Introduction

PSA screening has led to a dramatic increase in the incidence of prostate cancer, with the majority of cases currently diagnosed at earlier, clinically favorable stages. Since prostate cancer grows slowly, men diagnosed with this disease might die of causes unrelated to their cancer. Thus, active surveillance is a valid option for men who fit the recommended criteria and do not want to consider any type of invasive or radical treatments. While studies on active surveillance have shown a 10-year overall survival rate of approximately 80%, there is still a lingering concern of allowing a potentially curable cancer to progress to incurable disease before establishing definitive treatment. However, a recent prostate intervention vs observation trial (PIVOT trial) by Wilt et al indicated that for men with low-risk tumors, no distinct differences were seen in overall or cancer-specific survival benefits when comparing radical prostatectomy with active surveillance. The PIVOT trial reported that 171 of 364 men (47%) in the radical prostatectomy group died, while 183 of 367 men (49%) in the observation group died. A strategy of incorporating focal therapy as definitive treatment for selected men with focal disease and clinically significant cancer may reduce the number of men who will require treatment while on active surveillance. Considered a minimally invasive treatment, questions related to focal therapy include patient selection, evaluation of treatment success, and...
the best technology to use. The technology most commonly available for focal therapy is cryosurgery. This technology allows for treatment of selected areas within the prostate in which cancer is present while sparing noncancerous areas through a transperineal, percutaneous approach using ultrasound imaging.

**Cryobiology**

The mechanism of cell death in tissue treated with cryotherapy includes direct cellular injury that occurs secondary to cellular dehydration and the formation of ice crystals within the cell. As the tissue begins to freeze, solute concentration increases outside of the cell, resulting in osmotic dehydration. The dehydration causes disruption of intracellular proteins and destabilization of the cell membrane. Additionally, freezing results in stasis within the blood vessels of the prostate gland, leading to tissue necrosis secondary to ischemia. The treatment may be selectively applied to part of the prostate-bearing cancer and could potentially reduce the morbidity associated with whole gland treatment.

**Procedure**

Cryotherapy is performed under anesthesia, with the patient in the lithotomy position through a transperineal percutaneous approach. A 7.5-MHz ultrasound probe is utilized for real-time visualization of the prostate and attached to an ultrasound probe stand secured to the surgical table. A mapping grid is placed close to the perineum attached to the ultrasound stand, and 17-gauge cryoprobes are introduced percutaneously into the area to be treated within the prostate gland under ultrasound imaging guidance. Temperature probes are placed in Denovilliers’ fascia, apex of the prostate, and external urinary sphincter to monitor temperature in these areas during the procedure. A flexible cystoscopy is performed, and a 0.038 semi-rigid guide wire is inserted, the cystoscope is removed, and a urethral warming catheter is placed over the guide wire. The procedure begins by delivering argon gas, and freezing of the area is monitored with ultrasound imaging. After adequate freezing is achieved, the thawing part of the procedure is then conducted using hydrogen gas. The process is repeated one more time. Once the procedure is completed, the cryoprobes, temperature probes, ultrasound probes, and urethral warmer are removed, and an 18 Foley catheter is inserted and left indwelling. The patient is discharged home on the day of the procedure, and the catheter is removed 1 week later.

**Evaluation of Patients for Focal Therapy**

Prostate cancer presents more often as multifocal disease. However, most of the areas are considered to harbor insignificant tumors. It is hypothesized that the index lesion (largest tumor volume within the prostate) and occasionally a secondary index lesion will determine the biological potential of the cancer. Bott et al reported that the index lesion comprised 73% of tumor volume in a total of 374 tumor foci examined. This has led to considering a more preservative approach to treating prostate cancer, including hemi-ablation (half-gland treatment) and focal ablation. Several diagnostic modalities are being investigated to improve the selection of candidates for focal therapy.

Three-dimensional pathological mapping (3DPM) of the prostate gland has been proposed as a method to stage patients prior to focal therapy. In a study of 140 patients, 3DPM of the prostate gland was superior in detecting clinically significant prostate cancer compared to standard transrectal ultrasound (TRUS)-guided biopsy. The use of 3DPM of the prostate gland allowed precise location of the cancer for focal ablation. Sensitivity of the repeated TRUS biopsy in this study was 34%, with a false-negative rate of 52%. All cancers detected by the standard TRUS biopsy were also detected on 3DPM biopsies. Another study by Falzarno et al showed a 10% correlation between the unilaterality of cancer detected by TRUS with unilateral cancer in the final pathological finding.

