92.2 all</td>
<td>100</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>(39)El Hayek (5 years), n=21</td>
<td>41</td>
<td>3rd</td>
<td>&gt;1.0</td>
<td>42.8 HR</td>
<td>-</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>(40)El Hayek (4 years), n=40</td>
<td>41</td>
<td>3rd</td>
<td>&gt;1.0</td>
<td>80 LR/42.8</td>
<td>-</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>(13)Prepelica (6 years), n=65</td>
<td>35</td>
<td>3rd</td>
<td>ASTRO</td>
<td>83 all</td>
<td>-</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>(41)Cresswell (1 year), n=31</td>
<td>9</td>
<td>3rd</td>
<td>&gt;0.5</td>
<td>60 LR/60HR</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(15)Polascik, n=50</td>
<td>18</td>
<td>3rd</td>
<td>&gt;0.5</td>
<td>90 all</td>
<td>100</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>(11)Jones (5 years), n=1198</td>
<td>24</td>
<td>2nd/3rd</td>
<td>ASTRO</td>
<td>85 LR/73</td>
<td>-</td>
<td>14.5/38</td>
<td>-</td>
</tr>
<tr>
<td>(42)Hubosky (2 years), n=89</td>
<td>11</td>
<td>3rd</td>
<td>&gt;0.4</td>
<td>74 LR/70</td>
<td>-</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>(9)Cohen (10 years), n=204</td>
<td>151</td>
<td>2nd</td>
<td>Phoenix</td>
<td>81 LR/74</td>
<td>-</td>
<td>25.6</td>
<td>-</td>
</tr>
<tr>
<td>(18)Chin (8 years), n=33</td>
<td>105.2</td>
<td>3rd</td>
<td>ASTRO</td>
<td>17 locally</td>
<td>60</td>
<td>22.6</td>
<td>100</td>
</tr>
<tr>
<td>(19)Donnelly (5 years), n=122</td>
<td>100</td>
<td>3rd</td>
<td>Phoenix</td>
<td>75 all</td>
<td>90</td>
<td>7.7</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO, American Society for Therapeutic Radiology and Oncology; BR, biochemical recurrence; ADT, Androgen Deprivation Therapy; OS, Overall Survival; bDFS, biochemical Disease Free Survival; HR, High Risk; IR, Intermediate Risk; LR, Low Risk.
no difference was noted in disease-specific survival (DSS) and overall survival (OS) (17). In 2012, the same group published their follow-up data. Sixty-two patients completed the trial with a median follow-up of 105.2 months. No difference was noted in OS and DSS, but the bDFS continued to be significantly lower in the PCS group compared to the EBRT group at 8-years (17.4% versus 59.1%, \( p=0.01 \)) (18).

Another randomized trial conducted by Donnelly and associates compared EBRT and PCS for men with localized PC (the majority were high risk patients). They randomized 244 patients to receive either PCS or EBRT (median dose 68 Gy) and the median follow-up was 100 months. A repeat cryosurgery was allowed for patients who had a PSA recurrence within 6 months from initial treatment (only 1 patient underwent second treatment within 6 months). All patients received LHRH agonist prior to the definitive treatment. The primary endpoint was defined as disease progression 36 months after randomization. This was based on a trifecta definition which included radiologic evidence of metastatic disease, initiation of further antineoplastic therapy or biochemical failure. When defining biochemical recurrence as two consecutive rises in PSA with a final value >1.0 ng/ml, an insignificant difference in disease progression was noted at 36 months, 23.9% versus 23.7%, favoring the EBRT arm. Using the Phoenix criteria, the rates for the PCS and the EBRT groups were 17.1% and 13.2%, respectively. However at 84 months the failure rate was lower in the PCS group compared to the EBRT group, 27% versus 31.7%, respectively. Moreover, at 36 months the positive biopsy rate was higher amongst patients treated with EBRT (28.9% versus 7.7%). The 5-year OS rates were similar (PCS 89.7% versus EBRT 88.3%) and both treatment modalities were well tolerated (mostly grade 1-2 toxicities reported). PCS was associated with more acute urinary dysfunction and worse sexual functioning at 3 months and at 3 years (19, 20).

