Review Article – Urological Oncology

Grand J Urol 2021;1(3):128-132
DOI: 10.5222/GJU.2021.87598

Focal Ablation Therapies in Prostate Cancer

Prostat Kanserinde Fokal Ablasyon Tedavileri

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Cite as: Adsan O. Focal ablation therapies in prostate cancer. Grand J Urol 2021;1(3):128-132.

Submission date: 15 February 2021 **Acceptance date:** 06 April 2021 **Online First:** 19 April 2021 **Publication date:** 20 September 2021

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Abstract

Focal ablation therapies in prostate cancer have been actively evaluated in the light of recent literature. According to published data,focal ablation therapies appear to be well tolerated and have an acceptable side effect profile. Moreover, while clinical outcomes were not homogenous, short-term oncological results of some focal ablation therapies such as laser and irreversible electroporation (IRE) have been found as good as curative ones. While waiting long-term oncological results, focal ablation therapies in prostate cancer are beinmg used increasingly.

Keywords: focal therapy, ablation therapy, prostate cancer, MRI

Öz

Prostat kanserinde fokal ablasyon tedavileri güncel literatür eşliğinde aktif olarak değerlendirilmiştir. Yayınlanan verilere göre, tedaviler iyi tolere ediliyor ve kabul edilebilir bir yan etki profiline sahip görünüyor. Dahası, klinik sonuçları homojen olmamakla beraber, lazer ve irreversible elektroporasyon (IRE) gibi bazı fokal ablasyon tedavilerinin kısa vadeli onkolojik sonuçları, küratif tedavinin sonuçları kadar iyi bulunmuştur. Uzun dönem onkolojik sonuçları beklerken, prostat kanserinde fokal ablasyon tedavileri giderek daha fazla kullanılmaktadır.

Anahtar kelimeler: fokal terapi, ablasyon tedavisi, prostat kanseri, MRI

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Introduction

Localized prostate cancer is the most common cancer in males today [1]. Most commonly used curative therapy methods among the therapies applied for prostate cancer are surgery or radiotherapy-based treatment modalities. However, these therapies have severe short-, and long-term side effects [2]. Active surveillance and follow-up protocols aim to save the patients from treatment-related side effects. Known slow progressive course of prostate cancer can only enable follow-up through surveillance in some prostate cancer types. Severe side effects which may be caused by complete resection or treatment of especially low- or intermediate- risk prostate cancer may shadow treatment success. Although complete resection or radiotherapy of the prostate in high volume or high-risk prostate cancer is still an important treatment option, imaging-guided focal ablation therapies in other prostate cancer types have currently become important treatment alternatives [3].

Magnetic resonance (MR) imaging has made an undeniable contribution in popularization of focal ablation therapies in prostate cancer. Targeted biopsies have now replaced standard biopsies in prostate cancer thanks to multiparametric MR imaging. Focal ablation or hemiablation options has been started to be used in visible prostate lesions. Focal ablation therapies have become the standard treatment option in renal cell carcinoma and solid organ tumors such as thyroid, liver, breast and pancreas. Multifocal character of the tumor is the most important obstacle for the focal ablation therapies in prostate cancer. In addition, the close proximity of the tumor to rectum and nerves controlling erectile and the need to preserve continence mechanism are vital issues worth considering.

Lesions over 0.5 cm3 are known as clinically significant cancer markers in prostate cancer. Based on prostate cancer surveillance studies, prostate tumors less than 1.3 cm3 have a lower possibility of becoming clinically significant. It should not be forgotten that clinically insignificant tumors under 0.5 cm3 in size can be aggressive or can reach high volumes. Thus random biopsy is still the standard application in addition to the pathological samples taken from the target lesion [4].

The objective of this review was to compare the focal ablation techniques used recently in prostate cancer treatment.

