Prostate Thermal Therapy: Technologies and Treatment Strategies

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ABSTRACT

Benign prostatic hyperplasia is a frequent benign disease that often requires surgical intervention. Prostate cancer affects 250,000 men annually, with surgery and radiation therapy the common form of treatment. Numerous biological and clinical investigations have demonstrated that HT in the 41-45°C range can significantly enhance clinical responses to radiation therapy, and has potential for enhancing other therapies such as chemotherapy, immunotherapy, and gene therapy. Furthermore, high temperature hyperthermia (greater than 50°C) alone is being used for selective tissue destruction as an alternative to conventional invasive surgery. Thermal techniques are being utilized to complement existing courses of treatment or provide minimally invasive alternative to surgery with less complications, and morbidity for each of these diseases. This article reviews a selection of heating technology and strategies specific to prostate thermal therapy, which are either in clinical use or currently under development. Transurethral, transrectal, and interstitial systems are discussed for RF current, laser, microwave, ultrasound, and thermal conduction heating technology.

Keywords: Prostate, Thermal Coagulation, Hyperthermia, BPH, Cancer, Thermotherapy

1. INTRODUCTION

1.1 Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and will affect over 800,000 men per year in the United States (23 million worldwide for moderate to severe symptoms). The incidence of BPH in the male population increases with age, and has been reported as ranging between 50-75% for males 50-60 years of age, and close to 100% for over 80 years of age [1]. Both obstructive and irritative symptoms are generated by hyperplasia or abnormal growth of the transition zone and periurethral tissue surrounding the urethra. As the adenomatous tissue within the transition zone expands, it compresses or blocks the urethra. This central region of the prostate consists of both stromal and glandular components. Standard treatment options include drugs (α–blockers to relax smooth muscle in bladder neck and prostate, androgen ablation to suppress growth of glandular tissue), transurethral resection of the prostate (TURP), or open prostatectomy. The surgical TURP, considered the "gold standard" of treatment for BPH, resects or removes obstructive tissue directly and can provide good long term relief, improving patient symptoms and voiding functions [2, 3]. However, TURP

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procedures pose significant complications such as necessity of blood transfusion, incontinence, erectile dysfunction, and retrograde ejaculation. Plus, in approximately 15% of the patients a second surgical intervention may be required [4-6]. Prostate thermal therapy provides a minimally invasive treatment option with potentially less morbidity and complications, and lower cost compared to surgery.

1.2 Prostate Cancer

Adenocarcinoma of the prostate (CaP) is the most commonly diagnosed cancer in the U.S. male population. According to the American Cancer Society, there will be approximately 180,000 new cases diagnosed in 1999 and is the second leading cause of cancer death (second to lung cancer) with 37,000 in 1999. With the increasing use of prostate specific antigen (PSA) testing in conjunction with transrectal ultrasound (TRUS) and digital rectal exams, the increase in prostate cancer detection is significant. In addition, the number of new locally-advanced prostate CA cases are estimated to be over 38,000 annually. Approximately 45% of these patients receive radiation therapy. While early local control of disease approaches 80%, approximately 50% of patients undergoing radiotherapy recur over a three to five year period [7]. Ultimately, a much higher percentage fail either surgery or radiotherapy [8]. Current minimally invasive therapies such as radiation therapy, brachytherapy, and hormones offer an attractive alternative but have been shown to be slightly less efficacious than radical prostatectomy, but the concomitant reduction in morbidity is significant and often worth the compromise to the patients. There is, therefore, increasing interest in the use of other minimally invasive methods such as thermal ablative surgery or adjunct hyperthermia for the treatment of early stage disease or locally recurrent disease.

Contrary to BPH, prostate cancer frequently arises in the posterior-lateral aspects of the peripheral portion of the gland, and as the disease progresses will spread within the anterior-lateral and transition zones [9, 10]. In early stage disease, involvement of the anterior gland is less likely. A recent pathological study of radical prostatectomy cases [11] summarized disease location as follows: 56% of cases presented tumors extending within the distal 5 mm of the apex, 12% tumor extending within the proximal 5 mm of the base, 2.4% involvement of seminal vessicles, 95% involvement of the posterior gland, and 65% with anterior involvement. The cases of anterior involvement always included posterior involvement and possible extracapsular extension. Thus, the following treatment strategies are indicated with respect to thermal therapy: (1) when treating using high-temperature thermal therapy alone, the complete gland should be treated in a very controlled fashion including the distal extent of apex and proximal portion of the base in order to target probable microscopic extension of the disease; (2) may be possible to use adjunct localized thermal therapy to destroy focal disease in sites of extracapsular extension, or in the peripheral and posterior zones—this approach may allow use of less radiation exposure to sites such as bladder, rectum and urethra, thereby reducing complications. (3) Due to improved diagnostics (MRI, TRUS) it may be possible to localize the thermal therapy to the localized cancer lesion with an acceptable margin, yet preserve surrounding non-involved prostate tissue, thus potential preserving the most function with the least amount of complications.

1.3 Thermal Mediated Effects at Moderate and High Temperatures

In general, conventional hyperthermia or tissue heating at moderate temperatures (41-45°C) has been shown to promote changes in cellular dynamics, tumor microcirculation, and blood vessel permeability that can be exploited to enhance other therapies [12-14] potentially directed at prostate cancer. Immediate effects of thermal exposure in this regime include heat induced acceleration of metabolism, thermal inactivation of enzymes, and rupture of cell membranes. Delayed effects include intracellular and tissue edema, hyperemia with increasing blood flow, as well as an increase in blood vessel permeability and dilatation. For low temperatures and shorter times of exposure (non-lethal thermal doses) the damage due to thermal effects alone is reversible. For longer times or higher temperatures, cellular repair mechanisms can no longer keep up or lose function due to thermal damage of key enzymes , and cell death and tissue necrosis will occur within 3-5 days.

