KAFKAS TIP BİLİMLERİ DERGİSİ
Kafkas Journal of Medical Sciences

DERLEME / *REVIEW*

Kafkas J Med Sci Kafkas J Med Sci 2015; 5(1):18–24 • doi: 10.5505/kjms.2015.50023

Focal Treatment Alternatives in Prostate Cancer

Prostat Kanserinde Fokal Tedavi Alternatifleri

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ABSTRACT

The destiny of prostate cancer patients has been dramatically changed since the introduction of prostate specific antigen (PSA) into clinical use in late 1980s. Currently more men are diagnosed with localized, small, less aggressive and non-lethal prostatic carcinoma. Besides radical prostatectomy, cryosurgical ablation of the prostate, brachytherapy and high-intensity focused ultrasound have been accepted as alternative treatment options in clinically localized prostatic carcinoma.

In this review, we aimed to evaluate the success and complication rates of alternative focal treatment options as the primary outcome. The secondary outcome of this review was to define the candidate patients eligible for these procedures.

We searched the Medline using specified expressions including "focal treatment alternatives of prostatic carcinoma", "high-intensity focused ultrasound and cryosurgery of prostatic carcinoma" and "radiofrequency ablation of prostatic carcinoma". A total of 1173 papers related to the focal treatment options were analyzed and only 45 of them related to the subject were included.

There wasn't a controlled trial dealing with the topic. American Urologic Association guidelines have accepted cryosurgical ablation of the prostate as a therapeutic option; however the high-intensity focused ultrasound is still considered as an experimental treatment option, although it has been developed as a minimally invasive procedure with reduced morbidity and potentially with the same therapeutic efficacy in comparison with the surgical or non surgical options.

For patients meeting the variable criteria for regular follow up visits without intervention but experiencing anxiety with the feeling of losing active treatment options, focal therapies may be ideal alternatives. However, focal therapy options should be spared for patients with low to moderate risks. The radiologic and clinical stages should be below T2b and T2a, respectively. In addition, all candidates should be informed that the alternatives are considered as experimental and they may need an alternative treatment option in time. Focal therapy alternatives may be more realistic treatment options in the near future; however, well designed multicenter prospective randomized trials are required to provide evidence based data.

Key words: *cryotherapy; high-intensity focused ultrasound ablation; minimally invasive surgical procedures; prostatic neoplasms; therapeutics*

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Geliş Tarihi: 13.03.2014 • Kabul Tarihi: 03.02.2015

ÖZET

1980'lerin sonundan itibaren, prostata özgü antijenin (prostate specific antigen, PSA) klinikte kullanılmaya başlanmasıyla prostat kanseri hastalarının kaderi dramatik olarak değişti. Günümüzde daha fazla sayıda erkek lokalize, küçük, daha az agresif ve ölümcül olmayan prostat kanseri tanısı almaktadır. Klinik olarak lokalize prostat kanserinin tedavisinde, günümüzde radikal prostatektominin yanı sıra, prostatın kriyo–cerrahi ile ablasyonu, brakiterapi ve yüksek yoğunluk odaklı ultrasonografi de alternatif tedavi seçenekleri olarak kabul edilmektedir.

Bu derlemede, birincil sonuç olarak lokalize prostat kanserinde fokal tedavi alternatiflerinin başarısı ve komplikasyon oranları belirlemeyi amaçladık. Derlemenin ikincil sonucu ise bu işlemler için uygun olan aday hastaların tanımlanmasıydı.

"Prostat kanserinin fokal tedavi alternatifleri", "yüksek yoğunluk odaklı ultrasonografi ve prostat kanserinin kriyocerrahisi" ve "prostat kanserinin radyofrekans ablasyonu" tanımlamalarıyla Medline taraması yaptık. Toplamda 1173 makale değerlendirildi ve bunlardan içerik olarak uygun bulunan 45 tanesi derlemede kullanıldı.