Focal Ablation Types and Clinical Results

Irreversible Electroporation (IRE) (NanoknifeTM)

Many thermal-energy based techniques are used to induce cellular damage. While most of these operate with high thermal energy, some depend on cooling-based techniques. Irreversible electroporation (IRE) causes non-thermal cellular damage through a different system. Direct flow rhythmically applied with low energy on the cell induces cellular apoptosis by keeping all cell wall pores open. Energy used in IRE is provided through the needles inserted into the tissue. The energy applied through a special device is monitorized through ultrasound (US).

IRE was first applied in 16 locally advanced prostate cancer patients by Onik et al. Side effects such as erectile dysfunction and urinary incontinence were not observed in these patients [5]. Later on Valerio et al. published their IRE experience in 34 patients and mentioned inadequate treatment only in one patient [6]. In the study by Van den Bos et al., IRE treatment was applied one month before the operation in 16 patients who would undergo radical prostatectomy Histopathological evaluation of post-radical prostatectomy specimens showed satisfactory ablation in targeted areas without skipping any lesion [7]. IRE treatment was applied in 123 patients diagnosed with locally advanced prostate cancer in the largest biopsy- controlled study and ablation success rate up to 97% was achieved in the control biopsy samples taken from the treatment area at the end of 1 year. In this study, it was shown that urinary continence was achieved in 98.8% of the patients and potency didn't change in 76% of the patients at the end of 12 months [8].

Photodynamic Therapy (PDT)

In photodynamic tissue ablation tumoral tissue is destructed through the activation of vascular photo stimulators under light at certain wavelengths. As a result, the number of free radicals in the tissue increases. Following the intravenous application of photo stimulators, laser is applied transperineally or transrectally at certain wavelengths.

One hundred and sixteen stage cT1 and cT2b prostate cancer patients were treated in a prospective study performed using photodynamic therapy (PDT). Median PSA value was 6.4 ng/ml for patients with low and intermediate - risk prostate adenocarcinoma. While no clinically significant cancer was detected in any of the patients, clinically insignificant cancer was detected in 46% of the patients at the end of six months. While no continence data was available, 88.4% of the patients had maintained their potency [9,10].

High-intensity Focused Ultrasound (HIFU)

In high-intensity focused ultrasound therapy, tissue ablation through thermal energy is accomplished using focused ultrasound. Temperature over 60 °C is generally achieved in the tissue. HIFU induces formation of coagulation necrosis and cavitations in the targeted tissue. It is the only system among focal applications which doesn't use needles or electrodes. It can be applied transrectally or transurethrally using the new high-intensity focused ultrasound (HIFU) systems.

Many studies including more than 300 prostate cancer patients have been performed. The results are variable due to the non-homogeneous character of the studies and different application methods. Targeted prostate biopsies were performed in most patients. Secondary treatment starting rate was reported as 7.8% in the studies completing post-treatment 12 surveillance months. While continence rate was reported as 100%, potency was maintained in 88% of the patients [11–13].

Cryotherapy

This ablation system uses thermal energy. Extreme tissue cooling causes cell death by inducing osmotic cell injury. Cooling is performed on the targeted area using transperineally