The localization of high-temperature hyperthermia at temperatures greater than 45-50°C can be used to selectively destroy or permanently alter tissue regions. In the high-temperature regime, thermal coagulation and thermal necrosis occurs in tissues exposed to temperatures greater than 50-55°C for a duration of 1-2 minutes [13] or shorter times for even higher temperatures. Thermal exposures to these high temperatures cause cellular and tissue structural proteins to undergo irreversible denaturation and conformational changes. These thermal effects are lethal and immediate, producing thermally coagulated tissue. On the extreme end, temperatures close to or greater than 100°C generate less subtle effects, such as explosive vaporization and ablation of tissue.

The expression of the above thermally mediated effects is a dynamic process and can be tied to a thermal isoeffect dose or normalized temperature exposure ($EM_{43°C}$= Equivalent Minutes at 43°C). This thermal dose is linearly proportional to exposure time and exponentially related to temperature elevation during exposure [15-17]. The thermal isoeffect dose concept can be used to convert between different heating protocols for different times and temperatures to a value of $EM_{43°C}$ required for a given thermal effect on tissue. As a general rule, for temperatures equal or greater than 43°C, the required thermal exposure time is reduced by approximately 50% for each degree increase. For temperatures below 43°C, the required exposure time is increased by a factor of four for each degree decrease in exposure temperature. For example, thermal exposures of approximately 120 min at 43°C (120 EM43°C) have been demonstrated to be cytotoxic to prostatic cancer cells [18]. This same biological effect could be produced by maintaining 45°C for 30 min, or 42°C for 480 min. This concept can apply to coagulation as well. For example, if 1 min exposure at 56°C coagulates prostatic tissue, then approximately 2s exposure at 60°C will produce similar effects. These thermal dose thresholds do vary according to tissue type and cellular effects [16]. Relevant examples include rectum necrosis after 100 EM 43°C [19], muscle necrosis after 240 EM 43°C, brain necrosis after 25 EM 43°C [16]. The thermal dose concept is important for understanding the rationale and comparing different heating strategies.

1.4 Difficulties in Prostate Heating

Several difficulties or obstacles arise when trying to localize and control heating to target regions or tumors sites in the prostate gland. The dimensions or geometry of target regions are often irregularly shaped in both lateral extent and the depth dimensions. The typical prostate is wedge-shaped in the longitudinal extent, with the apex being more narrow than the base, plus the urethra is not centered and varies in transverse position within the gland. Furthermore, thermal properties (thermal conductivity, energy absorption, and blood perfusion, thermal sensitivity) are both heterogeneous and dynamic as well [20-22]. The prostatic target regions may be neighboring thermally sensitive tissue, such as rectum, bone or nerves. The thermal heat transfer processes are dominated by heterogeneous distributions of blood perfusion and thermally significant blood vessels (>.1 mm OD), which in turn cause local heterogeneities in the temperature distributions and redistribute thermal energy to other tissue regions. This is typically encountered in the prostate, which often has more vascularity and increased perfusion in the peripheral posterior portion of the gland [22, 23]. These blood flow characteristics often change during the course of a treatment, and can shut down completely in coagulated regions or substantially increase in response to heating [24]. The effects of heterogeneous temperature distributions are exaggerated when looking at tissue effect due to the non-linear relationship of temperature to thermal dose. The effectiveness of hyperthermia has been shown to be strongly dependent upon the temperature uniformity and $EMT_{90}43°C$ (equivalent minutes at 43°C) delivered. With many of the current heating technologies, the required temperatures and thermal doses throughout the complete target volume have been difficult to achieve on a regular controlled basis [25]. The use of high-temperature technology requires precise localization of heating energy, especially nearby critical normal structures such as sphincters and nerves. In order to enhance these HT treatments as stand alone or adjunct therapy and improve efficacy and continuity of treatment for prostatic disease, techniques with the ability to spatially localize and control the heating distributions are tantamount.

1.5 Specific Objectives Of Prostate Thermal Therapy

With regards to treatment of BPH, prostate thermal therapy provides a minimally invasive treatment option with potentially less morbidity and complications, and lower cost compared to surgery. The thermal goal or target is two-fold: conventional HT to generate some tissue necrosis, thermal necrosis and/or coagulation for destruction of smooth muscle and glandular components [26] within the periurethral tissues, thereby reduces neuromuscular tone. These tissues comprise the central lateral-anterior component of the prostate gland. The destruction of α-receptors or sensory nerves in the prostate stroma is a possible explanation for reduction of irritative symptoms (as noted during α-blocker therapy). Higher temperatures can be used to coagulate tissue, and after tissue is reabsorbed (shrinkage) or sloughed off, a larger urethral cavity is formed thereby providing obstructive relief. The tissue between or including the bladder neck and the verumontanum are the target, while avoiding damage to the sphincters, nerves, and rectum.

For treating localized prostate cancer with thermal therapy, there are many possible thermal goals or strategies. One strategy would be the application of moderate hyperthermia (41.5-45°C range) as an adjuvant to radiotherapy [27, 28] or chemotherapy

[29, 30]. Typically, hyperthermia treatments are usually for a period of 30-60 minutes and applied once or twice a week, sequentially or in close proximity to course of radiation therapy (RT). Hyperthermia is a radiosensitizer which increases radiation damage and prevents subsequent repair. Plus, hyperthermia is directly cytotoxic, especially in deprived microenviroments with low blood supply, hypoxia, low pH, such as commonly encountered in portions of a malignant tumor. This response is significantly enhanced when heat and radiation treatments are applied simultaneously [16, 27, 31]. Fortuitously, prostate cancer cells have been shown to be more sensitive to HT damage and demonstrate preferential heat-induced radiosensitization [32] over normal prostate cells. In addition, prostate cancer sites are typically hypoxic [33], meaning resistant to radiation therapy yet sensitive to heat treatment. This indicates a strong potential role for HT in conjunction with either external beam radiation therapy or interstitial brachytherapy. In general, a strong clinical rationale exists, where recent Phase-III randomized trials for treating melanoma [34], glioblastoma multiforme [35], and chest wall recurrence of breast cancer [36] showed that the addition of hyperthermia treatment to RT significantly increased the rate of tumor response and tumor free survival when compared with radiation therapy alone. To date, there have been no reported randomized Phase III studies of HT + Radiation for localized prostate cancer. Furthermore, conventional HT can also be used to enhance the uptake and effect of liposomal chemotherapy [37-39], immunotherapy and gene therapy [40], but this technology is still very new.