**FOCAL CRYOSURGERY**

The goal of focal cryosurgery (FCS) is to treat the area within the prostate containing the clinically significant lesion while minimizing the side effects associated with whole gland treatment. The first challenge is to appropriately select candidates as many men with early, localized prostate cancer are better managed by active surveillance. With improvements in imaging technology and biopsy protocols, FCS has become a more feasible treatment option, especially for men with low volume tumors who are interested in maintaining potency.

### Table II. Complications related to primary cryosurgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>Incontinence (%)</th>
<th>Impotence (%)</th>
<th>Fistula (%)</th>
<th>Need for TURP (%)</th>
<th>Voiding Symptoms (%)</th>
<th>UTI (%)</th>
<th>Stricture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(38)Ko</td>
<td>None</td>
<td>-</td>
<td>None</td>
<td>-</td>
<td>33</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>(16)Lian</td>
<td>4</td>
<td>64.1</td>
<td>None</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>none</td>
</tr>
<tr>
<td>(39)El Hayek</td>
<td>12</td>
<td>93</td>
<td>None</td>
<td>8</td>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(40)El Hayek</td>
<td>12.5</td>
<td>96.4</td>
<td>None</td>
<td>9</td>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(13)Prepelica</td>
<td>3.1</td>
<td>-</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(41)Cresswell</td>
<td>-</td>
<td>100</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(15)Polascik</td>
<td>3.7</td>
<td>100</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>(11)Jones</td>
<td>2.9</td>
<td>91</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(42)Hubosky</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>none</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: TURP, Transurethral Resection of Prostate; UTI, Urinary Tract Infection
Onik et al. published their pilot study in 2002 in which they treated 9 patients with FCS demonstrating safety and feasibility. More recently, they reported their experience in 48 patients with low or intermediate risk PC. At a mean follow up of 54 months, they found that 45 (94%) patients had stable PSA according to ASTRO criteria. The post-treatment biopsy rate was 53% at 1 year and more importantly, no recurrences were detected. They also reported excellent functional outcomes, with a potency and urinary continence rates of 90% and 100%, respectively (21).

In 2007, Ellis and associates reported their outcomes in 60 patients with FCS. The majority (90%) of patients had low or intermediate risk PC. The bDFS rate was 80.4% (ASTRO criteria) at a mean follow-up of 16.7 months. Thirty-five patients underwent post-treatment biopsy and 14 (23.3%) had evidence of recurrent disease after their initial treatment. Eleven patients underwent a second cryoablation and 66% were subsequently cancer free. Twenty-four (70.6%) of the 34 patients who were potent pre-operatively regained potency within 12 months. Two (3.6%) had minor urinary incontinence after 6 months of follow-up, without requiring pads (22).

Another small study by Lambert et al was published in 2007. They treated 25 men with unifocal (clinical T1c), low or intermediate risk PC. Since only part of the prostate was treated, they defined a biochemical recurrence as a PSA nadir + 2 ng/ml or PSA nadir of less than 50%, and those patients who failed treatment underwent a post-treatment biopsy. According to the previously described definition, 21 (84%) of 25 patients had no evidence of biochemical recurrence at a mean follow up of 28 months. Seven patients underwent post-treatment biopsy and recurrent tumor was detected in 3 patients, although 2 of them had contralateral lesion. No patient reported urinary incontinence and 17 (71%) remained potent (23).

Bahn et al treated 31 patients with unilateral, low or intermediate risk PC. Post-treatment PSA levels were available for 28 patients. The mean follow-up was 70 months and the bDFS (ASTRO) was 92.9%. Twenty-five patients underwent on average 2.36 post-treatment biopsies with a negative of 96%. Thirteen (48.1%) men regained full potency in addition to 11 (40.7%) who required oral pharmaceutical agents. No other complications were reported, including urinary incontinence (24).