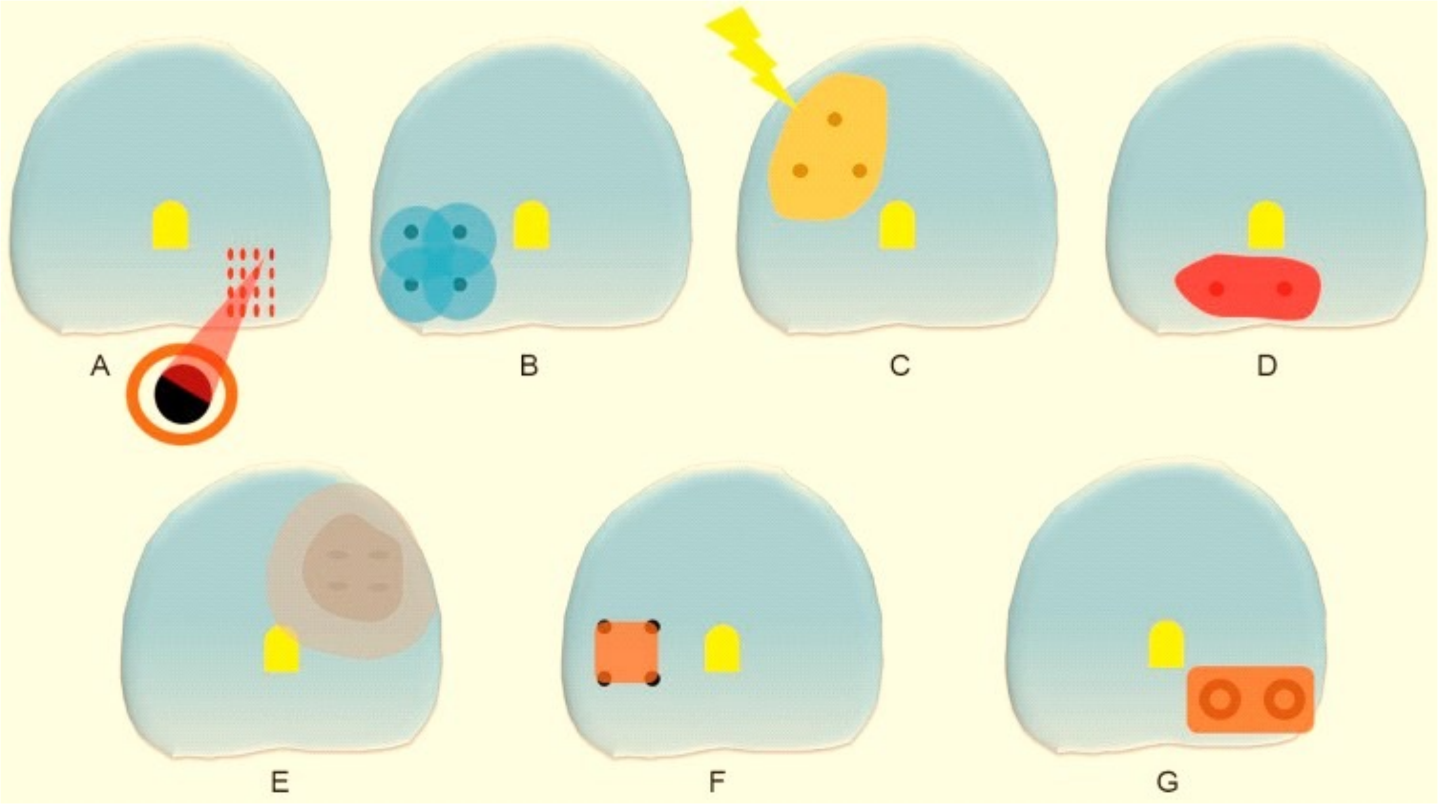

Figure 1. Focal ablation therapies used for prostate cancer treatment. A: high-intensity focused ultrasound (HIFU); B: cryotherapy; C: photodynamic therapy (PDT); D: focal laser ablation (FLA); E: brachytherapy; F: irreversible electroporation (IRE); G: radiofrequency ablation (RFA) (Valerio M, et al. New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. Eur Urol 2016 reproduuced with permission obtained from authors).

inserted needle electrodes. Ice ball image is seen between cryo-needles.

A quite high number of patients have been treated and followed up for longer periods of time. Most of these studies had a retrospective design. Secondary treatment has been started at a rate of 7.6% in the studies with one-year follow-up period. Severe side effects were reported in 2.5% of the cases. Continence was preserved in 100%, and, potency was maintained in 81% of the patients [14–17].