Konuyla ilgili kontrollü çalışma yoktu. Amerikan Üroloji Derneği kılavuzları, prostatın kriyocerrahi ablasyonunu tedavi edici bir yöntem olarak kabul etmektedir; ancak cerrahi ve cerrahi dışı alternatiflerle kıyaslandığında, daha az morbidite ve olasılıkla aynı tedavi etkinliğine sahip minimal invasiv bir yöntem olarak geliştirilmesine rağmen yüksek yoğunluk odaklı ultrasonografi ise hala deneysel olarak kabul edilmektedir.

Girişim yapılmadan düzenli takip edilme kriterlerini yakalayan ancak aktif tedavi şansını kaçırma hissiyle anksiyete yaşayan hastalarda, fokal tedaviler iyi alternatifler olabilir. Ancak, fokal tedavi seçeneği düşük ve orta dereceli riski olan hastalar için saklanmalıdır. Radyolojik ve klinik evre sırasıyla T2b ve T2a'nın altında olmalıdır. Ek olarak, adaylar alternatiflerin deneysel olduğu ve zaman içinde tedavi seçeneğinin değiştirilmesine ihtiyaçları olabileceği yönünde bilgilendirilmelidirler. Yakın gelecekte fokal tedavi alternatifleri daha gerçekçi tedavi seçeneklerine dönüşebilirler, ancak kanıta dayalı veri sağlamak için iyi desenlenmiş, çok merkezli randomize prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *kriyoterapi; yüksek yoğunluklu odaklanmış ultrason; minimal invazif cerrahi işlemler; prostat neoplazileri; tedaviler*

Introduction

The incidence of prostatic carcinoma (PCa) has increased all over the world since the clinical use of prostate specific antigen (PSA) as a screening tool. The screening policy has caused an increase in over detection and over treatments of clinically insignificant tumours that do not threaten patients' life. Overdetections of PCa bring a new dilemma about the patients' quality of life (QoL). In addition, patients with clinically insignificant tumours experience serious anxiety following the diagnosis of localized prostate cancer and search for curative treatment methods with permanent curative results. For patients meeting the variable criteria for regular follow up visits without intervention but experiencing anxiety with the feeling of losing active treatment options, focal therapies may be ideal alternatives.

Besides radical prostatectomy, cryosurgical ablation of the prostate (CSAP), brachytherapy and high-intensity focused ultrasound (HIFU) have been accepted as alternative treatment options in clinically localized prostatic carcinoma (PCa)[1–4].

American Urologic Association guidelines have accepted cryosurgical ablation of the prostate as a therapeutic option. However the high-intensity focused ultrasound is still considered as an experimental treatment option, although it has been developed as a minimally invasive procedure with reduced morbidity and potentially with the same therapeutic efficacy in comparison with the surgical or non surgical options.

Cryosurgery of the Prostate

Cell death is induced by dehydration in cryosurgery, which depends on freezing techniques. Dehydration causes protein denaturation, vascular stasis, microthrombus and direct rupture of cellular membranes by ice crystals. As a result of this cascade, microcirculation is detoriated with apoptosis and ischaemia[1–4].

For freezing prostate tissue 12–15F and 17F cryoneedles are used under the guidance of transrectal ultrasound (TRUS). Thermo-sensors and a urethral warmer are placed at the level of external sphincter and bladder neck. A temperature of -40°C is achieved in the mid-prostate gland and the neurovascular bundle with a two freeze thaw cycles.

CSAP is indicated with a tumor extended beyond the prostate[1–3]. The optimal size of the prostate should be below 40 ml. In case where the prostate size is more than 40 ml, the size should be reduced using hormonal therapies for avoiding the technical difficulties during placing the cryoprobes. PSA levels and Gleason score should be less than 20 ng/ml and 7, respectively. Patients having a life expectancy of more than 10 years should be informed about the lack of evidence dealing with long term results of the treatment modalities.

It is important to bear in mind that patients undergoing radical prostatectomy (RP) have a very low mortality risk (2.4%) for the next 10 years following the surgery[5]. Enhanced techniques like third generation cryosurgery, transperineal, gas driven probes have evolved the outcomes of the modality[6–11]. Globally accepted PSA level after this procedure has not been defined yet, due to lack of certain success and failure universal criteria depending on PSA levels. Some centers accept PSA values <0.1 ng/ml as a therapeutic success level, whereas some use the failure criteria of American Society of Therapeutic Radiology and Oncology (ASTRO) which requires three consecutive inclines in PSA level.

