

## Focal Cryotherapy in Low-Risk Prostate Cancer: Are We Treating the Cancer or the Mind?

### *The Cancer*

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### INTRODUCTION

In the era of PSA screening, prostate cancer faced a dramatic increase in incidence. Early detection of asymptomatic disease leads to majority of patients being diagnosed at earlier clinical stages (1). Currently, up to 90% of the patients diagnosed with prostate cancer in United States have localized disease (2). With modern cancer treatments available, patients and physicians struggle to decide among available treatment options with curative intent. Physicians and patients need to select which treatment modality will treat their cancer without morbidity. Thus, we had a surge of the development of less invasive treatments including laparoscopic and robotic surgeries, and ablative therapy.

### *Overtreatment and Less Invasive aggressive therapy for Localized Prostate cancer*

In the PSA era, overtreatment of prostate cancer patients became a clinical and public health controversy. Therefore, active surveillance became popular and recommended in selected localized, low and intermediate prostate cancer patients (3, 4). Conversely, the lack of aggressive treatment after diagnosis of cancer may lead 50% of patients enrolled in watchful waiting cross to active treatment in a period of 5 years post-diagnosis (5, 6). Another issue is the limitations of ultrasound guided biopsies that cannot accurately grade the disease since the pathological upgrade of prostate specimens after radical prostatectomy is often seen when compared to pre-operative pathological findings (7-10).

In addition one cannot forget the emotional burden of the diagnosis of cancer and anxiety that frequently drives patients in active surveillance to seek for active treatment (11). Currently, aggressive treatment may be necessary in patients with moderate/high-risk prostate cancer (3, 4).

Unfortunately, there is no cookie cutter solution for prostate cancer patients and individual preferences, beliefs, and social economic status play a pivotal role in patient's decision making. Minority status, age, marital status, race, and D'Amico risk stratification are associated with patients who opt for less invasive treatment of localized prostate cancer (12, 13).

The American (AUA) and European Urological Associations (EAU) recommend active surveillance and monotherapy treatment options for men with low-risk prostate cancer. While, for patients with intermediate or high risk prostate cancer, the mono or multimodal therapies may achieve better cancer control (3, 4).

In 2008, the AUA's best practice statement on cryosurgery affirmed that cryosurgery is an option for patients with organ confined disease (14).

The advent of new generation cryotechnology machines, smaller probes with better control of the ice ball and better ultrasound definition made prostate cryoablation well-established and accepted worldwide technique to treat localized prostate cancer minimizing risk of urinary incontinence, erectile dysfunction, and recto-urethral fistulas when compared to earlier experiences (15-17).

Potentially, targeted or focal cryoablation of prostatic tumors may treat localized diseases decreasing the morbidity and reducing the number patients over treated with aggressive and debilitating treatments (14). The concept of targeting the cancer inside the prostate without collateral damage to the rectum, neurovascular bundles, bladder neck, and urinary sphincter is attractive and evolving (18, 19).

Controversy still exists regarding the benefits of aggressive therapy (radical prostatectomy) versus non-aggressive management of prostate cancer and the lack of survival benefits with surgery, as seen in The Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the Scandinavian Prostate Cancer Group SPCG-4 trial (20, 21).

Critics of focal cryoablation of localized prostate tumors argue that prostate cancer is known to be multifocal. A dominant lesion is often accompanied by other smaller low-grade lesions. However, with novel genetic profiling tests and better understanding of the index lesion we can better select patients for this specific treatment modality. The index lesion is associated with the highest Gleason grade, presence of lymph node metastasis, genetic profiling and other pathological determinants of progression (22-25).

Recently, the Cryo Online Data (COLD) Registry reported 1160 patients that had focal prostate cryoablation, showing an increase from 2.1% (1999) to 38.2% (2007) of cryoablation patients that received this targeted therapy for localized prostate cancer (26).

The biochemical recurrence-free survival (ASTRO criteria) for patients stratified by risk group after focal therapy was similar to whole gland cryoablation at two years clinical follow-up (26). Pathological recurrence rates during follow-up were also similar when comparing focal cryoablation with whole gland cryoablation. Since the eligibility criteria for focal cryotherapy was not defined and this study was done retrospectively, further analysis should be done.