The use high-temperature thermal therapy to thermally coagulate or necrose the prostate gland is another strategy. Due to the potential for microscopic extension of cancer throughout the gland, the whole prostate gland should be targeted for complete therapy, especially if the sole form of treatment. However, in certain circumstances there may be significant benefit to use the HT as adjunct to treat or debulk the local tumor and potentially reduce treatment limiting radiation dose to the rectum, nerves, or bladder.

2. TECHNOLOGY AND HEATING STRATEGIES

Prostate thermal therapy can be delivered by interstitial, transurethral, transrectal, or external applicators. The therapy is often applied using RF currents, microwaves, ultrasound, laser and thermal conduction sources. The following section of this article reviews some of the devices from each modality and applicator approach that are designed for treating localized disease, and may have a significant impact on prostate thermal therapy. Techniques for RF and laser surgery (TURP), and deep regional or whole body hyperthermia are not presented, but reviews of this technology can be found elsewhere[41, 42]

2.1 Microwave Heating Technology

Transrectal Microwave Heating Devices

Some of the early studies of localized prostate heating were via the transrectal approach using microwave (MW) applicators for treating cancer [43-45]. Most applicators were operated at 2450 MHz, with 915 MHz and 434 MHz [46] less common. Some versions of applicators incorporated chokes to contain the radiation pattern to the distal 4 cm of the applicator and directional (180° or 360°) radiation patterns to better direct the heating to

the prostate [45]. In order to reduce complications such as rectal fistula, cooling systems (12-14°C water) are incorporated to protect the rectal mucosa and rectal wall from overheating. Nonetheless, rectal burns remained a serious complication associated with this technique [47, 48]. This is problematic with transrectal MW techniques, since the rectal tissue lies between the target (prostate) and the applicator and is thermally sensitive, with heat damage occuring at thermal dose thresholds of 43°C for 30 min or 30 EM $_{43°C}$ [19, 49]. The typical treatment protocol was to apply hyperthermia (42-44°C) for multiple 1 hour sessions, twice weekly, as an adjunct to external beam radiation therapy (RT) to the whole prostatic mass. Apart from positive results for tumor treatment, it was noted that prostate heating also provided some relief from irritative and obstructive symptoms associated with BPH. This led to subsequent study of transrectal MW hyperthermia for treating BPH [47, 50-53]. Many of these later studies on BPH were performed using the Prostathermer, a commercial system operated at 915 MHz. Multiple 60 minute heating sessions (6-8) were required, for overall treatment duration of up to a month [47, 51] with a total of six on average. During these treatments, rectal and urethral temperatures were monitored, with prostatic urethra temperatures between 40 and 43°C typical. These temperature measurements were suggestive that transrectal thermal therapy delivered a uniform and safe distribution of heat in the prostatic substance and urethra [54]. However, treatments within this temperature range and exposure caused little tissue destruction and minimal edema, and thus did not create any notable histological changes in prostate tissue. Accordingly, the outcome of these studies indicated only minor and short duration improvement in symptomatic and objective responses within a month of treatment. In retrospect, it is apparent that the thermal exposures were too low to generate durable clinical responses for treatment of BPH. Furthermore, it has been demonstrated that transrectal MW applicators are not a suitable energy source for heating more than approximately 2 cm from the rectal wall without overheating the rectum [55]. This is due to the high attenuation of MW energy in soft tissue and the significant radial or geometric losses from the antenna, leading to efficient heating of the posterior portion of the gland, but limited heating to the areas in anterior and central gland-the target region for treating BPH. Furthermore, maintaining positioning of the applicator is problematic, whereas changes in the contact area with the rectum or position within the rectum would dramatically change the heating pattern. One approach to improve heating was to combine a transrectal and transurethral MW applicator for more controlled therapy of the whole gland [56].

Transurethral Microwave Heating Devices

A more direct approach utilizes transurethral MW applicators to localize the heating energy and maximum temperature within the prostate tissue surrounding the urethra. Early developments centered on an array of either 2-3 dipole antenna [57] or a single helical antenna mounted within non-cooled modified Foley catheter[58, 59]. The helical antenna design was more acceptable due to a more cylindrical shaped heated region with more consistent heating profiles, as would be expected since dipole antennas are very sensitive to insertion depth within tissue. Temperature monitoring via thermistors or fiber-optic probes built into the applicator were used to control the temperatures to 44-48 °C at the applicator/urethra surface. Extensive thermometry measurements have demonstrated that these applicators generated an effective treatment volume of 15 mm diameter x approximately 3- 4 cm long [60]. Initial clinical studies of transurethral hyperthermia (TUHT) for treating BPH typically applied 6-10 treatments over the course of 5 weeks, and clearly indicated TUHT had fewer complications and statistically better

responses than transrectal heating with microwave energy [61, 62]. Most notable advantages: balloon catheters can ensure reproducible position of the heating applicator within the prostate, plus the heating can be localized directly in the adenomatous tissue target region without overheating the rectum. This is ideal for treating typical of BPH. By localizing the heating to the transistion zone adenoma, higher temperatures can be achieved without concurrent damage to surrounding non-targeted tissues outside of the gland.

