FRIGID ZONE **MEDICINE**
Mini Review • DOI: 10.2478/fzm-2023-0032

Prostate cryoablation: A mini review

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Abstract

In recent years, cryotherapy has gained increasing acceptance as a treatment for prostate cancer, offering complementary therapeutic benefits when combined with radical surgery and radiotherapy. Despite the potential for surgical complications, it stands as a safe and viable therapeutic modality. Cryotherapy provides an efficient approach for elderly patients, especially those with compromised physical conditions and individuals experiencing recurrence after initial treatment. It has shown promise in extending survival periods and improving the overall quality of life for these patients. This article aims to comprehensively examine the developmental trajectory, surgical techniques, indications, therapeutic outcomes, and potential complications associated within prostate cancer treatment.

Keywords

prostate cancer; prostate cryoablation

Received 24 October 2023, accepted 6 December 2023

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1 Introduction

Prostate cancer stands as the most prevalent malignancy among men worldwide, and marked by notably high incidence and mortality rates[1-2]. Notably, the incidence of prostate cancer in China has shown an upward trend in recent years[3]. Presently, treatment strategies for prostate cancer encompass a spectrum including radical prostatectomy, radiation therapy, active surveillance, endocrine therapy, among others. However, both radical prostatectomy and radical radiotherapy continue to serve as the established benchmarks for managing early localized prostate cancer. Conversely, for elderly and medically frail individuals coping with multiple underlying conditions, prolonged catheter use, or those unsuitable for open surgery, cryotherapy emerges as the preferred option owing to its minimally invasive nature and lower risk of complications. This paper aims to consolidate the developmental chronology, surgical techniques, indications, therapeutic outcomes, and potential complications associated with cryoablation in the context of prostate cancer treatment.

2 Basic principle and developmental history

Cryotherapy for the treatment of prostate cancer made its debut in the 1960s, employing liquid nitrogen cryoprobes inserted through the urethra with guidance from digital rectal examination. This technique gradually evolved to expand the volume of frozen tissue[4]. However, due to technological and equipment constraints, the therapeutic efficacy remained suboptimal, with the local recurrence rate exceeding 66%.

In 1988, Onik *et al*.[5] pioneered a significant advancement by introducing synchronous ultrasound for monitoring tissue freezing process and detecting ice hockey progression. This innovative approach involved freezing prostate cancer through perineal skin puncture, resulting in favorable outcomes and further propelling the advancement of cryotherapy.

The subsequent breakthrough came with the development of multi-freezing probe devices. These devices augmented the number of probes while limiting the freezing volume of each, enabling more precise control over temperature and freezing range. This enhancement facilitated targeted treatment of tumor tissue while minimizing the impact on neighboring healthy tissues.

Moreover, the introduction of a urethral insulation device and intraoperative temperature measurement probe played a pivotal role in the loss of necrotic tissue in the prostate and adjacent areas after freezing. This development significantly mitigated the risk of complications such as urinary retention and urinary incontinence.

The core principle of cryoablation primarily involves around tissue destruction through a cycle of freezing and thawing[6]. Its mechanism predominantly involves direct cell damage, vascular-related damage, and immune regulatory mechanisms[7].

During the initial freezing phase, the cooling process triggers the formation of extracellular ice crystals, leading to the movement of intracellular water into the extracellular space and an ensuing rise in intracellular osmotic pressure. This dehydration prompts cellular shrinkage, causing harm to the cell membrane and organelles. The rapid drop in temperature during quick freezing leads to the formation of intracellular ice crystals, resulting in irreversible damage to organelles such as mitochondria and endoplasmic reticulum, culminating in cell demise. Subsequent to this, the melting of extracellularice crystals during the thawing phase reduces the osmotic pressure of extracellular fluid, inducing cellular edema and rupture. In addition, the concentration of extracellular fluid lowers its freezing point, hastening the formation of intracellularice crystals during the rewarming, intensifying cellular damage. Delayed injury generally occurs within hours to days after freezing, primarily due to microcirculatory blockage. The treatment area undergoes rapid temperature fluctuations during freeze-thaw cycles, exacerbating dehydration of microvascular endothelial cells, protein degradation, lipid layer disruption, and damage to microvascular linings. These cumulative effects trigger the formation of ice crystals and microvascular clots, leading to platelet aggregation, vascular blockage, local ischemia, and cell apoptosis. Notably, this process significantly impacts lesions in the peripheral region of the target area[8]. Furthermore, frozen necrotic tumor cells can sensitize dendritic cells, activate T lymphocytes, and induce immune responses, further contributing to the treatment's therapeutic effect[9].