Another retrospective study by Bahn et al was published in 2012. Seventy-three men with clinically unilateral, low to intermediate risk (PSA <20, Gleason score <7, clinical stage T1-T2b) PC were included and treated with FCS. These patients were followed on average for 3.7 years. They did not define biochemical failure but reported a 70% lower post-treatment PSA level (1.6 ng/ml versus 5.9 ng/ml). A post-treatment biopsy was recommended at 6-12 months and then yearly and as indicated. Of the 48 patients who underwent biopsy, 36 (75%) had no evidence of recurrent tumor. The majority (92%) of the positive biopsies were found in the untreated contralateral gland. All patients were completely continent and 86% regained potency sufficient for intercourse. They also performed a pair matched analysis, comparing these patients with 68 men treated with radical prostatectomy. No significant difference was noted in salvage-therapy-free survival amongst these groups (25).

In 2010, Truesdale and colleagues published their results on 77 men treated with FCS at a single academic institution. They stratified patients according to the 2007 Task Force on Prostate Cancer and the Focal Lesion Paradigm (ITF-FLP) selection criteria (17 patients met the criteria) and defined disease progression according to the Phoenix criteria or positive biopsy results. Twenty-two (29%) patients underwent a post-treatment biopsy based on clinical suspicion and 10 (45.5%) were positive. Given these findings, the authors suggested that all patients treated with FCS should undergo post-treatment biopsy. The overall biochemical and pathological progression-free survival rates were 72.7% and 87%, respectively. Twenty-seven patients had at least 3 years of follow-up and the biochemical and pathological progression-free survival rates were 77.8% and 85.2%, respectively. Pre-treatment PSA level, Gleason score, number of positive cores, and tumor length were associated with disease progression (most of these factors are addressed by the ITF-FLP criteria). Interestingly, there was no survival difference noted when the stratified group was compared to the rest of the cohort (27, 28).

A small retrospective study by Hale et al reported on their experience with FCS in low risk patients. Twenty-six patients were treated and a biochemical recurrence was defined as an increase in PSA level of 0.50 ng/ml over nadir. At a mean follow-up of 19.1 months, the biochemical failure was
11.5%. Seven (27%) patients had erectile dysfunction after treatment and no urinary incontinence or voiding symptoms were reported (29).

Barret et al prospectively collected data on 106 patients to investigate the morbidity associated with focal therapy. Pre- and post-treatment PSA levels, International Prostate Symptom Score (IPSS), and International Index of Erectile Function (IIEF-5) were registered. Fifty (47%) patients were treated with FCS, 23 (22%) had vascular-targeted photodynamic therapy, 21 (20%) underwent high-intensity focused ultrasound, and 12 (11%) received brachytherapy. The baseline median PSA level in the FCS group was 6.2 ng/ml and at 3, 6, and 12 months post surgery 2.9, 2.8, and 2.5, respectively. The authors did not report biopsy outcomes but biopsy was recommended 1 year after treatment. The rate and severity of complications associated with FCS was acceptable. Nine (18%) patients experienced complications related to FCS. Five (56%) were grade 1 but there were two grade 3b. One patient developed a rectal fistula, requiring diverting colostomy and the other one had a urethral stricture requiring visual internal urethrotomy. At 12 months, the IPSS and IIEF-5 scores had decreased from 9 to 5 and 19 to 14, respectively (30) (Table III).

**SALVAGE CRYOSURGERY**

Approximately 25-30% of men treated with radiation for PC will have positive post-treatment biopsy (31-33). Many of those patients elect to undergo salvage treatment, either additional RT, RP or cryosurgery. Like for PCS and FCS, the definition of biochemical failure varies and most series define failure based on ASTRO, Phoenix, or a single PSA level.