Focal Laser Ablation (FLA)

In FLA, laser therapy is directly applied on the targeted area. Interstitial coagulation necrosis in the tissue is generally formed through the use of neodymium or diode laser. Thermal energy applied raises the temperature in the targeted tissue up to 60 °C. Increase in tissue temperature is monitored through thermal receptors during the operation. A single laser probe is generally used in transperineal or transrectal applications.

FLA has been performed on patients with low and intermediate risk, and average PSA value was reported as 5.4 ng/ml. As the long-term results of the patients have not been acquired yet, secondary application rate is not certain. Continence and potency preservation rates were reported as 100% [18,19].

Radiofrequency Ablation (RFA)

In RFA tissue ablation is achieved through thermal energy. Coagulation necrosis of the tissue is performed through the provision of alternative flow in the targeted area using the transperineally inserted needles..

Pathological results were reported for 15 patients who had received RFA before radical prostatectomy. Tumor persisted in all patients. No other treatment aiming study was reported [20].

Discussion

There are six actively used systems now among focal ablation therapies **(Figure 1)**. Most of these uses a thermal energy source, and only IRE achieves tissue ablation using non-thermal energy. Radiation-based therapies used in brachytherapy should not be included, and evaluated within this group, because it is a locally applied alternative form of radiotherapy. Due to its adverse outcomes, RFA treatment is not actively used now. Transurethral applications can now be performed thanks to the renewed application apparatus of HIFU. The most important difference of HIFU from other methods is the direct energy focused by the probe without the use of any electrode or needle. Thermal damages which may form on nonlesioned areas can be more frequently encountered than other methods which is seen as a partial advantage of the method. This ablative effect was shown to continue at least 0.5 cm outside the targeted area in tissue ablations performed using thermal energy sources. It is known that the hotness of thermal energy source in cold or HIFU, laser treatments as in cryotherapy doesn't change this effect. Thus good mapping is required for the targeted areas to prevent treatment insufficiency.

Although the highest number of studies has been performed with HIFU and cryotherapy, many recent studies on PDT, focal laser ablation and IRE also continue. Easy applicability and clearer prediction of the borders of the region of interest of thermal effect constitute the most important characteristics of laser ablation. The results of the continuing prospective studies will present the treatment efficiency more clearly. The studies performed with IRE known as non-thermal energy source were similarly found to be quite successful. The rates of succesful oncological results at the end of follow-up periods of over one year were found to be equivalent to those of the radical interventions [4,8].

Relatively higher side effect incidence and morbidities of established curative treatments constitute the most important justification for more frequent application of focal ablation therapies. These curative treatments become a severe burden both for the patient and the treating health units. If the same oncological result will be acquired through less invasive treatment methods and if the side effect profile is lower, whatever treatment method you use will be more popular. Side effect rates of focal ablation therapies in applied for prostate cancer are quite lower than known curative treatment methods. They have very good results especially in terms of preservation of continence and potency. Similar results were acquired in limited studies comparing oncological results of these treatment modalities [8,10,13,19,20].

A great progress has been achieved in prostate cancer diagnosis and treatment thanks to the high performance provided in multiparametric MR. We detect the lesions more clearly and correctly thanks to especially different diffusion characteristics of the tissues Thus, it is possible to recognize clinically important cancer focuses with rates up to 95% and to apply focal ablation therapy. In many multi-centered studies multiparametric MR has established its worth in the diagnosis and treatment follow-up in prostate cancer [21–23].

Conclusion

Conduction of the studies with different energy sources prevents making homogeneous comparisons among studies performed.. Standard patient approach couldn't be provided even in focal ablation therapies conducted with the same energy source. Thus, we couldn't get adequate, and accurate data from studies comparing outcomes of focal ablation therapies. But we expect that the focal therapy is now possible for the treatment of low-and intermediate-risk prostate cancer patients, and more importantly better results can be acquired.

Peer-review: Externally peer-reviewed.
Financial Disclosure: The author declares that this study received no financial support.

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