Another modality assisting with risk estimation is multiparametric prostate magnetic resonance imaging (MRI). Turkbey et al reported that multiparametric MRI has a positive predictive value of 98% to 100% and 68% sensitivity for detecting prostate cancer tumors > 5 mm in diameter. A study by Rastinehad et al reported 94% sensitivity for lesions in the peripheral zone of the prostate, with 99% specificity using multiparametric MRI. MRI/ultrasound fusion-guided biopsy is a more recent imaging modality that is under investigation. Pinto et al reported a detection rate of 89.5% using MRI/ultrasound fusion-guided biopsy.

Two newer promising modalities are histoscanning and real-time elastography. Prostate histoscanning incorporates spectral analysis and pattern recognition to detect cancer lesions. Simmons et al reported 90% sensitivity for cancer volume ≥ 0.20 mL and 72% specificity using histoscanning. Real-time elastography utilizes ultrasound and the compression nature of soft tissue to detect the index lesion. Walz et al reported 58.8% sensitivity and 43.3% specificity in locating the index lesion when using elastography alone. However, combining elastography and data from 12-core biopsies increased the sensitivity and specificity of locating the index lesion to 84.9% and 48.4%, respectively.

**Reported Series on Focal Cryotherapy**

Onik et al first reported on the use of cryotherapy as focal therapy. They reported on 9 patients with an average follow-up of 3 years. All of the patients had
a stable PSA at the time of reporting, and 7 of the 9 previously potent men maintained erectile function satisfactory for penetration. Three patients underwent bilateral gland ablation with an attempt to spare one of the neurovascular bundles, 1 patient had the area of the tumor ablated with a margin around the tumor, and the remaining patients underwent hemi-ablation. A follow-up report included 48 patients with a minimum follow-up of 2 years and an average follow-up of 4.5 years. Thirty-five of 48 men had a stable PSA according to the ASTRO definition. Potency was maintained in 36 of 40 men (90%) who were initially potent. All patients remained continent (Table).

The Cryosurgery On-Line Database (COLD) registry provides one of the largest data sets for patients treated with cryotherapy. A total of 1,160 patients were treated with focal therapy. The authors noted that in 1999, focal cryosurgery represented 2.1% of the treatments used for patients entered into the database. By 2007, the percentage had increased to 38.2%. Of the patients treated with focal cryotherapy, 47%, 41%, and 12% were stratified into low-, intermediate-, and high-risk groups, respectively. The 3-year biochemical-free survival was 74.7%. This is comparable to patients in the COLD database treated with whole gland cryotherapy. Maintenance of spontaneous erections and urinary continence was 58.1% and 98.4%, respectively.

Bahn et al reported on 73 patients treated with focal cryotherapy. The mean follow-up was 3.7 years. Using the ASTRO definition for PSA failure, 75% of patients were free of biochemical recurrence. Potency was preserved in 86% of patients, and 100% of the patients maintained continence.

Lambert et al reported on a cohort of 25 patients treated with focal cryotherapy. PSA failure was defined as nadir + 2 (Phoenix definition) or a decrease in the PSA of less than 50% of the pretreatment PSA value. At a mean follow-up of 2.3 years, the biochemical-free survival rate was 85%. Erectile function was preserved in 71% of the patients in this study, and no patients experienced worsening of their urinary symptoms.

Ellis et al reported on 60 men treated with focal cryotherapy, with a mean follow-up of 1.3 years. The biochemical-free survival rate was 80.4%, and the potency rate was 70.6% at 12-month follow-up. The incontinence rate was 3.6%; however, no patients required the use of absorbent pads for protection.