If a PSA nadir value is achieved <0.5 ng/mL with second generation CSAP, the low risk and high risk patients' biochemical disease free survival rates (BDFS) at five years are 60% and 36%, respectively[6,7]. A copious of authors had investigated the role of cryoablation. Onik et al. reported 48 patients, who underwent targeted focal therapy with the avoidance of treatment of one neurovascular bundle[12]. The follow up period for all patients was at least two years and overall median follow up was 4.5 years. Disease specific survival was 100%, and 94% of the cases had a stable PSA. Potency was preserved in 36 of 40 patients (90%), who were also potent before the treatment. All of them were continent, and 24 of the patients with a stable PSA value and a routine second prostate biopsy one year later had been disease free.

Lambert et al. preferred cryoablation to treat 25 patients with hemiablation of the prostate[13]. They reported that 21 patients (88%) were free of biochemical recurrence, which was defined as a reduction of PSA more than 50% at the 28th month of follow up. Of seven patients, who underwent post treatment biopsy, two patients had cancer in the contralateral gland and one patient had cancer in the area of the previous cryosurgery. The potency rate was 71% and there was no urinary incontinence.

Ellis et al. treated 60 patients with focal cryoablation of one lobe of prostate[14]. Eighty percent of the patients was free of biochemical recurrence during a median follow up of 15 months, which was based on ASTRO's failure criteria of three successive rises in PSA.

In a study, results of 31 patients, who underwent cryotherapy hemi-ablation were reported by Bahn et al.[15]. The biochemical recurrence free rate was 92% according to ASTRO criteria during a median follow up of 70 months. A mean of 2.3 post treatment biopsies were performed to these patients. Of the 25 patients, who had a follow up biopsy, 24 (96%) did not have any evidence of cancer. Potency was preserved in 89% and neither incontinence nor other complications were reported.

Long et al. reported CSAP results of 975 patients, who were enrolled into three risk groups[6]. The study period was 24 months and PSA thresholds were considered 1.0 ng/mL and <0.5 ng/mL. The five year BDFS rate for low risk group according to PSA values mentioned above was 76% and 60%, respectively. Intermediate risk group had a BDFS rate of 71% and 45%. The value was 61% and 36% for high risk group.

A recent meta-analysis studied the results of 566 cryosurgery related publications[16]; although there were no controlled trials, validated biochemical surrogate end points and survival data available for analysis. Depending on the definition of failure and risk groups, progression-free survival (PFS) of cryosurgery was reported to be between 36–92% (projected 1- to 7-year data). Approximately 72–87% of cases had negative biopsy results; however none of the data included biopsy results after the use of third generation cryotherapy machines.

PSA was evaluated in 63% of patients (110/176) during a 12 months period with regards to third generation machines[6–11]. Seventy-three percent (n=80) of these patients had a PSA nadir value below 0.4 ng/mL. If a cut off value of 0.4 ng/mL was used, 64.6% (42/65) of low risk patients would live free of biochemical progression.

Bahn et al. have reported a study having a longer follow up period[9]. The outcomes of 590 patients, who underwent CSAP for locally advanced and localized PCa were analysed. If a PSA cut off value lower than 0.5 ng/mL was used, seven year BDFS of low, medium and high risk groups would be 61%, 68% and 61%, respectively.

In a recent report, nerve sparing cryosurgery was defined as an experimental option[17]. Nine patients having unilateral PCa, which was confirmed on repeated biopsy specimen, underwent nerve sparing cryosurgery. CSAP was performed to the side of the positive biopsy, whereas negative side was protected against freezing.

Complications of CSAP for Primary Treatment of PCa

Erectile dysfunction is observed in 80% of patients and new generation systems seem not to affect the outcome of erectile dysfunction. The complication rates of third generation system are pelvic pain in 1.4%, incontinence in 4.4%, tissue sloughing in 3% and urinary retention in about 2% of the cases[6–11]. Fistula formation is a rare occasion and reported in <0.2% in modern series. Transurethral resection of the prostate (TUR-P) is required for approximately 5% of the patients due to subvesical obstruction.