Thus in the evolution of this approach, it was felt that applying higher temperatures (>48-55°C) for a single treatment (versus 6-8 for TUHT) would be desirable to generate more extensive tissue coagulation and necrosis within the prostate in order to provide more durable symptomatic relief and reduced obstruction [63]. Cooling of the urethral surface to temperatures of 45° C or less was incorporated to preserve the urethral mucosa, allow more power to be applied, increase penetration, and without a substantial increase in patient discomfort [63]. This higher temperature therapy has been refered to as transurethral microwave thermotherapy (TUMT). Several commercial devices have been developed for TUMT and used extensively in clinically studies. The Urologix Targis system uses a single helical-dipole hybrid microwave antenna (2.8 or 3.5 cm long, operating at 902-928 MHz) within a water-cooled catheter delivery system (Fig. 1). The helical coil is attached through a ground connection and a tap to the center conductor, and is within 0.4 cm of the positioning balloon [64]. The eccentric placement of the antenna within the body of the catheter yields a directional heating pattern which preferentially targets the anterior and lateral regions of the prostate while reducing exposure to the most posterior 45° sector near the rectum. During therapy, the impedance of the antenna is monitored, and the driving frequency varied in order to maintain efficient transfer of energy the prostate. The radiated microwave energy pattern is purported to closely correspond to the length of the helical windings with little feedline radiation, essentially coring out a zone of tissue centered between the bladder neck and verumontanum. Detailed temperature measurements have shown maximum temperatures in excess of 58° C out 5 mm from the applicator, and urethra and rectum were maintained below 39.6 and 40.8, respectively [65]. Histological studies indicated tissue necrosis out 1.6 cm radial depth correlating with the 45°C contour[66-68]. The Prostatron (Edap-Technomed) is a similar catheter-based technology with an integrated monopolar radiating antenna operating at 1296 MHz (Fig.2a). In this design, the junction between the inner and outer conductor is centered 1 cm distal of the positioning balloon, extending into the bladder neck. This configuration has been shown to produce symmetric heating patterns about the catheter axis; however, there are components of feedline radiation and energy deposition proximal to and including the bladder neck which potentially may lead to unwanted heating outside of gland, such as the external sphincter [64], especially during higher-power exposures.

Numerous clinical studies of these technologies have demonstrated a role of TUMT for treating symptomatic BPH by reducing symptoms (urinary frequency, urgency and intermittent flow), but to a lesser extent obstructive BPH symptoms (incomplete voiding of bladder) [69-72]. This has been explained by recent studies which have demonstrated that the therapeutic action of TUMT is to dennervate and destroy muscular components of the prostatic tissue, but not generate large zones of tissue necrosis and eventual tissue retraction or removal [70, 71].

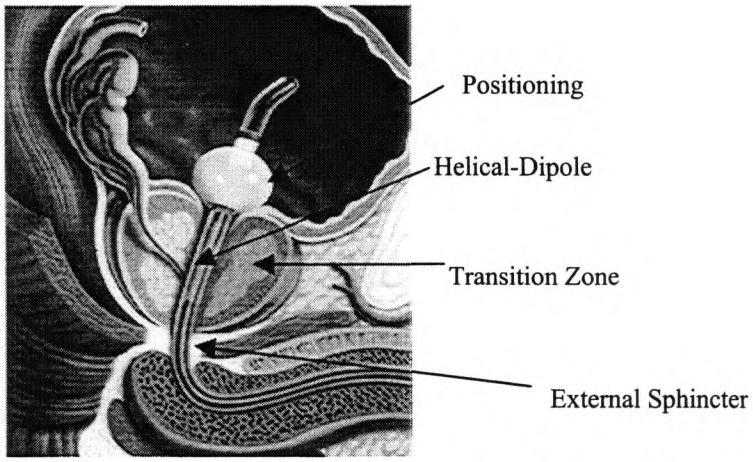

Fig. 1 Urologix Targis transurethral microwave thermotherapy catheter placed within the prostate for treating BPH (Photo Courtesy of Urologix, Inc.).

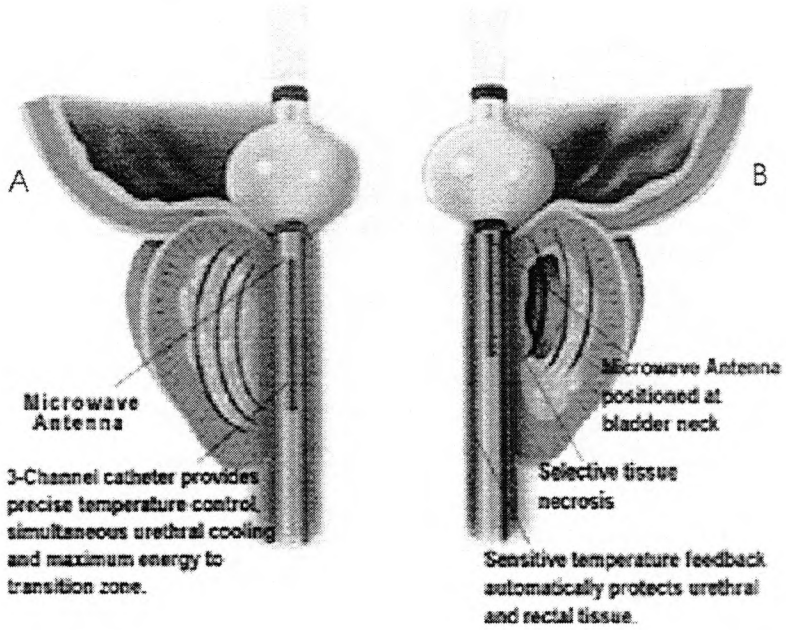

Fig. 2. Diagram of Prostatron monopole microwave applicator and catheter demonstrating (a) TUMT and (b) HE-TUMT protocols (Photo Courtesy of Edap-Technomed).