### Table III. Oncological and functional outcomes of focal cryosurgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow up (months)</th>
<th>BR</th>
<th>bDFS (%)</th>
<th>Potency (%)</th>
<th>Continence (%)</th>
<th>Gleason ≤6 (%)</th>
<th>Clinical tumor stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>(26) Ward, n=1160</td>
<td>36</td>
<td>ASTRO</td>
<td>75.7</td>
<td>58.1</td>
<td>98.4</td>
<td>74</td>
<td>87% ≤T2b</td>
</tr>
<tr>
<td>(28) Truesdale, n=77</td>
<td>24</td>
<td>Phoenix</td>
<td>72.7</td>
<td></td>
<td></td>
<td>65</td>
<td>100% ≤T2a</td>
</tr>
<tr>
<td>(25) Bahn, n=70</td>
<td>44</td>
<td>Biopsy +</td>
<td>75</td>
<td>86</td>
<td>100</td>
<td>41</td>
<td>99% ≤T2a</td>
</tr>
<tr>
<td>(22) Ellis, n=60</td>
<td>15</td>
<td>ASTRO</td>
<td>80.4</td>
<td>96.4</td>
<td>78.3</td>
<td>92.5% ≤T2a</td>
<td></td>
</tr>
<tr>
<td>(30) Barret, n=50</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>100</td>
<td>100% ≤T2a</td>
</tr>
<tr>
<td>(21) Onik, n=48</td>
<td>54</td>
<td>ASTRO</td>
<td>94</td>
<td>*</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(24) Bahn, n=28</td>
<td>70</td>
<td>ASTRO</td>
<td>92.8</td>
<td>90</td>
<td>-</td>
<td>74.3</td>
<td>-</td>
</tr>
<tr>
<td>(29) Hale, n=26</td>
<td>19.1</td>
<td>0.5 ng/ml</td>
<td>88.5</td>
<td>89</td>
<td>100</td>
<td>96</td>
<td>100% T1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>over nadir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(23) Lambert, n=25</td>
<td>28</td>
<td>Nadir +</td>
<td>84</td>
<td>71</td>
<td>-</td>
<td>52</td>
<td>100% T1c</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO, American Society for Therapeutic Radiology and Oncology; BR, biochemical recurrence; bDFS, biochemical Disease Free Survival.

*median IIEF-5 was 19 at baseline but 14 twelve months after treatment
Pisters et al published one of the first reports on salvage cryosurgery (SCS). They treated 150 patients with radiation recurrent PC, with either a single or double freeze-thaw cycles and defined a biochemical recurrence as a PSA level of >0.1 ng/ml. The patients treated with double freeze-thaw cycle were less likely to have a positive biopsy at 6 months compared to the group treated with a single cycle (93% versus 71%, p<0.02) and at a mean follow-up of 13.5 months, the bDFS was 65% versus 44% (p<0.03), respectively (5).

In 2008, Pisters et al reported the initial results from the COLD registry on SCS. They included 279 patients treated with SCS and the mean follow-up was 21.6 months. Based on ASTRO and Phoenix criteria, the 5 year actuarial bDFS rates were 58.9% and 54.5%, respectively. Moreover, 15 (32.6%) of the 46 patients who underwent post-treatment biopsy were found to have persistent or recurrent disease. The rates of incontinence, rectal fistula and the need for transurethral resection to remove sloughed tissue were 4.4%, 1.2%, and 3.2%, respectively (34).

In 2011, Williams et al published outcomes on 176 patients treated with SCS at a mean follow-up of 7.46 years. They used the Phoenix criteria, any radiologic, histologic, or clinical evidence of recurrent disease as a definition of recurrence. At 10 years, the disease free (DFS) and OS rates were 39% and 87%, respectively. Almost all patients (95.6%) underwent at least one post-treatment biopsy and 31 (17.6%) had a recurrent/persistent disease which is lower when compared to the COLD data. Their results also showed that the pre-salvage PSA level, pre-radiation, and Gleason score (>/=8) were associated with risk of recurrence and that a PSA nadir >1.0 ng/ml was predicted of early recurrence. At 10 years, the DFS rates for patients with pre-salvage PSA of <5 ng/ml compared to >10 ng/ml were 64% versus 6.7%, respectively (35).