In a clinical phase II trial, 75 men who underwent CSAP have been investigated for quality of life and sexuality following the procedure[18]. Most of the complaints disappeared during a 12 months period after CSAP according to the prostate-specific FACT-P questionnaire. Interestingly, when the data at 36 months was compared with 12 months' data, no significant changes were noted. In terms of sexuality, 37% of men were able to achieve intercourse 3 years after CSAP.

In a recent, prospective, randomized clinical trial, 244 men having organ confined PCa were enrolled to undergo either CSAP or external beam radiotherapy (EBRT)[19]. Sexual functions of these patients were compared at the postoperative period. EBRT group reported better sexual function after a follow up of three years.

HIFU of the Prostate

HIFU of the prostate was first reported in 1994 for treatment of benign prostatic hyperplasia. Gelet et al. first reported the results of its use for treating focal prostate cancer in 1996[20]. This technique depends on the damage caused by ultrasound's mechanical vibrations over a threshold of human's hearing threshold. It allows the focusing of ultrasound beams on a very narrow area ranging between 1–3 mm to 8–15 mm, depending on the transducer's characteristics[21]. Tissue damage is achieved by mechanical/thermal effects and

cavitation[22]. HIFU creates a temperature over 65°C and malignant tissues are damaged by coagulative necrosis. This heat produces cavitations due to the release of gas bubbles. Granulation tissue is formed by coagulation necrosis of the prostate with inflammatory response[23].

There are two commercially available transrectal HIFU devices for treating the prostate: Ablatherm® (Edap-Technomed, Lyon, France) and Sonoblate® 500 (Focus surgery, Indianapolis, USA). Both systems are approved for clinical use in many countries. The target treatment zone is heated for three seconds and then cooled for six seconds. The upper limit of the size of the prostate that can be treated by HIFU is 50 cm^3, due to limitations of ultrasound beams range. Thus, prior to treatment many centers prefer to perform TUR-P or androgen deprivation therapy to reduce the size of the prostate to the proper limits[24].

HIFU can be performed in the lateral position under general or spinal anesthesia. Ten gr/hour prostate tissue is heated, thus the procedure is time-consuming.

Results of HIFU in Prostate Cancer

Success criteria and oncological outcome of HIFU in prostate cancer create a dilemma, because there is not an international consensus about the outcome. A limeted number of PCa cases, <1000, have been reported in the literature.

In a published review, 150 articles dealing with oncological and functional results of HIFU were reported[16]. Like in CSAP, neither controlled trials and validated biochemical surrogate endpoints nor survival data were available for analysis. According to this recent review, HIFU had a PFS of 63–87% (3 to 5 year data), however, the median follow up period of these studies was between 12 and 24 months only[16].

Focal HIFU ablation was initially performed in 10 patients with a first generation machine undergoing subsequent radical prostatectomy[25]. Residual tumour was detected in seven of these patients. In another study, Muto et al. performed HIFU in 70 patients, 29 of them with localized prostate cancer, who had unilateral biopsy based evidence of cancer[26]. The ipsilateral transitional zone and bilateral peripheral zones were focally ablated. Negative biopsy rates at six and 12 months were 88.1% and 81.6%, respectively, during a median follow up of 34 months without differences between patients undergoing focal and whole gland ablation. Although sexual function was not assessed, the quality of life evaluation showed no significant differences in urinary morbidity between focal and whole gland therapy based on the UCLA-PCI and IPSS scores.

In one of the largest single center study, the results of 227 patients who underwent HIFU (Ablatherm®) for clinically organ confined T1–T2 PCa were analysed after a median follow up period of 27 months (12–121 months). The mean number of cycles per session was 419[27]. The projected five-year BDFS was 66% and it decreased to 57% in patients with PSA values between 4–10 ng/mL. Forty-three percent of patients required retreatment due to the persistence of the residual desiase. The rate of incontinence and bladder neck stricture decreased over time to 9% and 6% from 28% and 31%, respectively.