Newer treatment protocols are being investigated which use higher intra-prostatic temperatures, and currently being refered to as high-energy transurethral microwave thermotherapy or HE-TUMT [73-75]. The power levels are increased compared to TUMT in order to thermally ablate and coagulate large regions of tissue, possibly including the bladder neck. Tissue sloughing and retraction after treatment provides a means of securing more durable treatments and reduction of urethral obstruction and concomitant improvement in symptomatic and obstructive disease. This concept of higher temperatures and treating the bladder neck is illustrated in Fig. 2b, a depiction of the Prostatron 2.5 heating protocol.

The transurethral microwave techniques appear attractive for treating BPH since a relatively large portion of gland is heated, it is not necessary to uniformly treat the entire gland, techniques are fairly simple, and generally not painful. Potential shortcomings include inability to effectively shield heating away from rectum during high energy protocols and lack of control of thermal dose distribution. Essentially, the only control is power level; the heating distribution cannot be altered or shaped dynamically. Furthermore, transurethral application of MW's is not adequate to treat the peripheral and posterior portions of the prostate, which would be required for treating most cancer except those centered around the urethra [66, 67].

2.2 RF Heating Technology

Transurethral RF Heating Devices

RadioFrequency current heating techniques are currently being applied from within the urethra for hyperthermia or thermal coagulation of large volumes of prostate tissue. Examples of this approach include TransUrethral RadioFrequency (TURF) and TransUrethral Needle Ablation (TUNA). The TURF technique uses a flexible transurethral Foley-like catheter with an RF capacitively coupled electrode over a distal 1-2 cm segment, centered within the prostatic urethra and back 5 mm from the bladder neck (e.g. Thermex II[76-79],TURAPY XL, Pros-Eight [80]). Return electrodes are typically placed outside the body. A range of high-frequency RF driving frequencies are applied to produce symmetrical radiating energy patterns. Initially, the treatment regimen was 2-3 hours at 44-48°C maximum at the urethral surface, as measured by temperature sensing on the applicator surface . This approach has been shown to produce a small cylindrical core of hemorrhagic necrosis extending 12 mm diameter [81], and is limited in radial penetration by the $1/r^2$ losses of RF energy plus the applicator surface is not cooled. Noted that greater impact on irritative rather than obstructive symptoms. Newer TURF technology treats larger volumes to higher temperatures (80°C/1 hour) in order to relieve obstructive symptoms. The therapy catheters have integrated cooling and multiple temperature sensors to prevent damage of the sphincters and rectum.

The Transurethral Needle Ablation –TUNA delivery system is designed for treating BPH by selective localization of thermal ablation directly within the prostatic adenoma [82-85]. The TUNA applicator consists of a 22 F urethral catheter with twin needles that deploy from the tip, at either 90°, 45°, or 10° (See Fig. 3). These needles have retractable insulating sleeves that may be used to protect the urethral tissue. The insertion depth of the RF needles (i.e., 10-20 mm) and the insulating sleeves (i.e., 4-6 mm) are adjustable to accommodate different size prostate glands or treatment strategies—these parameters are often determined using transrectal ultrasound images. Temperature sensors are located in

the RF needle tips and within the catheter body to be used for monitoring and control of treatment. Typical treatment usually involves 3-4 lesions per lobe, (4-15 W at approximately 500 kHz), 3-5 min each. The lesions are highly localized, centered around the electrodes, and confirmed by histology to generate well demarcated lesions of 12 x 7 mm and 17 x 10 mm for durations of 3 and 5 minutes, respectively [86]. After each lesion, the applicator is drawn back in the urethra, repositioned and needles placed for the next lesion—leading to approximately 1 hour treatment time. During the treatment, the generator alters power according to impedance measurements and temperature measurements. The therapeutic goal is to achieve temperatures around 60-100° at needle tips and 40-50°C at the lesion periphery, while maintaining rectal and urethral temperatures below 42°C. Newer versions (VTS PROVu) are easier to use and allow for the treatment of the median lobe in addition to lateral lobes. The TUNA system allows directive treatment of target with preservation of urethra and prostatic capsule. Typically requires only local anesthetic with minor discomfort noted during a small percentage of treatments. Because of urethral preservation and deep coagulation, catheterization time is dramatically reduced. Proven symptomatic improvements with few side effects. Significant to note that complication rates for impotence and retrograde ejaculation are very low when comparing TUNA to other thermal ablation techniques.

Interstitial RF Heating Devices

Interstitial RF heating techniques have been used in clinical studies to apply hyperthermia as an adjunct for brachytherapy in the treatment of prostate cancer [87, 88]. Basically, RF electrical currents are applied between up to approximately 16 steel implant needles to localize the heating to the target region, which often encompassed the prostate gland. The temperature distributions are very difficult to control with this approach, and often required an inter-needle spacing approaching 1 cm.

Interstitial RF probes have also been developed for thermal ablation of liver tumors [89] and have recently been applied for treating localized regions of prostate cancer [90-93]. The RF electrodes consist of a single 15 g needle with a 1 cm active segment at the tip; three active umbrella needles deploy at 120° angles to each other from the tip to form a spherical volume approximately 2 cm diameter. The deployable needles have temperature sensors in the tip for feedback control and monitoring during the treatment. The probes are placed transperineally using ultrasound guidance. Once the tip of the needle is centered in the region of localized cancer, the umbrella needle elements are deployed. In patient studies the average coagulated lesion dimensions at histologic examination were 2.2 x 2.1x 2.4 cm^3, and were well defined and did not extend beyond the prostatic capsule. No complications (e.g., rectal wall injury) were noted, and indicated that RITA-induced lesions were safe, feasible, technically simple, and resulted in lesions well predictable in size and location [91].