Another retrospective study conducted by Wenske et al showed promising long-term outcomes for men treated with SCS for either RT (259 EBRT; 49 BT) or PCS (20) recurrent PC. They included 328 patients and reported 5- and 10-year outcome data. The DFS rates were 63% and 35%; the OS

**Table IV. Oncologic outcomes of salvage cryosurgery.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow up</th>
<th>Cryogen System</th>
<th>Failure definition</th>
<th>Median time to recurrence</th>
<th>bDFS (%)</th>
<th>OS (%)</th>
<th>Biopsy+ (%)</th>
<th>ADT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(43)Ng, n=187</td>
<td>39</td>
<td>3rd</td>
<td>Phoenix</td>
<td>-</td>
<td>56* at 5 years</td>
<td>92 at 8 years</td>
<td>16.6</td>
<td>71</td>
</tr>
<tr>
<td>(44)Ismail, n=100</td>
<td>33</td>
<td>3rd</td>
<td>ASTRO</td>
<td>-</td>
<td>59 at 3 years</td>
<td>-</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>(34)Pisters, n=279</td>
<td>22</td>
<td>2nd/3rd</td>
<td>Phoenix</td>
<td>-</td>
<td>54.5 at 5 years</td>
<td>-</td>
<td>32.6</td>
<td>na</td>
</tr>
<tr>
<td>(45)Cheetham, n=51</td>
<td>121</td>
<td>2nd/3rd</td>
<td>Phoenix</td>
<td>-</td>
<td>~25% at 10 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(35)Williams, n=176</td>
<td>7.46y</td>
<td>2nd</td>
<td>Phoenix</td>
<td>2.3y</td>
<td>39 at 10 years</td>
<td>87 at 10 years</td>
<td>17.6</td>
<td>na</td>
</tr>
<tr>
<td>(36)Wenske, n=328</td>
<td>47.8</td>
<td>2nd/3rd</td>
<td>Phoenix</td>
<td>55</td>
<td>35 at 10 years</td>
<td>45 at 10 years</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*if pre-treatment PSA <4 ng/ml
rates were 74% and 45%; and the disease specific survival (DSS) rates were 91% and 79%, respectively. Fifty-five (16.7%) were treated with focal salvage cryotherapy, of which 27 (49%) had recurrence and the DFS, OS and DSS rates at 5 and 10 years were 47% and 42%; 87% and 81%; and 100% and 83%, respectively. A PSA nadir was the only significant predictor of recurrence in a multivariate analysis. Urethral stricture was the most common complication noted and was found in 15 patients (4.6%). Eleven (3.4%) patients required TURP or photoselective vaporization of the prostate due to bladder outlet obstruction. Rectourethral or urethroperineal fistula were found in 6 patients (1.8%). They did not report the rates of urinary incontinence or impotence but instead reported 3 (0.9%) patients requiring artificial urinary sphincter or male sling placement and another 3 (0.9%) patients who underwent penile prosthesis placement (36).

Partial SCS is another treatment modality. In 2008 Eisenberg et al published their initial results with partial SCS. They included 19 patients with biopsy proven recurrent PC after RT, who met the criteria of having unilateral disease and <50 cc prostate gland. At a median follow-up of 18 months the bDFS (ASTRO) was 89%, 67%, and 50% at 1, 2, and 3 years, respectively. Ten patients underwent a biopsy at 1 year after treatment and only one patient had persistent or recurrent tumor on the contralateral side (37) (Table IV).

CONCLUSION

With emerging favorable intermediate and long-term oncologic and functional outcome data, cryosurgery is increasing in use as a treatment option for localized PC. Cryosurgery has been utilized in the primary and salvage settings and more recently FCS has been introduced as a treatment option for men with unilateral low volume disease interested in maintaining potency. While many studies have been published addressing cryosurgery in different settings (PCS, FCS, SCS) it is difficult to compare both oncologic and functional outcomes. Variation in the definition of biochemical failure; variable use of androgen deprivation therapy and follow-up protocols call for prospective studies to evaluate the true impact of this technology in the management of localized prostate cancer as compared to available options.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