3 Indications and applications for cryoablation

The Chinese consensus on cryoablation for prostate cancer indicates specific scenarios suitable for this treatment approach. First, it is recommended for patients with localized prostate cancer, including those with low-risk prostate cancer; intermediate-risk prostate cancer patients who are unsuitable for radiotherapy or surgical interventions due to factors like obesity, prior rectal radiotherapy, or extensive pelvic surgery history; prostate volume of approximately 40 mL to ensure effective freezing range. If the volume exceeds 40 mL, neoadjuvant endocrine therapy is suggested to reduce gland size initially. If the volume exceeds 40 mL, neoadjuvant endocrine therapy is recommended to reduce gland size initially. However, it is not recommended for patients with high-risk localized prostate cancer, except in the context of clinical trials[10-11]. Second, salvage therapy (salvagecryosurgery) for local recurrence post-radiotherapy is recommended preferably over salvage prostatectomy for patients experiencing local recurrence following external radiotherapy or radioactive particle implantation. Suitable conditions include patients with confirmed local recurrence through needle biopsy after radiotherapy, a Prostate-specific antigen (PSA) level < 10 μg/L, and confirmed absence of distant metastasis through imaging[12]. Additionally, the National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) guidelines offer further insights. Consensus for cryoablation of prostate cancer related to NCCN or AUA can also be found. NCCN guidelines endorse cryosurgery and high-intensity focused ultrasound as local therapy options for radical treatments in recurrent or metastatic diseases. AUA guidelines from 2022support whole gland or focal cryoablation as options in intermediate-risk prostate cancer, but they recommend considering this after other radical treatments like radiation therapy or surgical prostatectomy. It is emphasized that there is a lack of direct comparison trials. For unfavorable intermediate-risk and high-risk prostate cancer, ablation is suggested in trial settings. However, for patients who are unwilling or unable to undergo standard treatments with intermediate-risk disease, cryoablation can be an option. Low-risk patients considering prostate cryoablation should be informed that current evidence does not substantially favorablation over active surveillance.

4 Therapeutic efficacy

Compared to whole gland cryotherapy, focal prostate cryotherapy has a similar short-term recurrence-free survival rate, yet it notably excels in preserving postoperative urinary control function, especially in terms of sexual function preservation (Table 1)[13]. In an analysis by Ward *et al*.[14], data from 1,160 newly diagnosed prostate cancer patients treated with focal cryotherapy from the International Cryotherapy Online Database (1997 to 2007) revealed the 3-year survival rate without biochemical recurrence (BCR) at 75.7%. Remarkably, 98.4% of patients achieved postoperative urinary continence without relying on urine pads, 58.1% retained their sexual function, and only one patient developed a rectal urethral fistula. Likewise, Li *et al*.[15] reported findings from 91 cases of local recurrence after radiotherapy in the same database (2002 to 2012), focusing on data pertinent to focal cryotherapy for prostate cancer. The survival rates without biochemical recurrence at 1, 3, and 5 years post-surgery were 95.3%, 72.4%, and 46.5%, respectively. Additionally, 94.5% of patients attained postoperative controllable urination without the need for pads, and 50% of patients retained their sexual function. Moreover, Valerio *et al*.[16] conducted asystematic evaluation of focal cryotherapy data from 3,230 prostate cancer patients, with a median follow-up time of 26 months. Their results demonstrated a 100% overall survival rate and tumor-specific survival rate. Postoperative biopsy revealed clinically significant prostate cancer in 5.4% of patients,

Table 1 Therapeutic efficacy and complications of cryotherapy for prostate cancer