Another interstitial technology that deserves mention is the transurethal placement of a saline-cooled RF electrode into a lobe of the prostate for possible treatment of BPH or cancer. A 26 g needle with a 5 mm active region at the tip is inserted through the urethra to the target region using a cystoscope [94]. Cooled saline flow of 2 ml/min out the needle prevents dessication or extreme ablation at the needle surface, thereby allowing higher energy densities to be delivered and subsequently larger volumes of coagulation. In vivo studies in canine prostate glands indicated reproducible 1.8-5 cm3 lesions over 30-90 s power application.

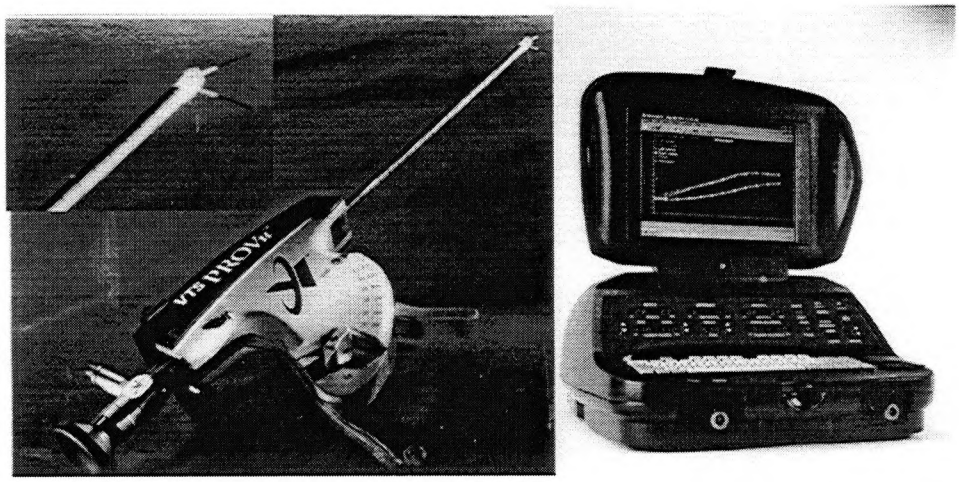

Fig.3. Transurethral Needle Ablation-TUNA- energy delivery catheter and portable RF generator and treatment control unit (Photos Courtesy of VidaMed, San Jose, Calif.)

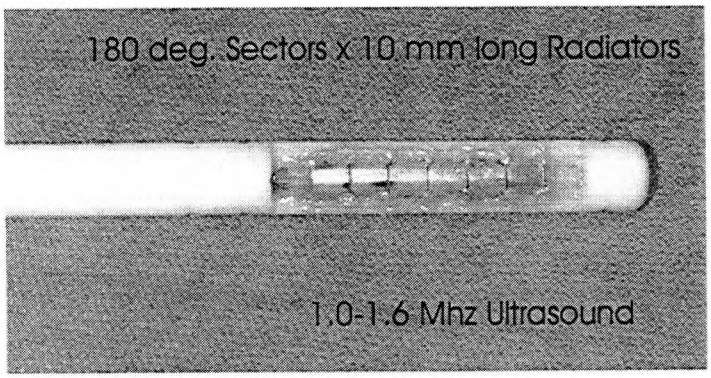

Fig. 4. Transrectal ultrasound applicator. Individual power control to each sector to tailor heating distribution. Water-cooling bolus not shown.

2.3 Ultrasound Heating Technology

Transrectal Ultrasound Applicators

The initial developments of transrectal intracavitary ultrasound applicators for prostate thermal therapy utilized linear arrays of PZT tubes [95, 96]. These applicators consist of a linear segmented array (4-8) of sectioned PZT tubes (180° sections, 10 mm long, 1.5 cm OD), each under separate power control and operating between 1-2 MHz. The transducers were mounted on a plastic structure which facilitated support and placement in the rectum, as well as temperature regulated water flow within an expandable bolus (See Fig. 4). The sectors of cylindrical ultrasound transducers shaped and directed the heating field in an ~120° arc to the target volume. The heating energy is emitted radially from the length of each transducer segment and the power applied along the length of the applicator is adjustable for tailoring the heating distribution to fit the prescription within the intended target region extending from apex to base. Theoretical studies and *in vivo* thermal dosimetry measurements indicated that these applicators could therapeutically heat tissues 3-4 cm deep from the rectal cavity wall, which is sufficient to treat most prostate glands, while proper cooling of the bolus will maintain the rectal mucosa at sub-therapeutic temperatures. This is a notableimprovement in heating penetration compared to the transrectal microwave heating techniques. Devices of this design scheme have been implemented in a phase I feasibility and toxicity trial [97], which evaluated transrectal ultrasound hyperthermia given with concurrent standard external beam irradiation in the treatment of locally-advanced adenocarcinoma of the prostate. Temperatures ranging between 40.6-43.2 were reported for a total of 14 patients. Newer versions of this applicator have added four sectors on each tubular section, for 16 channels total, and thus adds additional control of the heating in the angular expanse as well as longitudinal control [98]. Furthermore, these devices are being fabricated MRI compatible and the feasibility of MR monitoring of hyperthermic temperature rises are being investigated [99]. These applicators are ideally suited for applying conventional hyperthermia to the whole prostate gland, and may be useful for radiation or chemotherapy plus heat. Improved heating penetration and control of power deposition over transrectal microwave applicators offer potential to heat more of the gland without complications to rectal tissue.