### Table. — Clinical Characteristics and Oncologic/Functional Outcomes of Focal Cryotherapy

<table>
<thead>
<tr>
<th></th>
<th>Onik17</th>
<th>Ward18***</th>
<th>Bahn19</th>
<th>Lambert20</th>
<th>Ellis21</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>48</td>
<td>1,160</td>
<td>73</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>Average Age (yrs)</td>
<td>N/A</td>
<td>68</td>
<td>64</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Average Follow-up (yrs)</td>
<td>4.5</td>
<td>1.8</td>
<td>3.7</td>
<td>2.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Gleason Score, No. of Patients (%)</td>
<td>N/A</td>
<td>≤ 6: 844 (74)</td>
<td>7: 240 (21)</td>
<td>≥ 8: 64 (6)</td>
<td>6: 30 (41)</td>
</tr>
<tr>
<td>Clinical Stage, No. of Patients (%)</td>
<td>N/A</td>
<td>≤ T2a: 1,013 (87)</td>
<td>≥ T2b: 147 (13)</td>
<td>T1c: 41 (56)</td>
<td>T2a: 31 (43)</td>
</tr>
<tr>
<td>Risk Category, No. of Patients (%)*</td>
<td>N/A</td>
<td>Low: 541 (47)</td>
<td>Int: 473 (41)</td>
<td>High: 143 (12)</td>
<td>Low: 24 (33)</td>
</tr>
<tr>
<td>Average PSA (ng/mL)**</td>
<td>Pre 7.8</td>
<td>Post 2.2</td>
<td>Pre 7.2</td>
<td>Post 2.15</td>
<td>Pre 5.9</td>
</tr>
<tr>
<td>Biochemical Disease-free Survival (%)</td>
<td>94</td>
<td>74.7</td>
<td>75</td>
<td>85</td>
<td>80.4</td>
</tr>
<tr>
<td>Incontinence (%)</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td>Potency Maintained (%)</td>
<td>90</td>
<td>58.1</td>
<td>86</td>
<td>71</td>
<td>70.6</td>
</tr>
</tbody>
</table>

* Risk categories were based on D’Amico risk stratifications.

** PSA nadir > 50% was indicative of biochemical disease-free survival.

*** Certain data are not available for some patients in this study.

NA = not available, Int = Intermediate.
Discussion
The optimal management for localized prostate cancer is controversial. While men with low-risk and selected intermediate-risk prostate cancer can be managed by active surveillance, the majority of men with early prostate cancer are radically treated with either surgery or radiation therapy. With better patient selection by defining the biological potential of the cancer and with improvements in technology to follow these men, active surveillance will become more widely used. For low-risk and some intermediate-risk patients, active surveillance is usually recommended since the cancer is noninvasive and has an overall survival rate comparable to other radical treatments. Nevertheless, there is a subset of men with early cancer who will benefit from active treatment; however, they also may benefit from focal treatment of their localized cancer without subjecting them to the potential risks and complications of radical local treatment.

Outcomes of the cryosurgery series show a biochemical disease-free survival rate of approximately 80% at 3 to 5 years with minimal incontinence and high potency rates. However, weaknesses from these series include the small number of patients in each series, inconsistent patient follow-up, and the use of the ASTRO definition for biochemical recurrence that was intended for use in patients treated with radiation therapy. The COLD registry, while large in numbers, represents nonstandardized treatment and a compilation of cases from multiple surgeons with variable levels of experience. Additionally, some of the cases are doubly reported as single-institution series.

While the literature on focal cryotherapy for clinically localized prostate cancer is still limited, the number of procedures is increasing when compared to whole gland cryosurgery. In 2008, the American Urological Association published a “Best Practice Statement on Cryosurgery,” which recommended that patients treated with focal cryotherapy should be included in a registry for future analysis. The report also notes the challenges in determining which patients may be offered focal cryotherapy safely. Prospective trials with adequate follow-up are needed. These trials should also include more precise criteria for selecting patients for focal cryotherapy. Finally, there is also a need to better define cancer progression.

Conclusions
The use of prostate-specific antigen to screen for prostate cancer has led to a downward stage migration. Treatment options for newly diagnosed prostate cancer are numerous. A review of the recent literature demonstrates increasing use of minimally invasive treatments, including the use of focal therapy in the treatment of localized prostate cancer. Focal cryotherapy yields short-term biochemical disease-free survival comparable to whole gland treatment modalities in men with low-risk prostate cancer while providing better functional outcomes.

References