Reference	*n*	Therapeutic efficacy	Complications
Ward *et al*.[14]	1160	3-year biochemical recurrence (BCR)-free survival 75.7%	urinary incontinence 1.6% impotence 41.9%
Li *et al*.[15]	91	1, 3, 5-year BCR-free survival: 95.3%, 72.4%, and 46.5%	urinary incontinence 5.5% impotence 50%
Valerio *et al*.[16]	3230	overall survival: 100%	urinary incontinence: 0 impotence: 19.5%

while 13% had clinically insignificant prostate cancer. Furthermore, 7.6% of patients received post-operative local treatment, 100% achieved postoperative urinary continence without the need for urine pads, and 81.5% retained preserved sexual function. Chen *et al*.[17] demonstrated that for high-risk prostate cancer, biochemical recurrence rates at 1, 3, 5, and 10 years were 92.6%, 76.6%, 66.7%, and 50.8%, respectively. Importantly, at 10 years, metastasis-free, cancer-specific, and overall survival rates were as high as 89.5%, 97.4%, and 90.5%, respectively. Nevertheless, there remains a scarcity of long-term follow-up data on focal cryotherapy for prostate cancer, emphasizing the need for further research into its long-term tumor control efficacy.

Moreover, a report suggests that cryotherapy and radical prostatectomy yield comparable oncologic outcomes for unilateral prostate cancer[18]. In a study reported by Donnelly and colleagues, 224 patients diagnosed with T2 or T3 disease were randomly assigned to receive either cryotherapy or external beam radiation therapy (EBRT), with all patients undergoing neoadjuvant androgen deprivation therapy (ADT)[19]. Their investigation revealed no significant difference in 3-year overall survival (OS) or disease-free survival (DFS) between the two treatments. However, patients who underwent cryotherapy reported experiencing poorer sexual function.

5 Complications

As extensively documented, early cryotherapy is associated with numerous complications, which have markedly decreased owing to advancements in imaging technology and the utilization of urethral heaters and thermocouples. The most prevalent complications include: (1) Erectile dysfunction: Nearly all patients undergoing total prostate cryoablation experience erectile dysfunction post-surgery. This could be ascribed to ice hockey extending beyond the prostate gland, damaging the vascular and nerve bundle area, and reducing blood supply to the penile arteries. Multiple freeze-thaw cycles are associated with higher rates of erectile dysfunction. For young patients or those desiring for preserving erectile function, partial prostate ablation with nerve preservation could be considered in suitable cases. Nevertheless, strict adherence to the indications is crucial for this procedure. (2) Urinary incontinence: Cryotherapy-induced urinary incontinence may result from direct damage to the perineal nerves, urethral mucosa, urethral sphincter, scar formation, and unstable bladder detrusor function. (3) Urethral stenosis: Recent studies indicate a current incidence of this complication below 3% due to advances in refrigeration technology. (4) Urethral rectal fistula: Occurring primarily in patients undergoing salvage cryotherapy, the incidence of urethral rectal fistula after prostate cryotherapy remains relatively low, typically not exceeding 0.4%[20]. Accidental extension of ice hockey to the rectal mucosa leads to damage in the intestinal wall, resulting in fistula formation. (5) Other complications: These may include postoperative pelvic floor pain, extensive freezing of the bladder neck, or deep probe freezing into the seminal vesicle, potentially causing freezing of the ureteral opening or end and subsequent hydronephrosis.

6 Conclusion

Cryoablation, employing image-guided ablative modalities, presents an appealing approach for addressing focal lesions within the prostategland. While most published methods rely on ultrasound guidance in the operating room, there is a growing inclination toward MRI or MRI/ultrasound-guided focal cryoablation. Cryotherapy has emerged as a pivotal complement to radical prostate cancer treatment. It serves as an effective option, particularly for elderly patients, individuals with compromised physical conditions, and those experiencing relapse after initial treatment. As an essential adjunct in prostate cancer management, cryoablation has garnered popularity as a viable choice for patients with primary and locally recurrent prostate cancer. However, standardized indications and criteria for evaluating efficacy remain lacking, and there is limited research data on long-term effectiveness. The anticipation lies in accruing evidence from large-scale randomized controlled trials to comprehensively validate both its efficacy and safety. The potential evolution of focal cryotherapy for prostate cancer into a standardized treatment strategy for localized cases remains an exciting prospect for the future.

Author contributions

Li Z Y drafted, edited, and reviewed the manuscript. Zheng X edited the manuscript. Chen L H and Lai K T summarized relevant articles and data.

Ethics approval

Not applicable.

Source of funding

This work was supported by the National Natural Science Foundation of China (No.82203320).

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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