Various designs of phased arrays have been considered for transrectal prostate hyperthermia as well. As a direct extension of the transrectal applicators mentioned above, linear phased arrays of tubular sections have been considered to increase spatial control and depth of penetration [100, 101]. In general, these devices have 32-64 elements, operate between 0.5-1.0 MHz, with approximately 1.8-2.5 mm center to center spacing between elements, and were developed for conventional hyperthermia purposes. The focal zones are shaped as sectors of a toroid that can be electronically scanned along the applicator length and placed up to 4-5 cm deep throughout the prostate gland or a target region accessible from a body cavity. This approach may have some potential for conventional hyperthermia as an adjunct to drug or radiation therapy.

Transurethral Ultrasound Applicators

A transurethral multielement applicator, developed for prostate thermal surgery for the treatment of benign prostatic hyperplasia [102], follows a similar design strategy to the intracavitary devices for conventional hyperthermia (See Fig. 5). For this device, a segmented array is formed using complete cylindrical transducer segments attached end to end (3-4 elements, 2.5 mm OD x 6 mm long, 6.8-7.0 MHz, 180°-270° active sectors). The beam distributions from each tubular radiator are shaped in the angular dimension by modifications to the transducer surface, thereby directing the acoustic energy into the anterior and lateral portions of the prostate gland. This configuration minimizes overheating and damage to rectal tissue compared to current microwave technologies. The ultrasound applicator is inserted within a multi-lumen catheter delivery system (4 mm OD, 5-6 mm OD after balloon inflation), which allows circulation of temperature regulated water to control the urethra/catheter interface temperature. For this application, temperatures between 50-80 °C can be obtained within a 10 minute treatment time at 1.5-2 cm radius [102-104], and are used to thermally coagulate and necrose obstructive tissue regions in lieu of surgical procedures. In this application, the ability to shape the ultrasound field to direct and control high amounts of heating energy directly into the target region while avoiding the rectum affords significant advantages over currently used microwave, laser and RF devices for transurethral thermal coagulation. This technology is in final stages of testing but has not been implemented in human clinical trials.

Transrectal, High-Intensity Focused Ultrasound Applicators

High-intensity focused ultrasound (HIFU) technology utilizes sharply focused ultrasound transducers which produce small intense focal patterns capable of producing selective or well localized thermal damage deep within the body, while avoiding non-targeted surrounding tissues [105, 106]. Transrectal (HIFU) applicator design strategies have been developed specifically for applying high temperature treatment of prostate tissue. These include a mechanically scanned fixed focus HIFU system combined with on-line B-mode imaging capabilities, introduced for the treatment of BPH [8, 107-109] and later utilized on a limited basis for treating cancer [110]. The SONOABLATE applicator consists of a 30 mm long x 22 mm wide curved rectangular transducer operating at 4 MHz with a 2.5, 3.0, 3.5, or 4 cm focal length selected based upon size and shape of the prostate (See Fig. 6). The 4 s sonications produce ~ 2x2x10 mm3 coagulated lesion per shot, with a 12 s delay between shots. Average intensities between 1680-2000 W cm^{-2} are typical and elevate the tissue to temperatures up to 80-100°C. Exposures to these temperatures for short periods of time generates lethal thermal doses that generate a well defined zone of thermal coagulation and necrosis. The rectal delivery probe is water-cooled to protect the rectum. Based upon a treatment plan derived from ultrasound imaging (transverse and longitudinal) from the same applicator, the power levels and positions of required sonication points are mechanically stepped in time (rotation angle, distance along urethra) to thermally coagulate the desired treatment volume. At these short sonication times and high acoustic intensities, the dimensions of the individual thermal lesions are relatively independent of persfusion changes [111]. For treating BPH the therapy zone is defined as the periurethral tissue between the bladder neck and verumontanum, and on some later studies has included the proximal 5 mm of the bladder neck. On average, thermally coagulated core of prostatic tissue approximately 1 cm in AP x 1.5 in lateral diameter x 1.9 cm long can be treated in approximately 25 min [112]. 30-40 ml prostates may be treated within 45 min timeframe. A silicone coated Foley catheter is kept in place during treatment for guidance and positioning of the prostate away from the rectal wall, plus

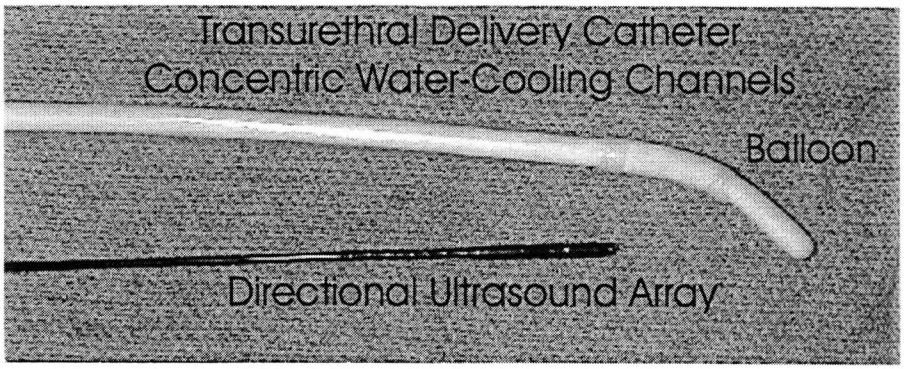

Fig. 5. Transurethral ultrasound applicator and water-cooled delivery catheter.