Similarly, a small prospective study evaluating focal cryoablation (hemi-ablation) was conducted in 56 patients with unilateral low-grade prostate cancer. A total of 86% of the patients had negative biopsies during the follow-up (27).

### ***Why cryoablation has a bad reputation?***

During early cryoablation experience, the use of liquid nitrogen and inability to create a controlled ice ball, archaic ultrasound technology and absence of urethral warmers resulted in high incidence of rectourethral fistula and urinary incontinence. Moreover, these events occurred in whole gland cryoablation and in post-radiation salvage therapy patients (15, 16, 26, 28). Currently, these complications are less frequent due to the new technology and they seldom during focal cryotherapy (26). In addition, patients that had normal erectile function before focal cryoablation were more likely to maintain function after the focal treatment (58%) when compared to whole gland treatment (32.3%) (26).

### ***Post-Radiation Targeted Therapy***

While salvage treatment of failed post-radiotherapy patients can result in high complication rates associated with surgery and miss the opportunity for curative treatment (29). The complication rates for robotic-assisted salvage radical prostatectomy were as high as 47% with Clavien III-V in 35% of the patients. Within three years of follow-up, potency was maintained in only 23% of the patients and urinary control was achieved in only 45% of the patients (30). Open radical prostatectomy also had high complication rates with urinary continence rated ranging from 36 to 81%, erectile function in less than 30%, and biochemical recurrence-free probability from 37 to 55% within 5 years. The estimated cancer-specific survival at 10 years ranged from 70 to 83% (31). Salvage focal cryotherapy achieved 95.3%, 72.4%, and 46.5% biochemical-free survival at 1, 3, and 5 years of follow-up (32). A total of 3.3% of patients experienced rectourethral fistula, 5.5% experienced incontinence, and 50% of the patients maintained sexual function after salvage treatment (32). The oncological outcomes of focal prostate cryoablation reported are comparable to open salvage radical prostatectomy with improved functional outcomes and lower complication rates. Sexual function after salvage focal cryotherapy has shown to be better when compared to whole gland salvage cryotherapy (32).

It appears that the cryoablative technology is efficient even in cases of radiation failure prostate cancer. Salvage whole gland cryoablation and focal cryoablation seem as reasonable options for curative treatment of this select group of patients (32-35).

## FUTURE

The options for the management of prostate cancer are transitioning to active surveillance and less invasive procedures (12, 15, 16, 36-38). The effectiveness of the treatment of localized prostate cancer will rely on accurate detection and localization of the prostate cancer cells in the body and the clinical relevance of these findings so we can efficiently select the right patients to the right treatment.

Three-dimensional computer models, alternative biopsy techniques, target biopsies, and tumor markers are potential tools that can be used to aid this task (37, 39-43).

We are still trying to understand the effects of the U.S. Preventive Services Task Force (USPTF) report discouraging PSA screening due to the imbalance of risks outweighing the benefits of prostate cancer diagnosis (44). However, it is our hope that the pre-PSA era of advanced stage prostate cancer at the time of diagnosis does not return to haunt us.

Despite the lack of randomized clinical trials comparing focal cryoablation of the prostate with other treatment modalities, the oncological and functional outcomes are pointing to a promising therapy for patients with localized disease (26, 33, 35, 45). One should not consider the focal cryoablation as “placebo” for patients that are good candidates for active surveillance but elect for an aggressive treatment option. The reality is that what we believe to be an ideal candidate for active surveillance may have a more aggressive cancer cell population or radiation resistant cells that can be treated with cryoablative technology.

Finally, the anxiety caused by the word cancer can affect the quality of life of patients and set stage to a well-known clinical challenge; “the sword of Damocles”, patients that cannot enjoy life with the idea of untreated cancer.

However, data are sought after to understand the selection of optimal patients for focal cryotherapy.

## CONCLUSIONS

Targeted or focal cryoablation of prostate tumors is a promising curative therapy for localized prostate cancer. Oncological outcome is comparable to available standard therapies with better functional outcomes and reduced morbidity when compared to whole gland cryotherapy. Challenges to effectively select the optimal patient for focal cryotherapy will depend on complete understanding of clinical relevance and imaging methodologies to detect localized prostate cancer cells in the body.

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