In another study, pre-treatment PSA value decreased to 2.4 ng/mL from 12 ng/mL[20]. However, positiviness of the prostate biopsies were 50% (n=7) during follow-up. Uchida et al. reported a three year biochemical recurrence free survival rate of 82% for 63 patients with clinical T1 or T2 cancers with the Sonoblate®[28]. Urethral strictures were noted in 24% of the patients.

A European multicenter study reported the efficacy of HIFU involving the data of 559 low and intermediate risk PCa patients[29]. During a follow-up of at least of six months, a negative biopsy rate of 87.2% was reported in 288 men. Re-treatment rate was 28%. After a follow up period of six months, PSA nadir was 1.8 ng/mL and determined in 212 patients. In addition, it was mentioned that a PSA nadir value might be achieved after 12–18 months following the initial procedure.

Blana et al. reported the outcomes of 146 patients after a median follow-up of 22.5 months, who underwent HIFU[30]. At the initiation of therapy, mean PSA level was 7.6 ng/mL and it decreased to 0.07 ng/mL after three months. However, the median PSA value increased to 0.15 ng/mL at the end of 22 months. Analysis was available in 137 men and 93.4% of these patients revealed a negative control biopsy. Treatment failure was found to be strongly associated with PSA nadir ($p<0.001$)[31]. Treatment failure rates of patients with a PSA nadir of 0–0.2 ng/mL, 0.21–1.00 ng/mL and >1ng/mL were 11%, 46% and 48%, respectively. Same authors have recently updated the outcomes in a study involving the data of 163 men, who were treated for clinically organ confined PCa. The actual DFS rate was 66% at 5th year and salvage treatment

was required in 12% of patients during a mean 4.8±1.2 years of follow-up[32].

In another study, HIFU was used for treating 517 men having locally advanced or organ confined PCa[33]. They accepted the biochemical failure criteria included in Phoenix guidelines, as PSA nadir of +2ng/mL. The BDFS was 72% for the entire cohort after a median follow-up of 24 months. The BDFS rate of patients having T1c, T2a, T2b, T2c and T3 stage at five years was 74%, 79%, 72%, 24% and 33%, respectively ($p<0.001$). The same rate of low/intermediate and high-risk groups at 5 years was 84%, 64% and 45%, respectively ($p<0.001$). The BDFS rate of patients, who were treated with or without neoadjuvant hormonal therapy at seven years was 73% and 53%, respectively ($p<0.001$). Various degrees of erectile dysfunction was observed at the postoperative period in 28.9% (33/114) of patients who were potent preoperatively.

The records of one hundred and thirty seven patients having PCa undergoing HIFU were evaluated retrospectively in a study[34]. During a mean follow up period of 36 months, disease relapsed in 22% of the patients. The overall five-year DFS rate was 78%. DFS rate of low, intermediate and high risk group at five years was 91%, 81% and 62%, respectively. Dysuria (n=33) and urge incontinence (n=16) were common side effects and repeated in 24.1% and 11.8% of patients after removing the urethral catheter.

Bouiter et al. evaluated the risk of incomplete transrectal HIFU ablation in terms of the location of PCa (basis/mid/apex)[35]. They analysed the outcomes of 99 patients undergoing HIFU ablation (Ablatherm®) with a 6mm safety margin at the apex. They performed systematic biopsies at three and six months after the initial treatment. Residual cancer was observed in 36.4% (n=36) of patients. Fifty of the biopsy sextants (8.4%) were positive; eight (16%) were in the basis, 12 (24%) were in the mid and 30 (60%) were in the apex. Statistical analysis revealed that the mean (95% CI) probability for a sextant to remain positive after HIFU ablation was 8.8% for basis, 12.7% for mid, and 41.7% for the apex. Erectile dysfunction and incontinence were less common, when a 6mm safety margin was used at the apex. It was mentioned that, in terms of location of residual cancer, apex was significantly the more frequently affected part.

During a mean follow-up period of 47 (2–70) months, Komura et al. reported the oncological outcomes of 144 patients having T1/T2 PCa[36]. Disease parameters relapsed in 39% of the patients. Urethral stricture was observed in 40% of the patients at the postoperative period. Interestingly, the value of five year DFS was significantly better in patients having stricture, when compared with patients without strictures (78.2% vs 47.8%, $p<0.001$) and more aggressive treatment was required for the carcinomas located at the apex of the prostate.

Complications of HIFU

Urinary retention is one of the most common side effects of HIFU and observed in nearly all patients. The patients are catheterized trans-urethrally or via a suprapubic tube for 12 and 35 days[20,22,27]. Bladder neck or urethral strictures seem to be the frequent late side effects according to the reports from whole gland HIFUs. Impotence is not investigated well in most of the studies, however ranges between 20% and 50%. Urethrorectal fistula is a rare; but challenging complication. The rate of fistulas has been reported exceedingly low in many series due to the use of new devices and modified software in the market, rectal cooling and robotic control of rectal distance.

Elterman et al. evaluated the frequency and type of complications in 95 patients having clinically organ-confined PCa, who underwent HIFU with Sonablate-500® device[37]. Two percent of the patients developed significant erectile dysfunction and 17% (7/41) had significant incontinence during a minimum follow-up of six months. Twenty (21.1%) and 17 (17.9%) patients required surgical treatment for late and early inferovesical obstruction, respectively.

Miscellaneous Modalities

Vascular targeted photodynamic therapy (VTP) involves the generation of cytotoxic agents in situ that results in tissue ablation and cell death. A photosensitizing drug, which is achieved by systemic or local administration, is activated with a specific wavelength light. It causes localized coagulation necrosis and vascular thrombosis around the tip of the optic fiber. The fiber is applied transperineally and ablation volume is titrated to $18cm^3$ in size step by step[38].

The use of the photosensitizer Tookad® (WST09) in the VTP of prostate cancer has been investigated in a recent study. Huang et al. reported that clinically significant volume of normal canine prostate tissue might

be destroyed with Tookad-VTP[39]. A pilot trial involving six patients, who had undergone focal VTP for clinically organ confined cancer showed evident ablative changes on MRI and achieved an average rate of 67% PSA declines[40]. Ahmed et al. reported a dose response by an increase in the volume of hypoperfusion observed on the post treatment MRI in 27 men[41]. This technology appears as a promising alternative; however long term follow up and quality of life outcomes need to be defined.

Laser induced interstitial thermotherapy (LITT) is another encouraging alternative that depends on the use of one or two source fibers for targeted necrosis and thermal coagulation. Lindner et al. reported LITT in 12 patients with low risk prostate cancer (T1c or T2a, PSA <10 ng/ml, 30% or less cores involved). Location was established with 12 sextant biopsies and multiparametric MRI[42]. The most common side effect was perineal discomfort (25%). The results of the treatment were evaluated by using MRI and biopsies. Four patients had residual tumour in the treated areas while six patients were disease free.

Pretherapeutic Assessment of Candidates for Focal Treatment

TRUS-guided biopsy regimens are not sufficient for selecting candidates due to systematic and random errors. A template–guided approach with transperineal prostate biopsy is the current gold standart for selecting the patients eligible for focal therapy[43,44]. This approach can rule in and rule out 0.5 and 0.2 mL volume PCa foci with 90% certainty, when a 5 mm sampling frame is used[45].

The destiny of prostate cancer patients has been dramatically changed since the introduction of prostate specific antigen (PSA) into clinical use in late 1980s. Currently more men are diagnosed with localized, small, less aggressive and non-lethal prostatic carcinoma. Besides radical prostatectomy, cryosurgical ablation of the prostate, brachytherapy and high-intensity focused ultrasound have been accepted as alternative treatment options in clinically localized prostatic carcinoma. For patients meeting the variable criteria for regular follow up visits without intervention but experiencing anxiety with the feeling of losing active treatment options, focal therapies may be ideal alternatives. However, focal therapy options should be spared for patients with low to moderate risks. The radiologic and clinical stages should be below cT2b and cT2a, respectively. In addition, all candidates should be informed that the alternative therapies are considered as experimental and they may need an alternative treatment option in time. Focal therapy alternatives may be more realistic treatment options in the near future; however, well designed multicenter prospective randomized trials are required to provide evidence based data.

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