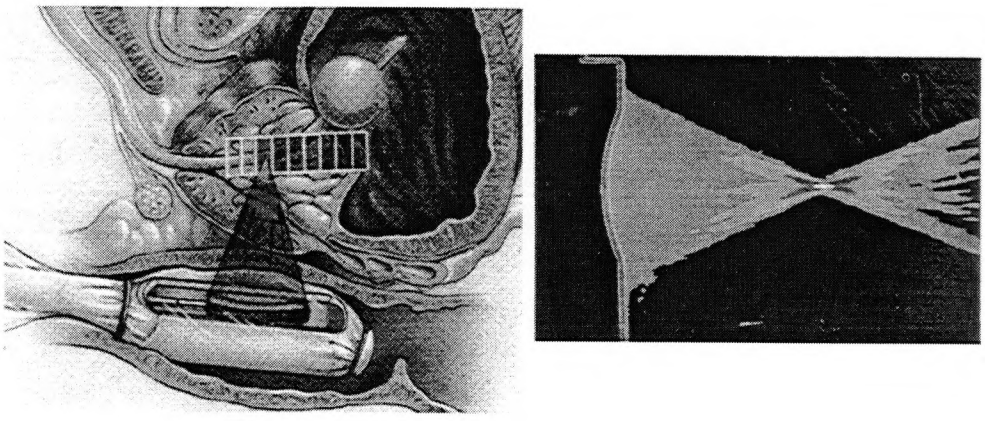

Fig. 6. Illustration of Sonoablate HIFU system and iso-intensity beam plot of the focused therapy transducer (Courtesy of Focus Surgery, Indianapolis, IN).

allowing the ultrasound to acoustically heat the catheter destroys the urethral tissue which eventually allows for tissue sloughing and increased treatment efficacy [109]. A notable improvement in response was also noted when a longer focal length applicator was used to treat larger volumes of tissue, including the anterior fibromuscular stroma. Complications did not include erectile dysfunction or retrograde ejaculation. Damage in a few cases to the seminal vessicles in order to treat bladder neck.

The EDAP- Technomed Ablatherm uses similar technology (2.25 MHz therapy, 7.5 MHz imaging), and has been implemented in recent clinical trials for treating prostate cancer [113, 114]. Early results indicated serious complications such as recto-urethral fistulas and rectal burns. However, problems were remedied with improvements to the applicator cooling. After treatment of 44 patients for prostate Ca, complete response rate at 1 year followup was 61%. Average treatment times were on the order of 1-2 hours, patients under general or spinal anesthesia. These studies indicate HIFU is a suitable option for treating localized prostate cancer in patients where radical prostatectomy or other procedures are not an option. Recently EDAP-Technomed has received FDA approval to begin trials in the United States.

Transrectal phased array applicators which provide for faster dynamic electrical scanning and potentially more flexibility in focal shape and positioning have been devised for transrectal intracavitary applications of HIFU as well [115-118]. These include MRI compatible intracavitary applicators which facilitate simultaneous MRI treatment monitoring [119]. These devices have significant potential for reducing treatment time and exposure to non-targeted tissues, while simultaneously allowing monitoring and assessment of thermal treatment.

Interstitial Ultrasound Applicators

Interstitial heating, although invasive, may be desirable since the heating sources are implanted directly into the tumor or target region, thereby localizing heat in the target volume and sparing more of the surrounding normal tissue. Additionally, interstitial implants are commonly used to localize a high radiation dose into a tumor (brachytherapy) and thus, adjuvant interstitial hyperthermia treatments are commonly combined with this form of interstitial radiation therapy [120].

There are two types of ultrasound applicator designs which can be implemented in prostate thermal therapy. Multielement ultrasound applicators with catheter-cooling (CC) demonstrate an improved radial penetration of heating over other technologies plus the ability to control the longitudinal power deposition along the length of the applicator [121-124]. The CC applicators (1-1.5 mm OD transducers, 10-20 mm long, 7-10 MHz) have circulating coolant channels integrated within the support structures to allow the applicator to be sealed in place within closed-end brachytherapy implant catheter (13 or 14 gage), as demonstrated in Fig. 7. The power to each individual tubular element of these multielement applicators can be adjusted to control the tissue temperature along the length of each catheter. The length and number of transducers within an applicator can be selected, depending on desired overall heating length and longitudinal resolution. Furthermore, the angular directivity of these applicators can be modified or shaped [125]. This feature provides critical adjustability for accommodating irregular target geometry, heterogeneities of tissue properties, and dynamic changes in perfusion such as will be encountered in heating prostate. Ideal technology for the combination of HDR

brachytherapy and sequential hyperthermia for treatment of local recurrence of prostate cancer, especially in a peripheral implant pattern.

Direct-coupled (DC) interstitial US applicators [126] are implanted directly into the tumor or target region, whereas the transducers plus acoustically compatible outer coatings essentially form the wall of the brachytherapy implant catheter (2.2-2.5 mm diameter). These applicators can accommodate simultaneous thermobrachytherapy via remote afterloading radiation sources, which may be useful for treating prostate cancer with long duration, moderate hyperthermia and simultaneous radiation therapy via LDR or HDR remote afterloaders [127]. Temperature sensors for treatment feedback can be located directly on the applicator surface and used for treatment monitoring and control (See Fig. 8.). Recent studies have demonstrated that integration of air-cooling along the inner-transducer surface can significantly increase the thermal penetration of these direct-coupled applicators in a practical configuration [128]. The DC applicator configuration maintains the same advantages of the CC applicators such as adjustable well controlled power deposition along the length and angular expanse, in addition to the ability to apply simultaneous radiation and temperature feedback.

Further investigations have demonstrated that catheter-cooled and direct-coupled interstitial ultrasound configurations have potential for thermal coagulative therapy [31, 129-133], with significant advantages over currently used microwave, laser and RF devices. Thermal dosimetry measurements within *in vivo* thigh muscle and dog prostate have indicated power output levels are sufficient, and that 2-4 cm diameter regions may be coagulated or thermally necrosed within 10-15 minutes in moderately perfused tissues. The energy deposition can be shaped as well (90-270° arc) [31, 125, 129, 130, 132-134], to protect non-targeted tissues or to use as a controlled beam shape to be swept through the target volume during real time lesion monitoring. Directional ultrasound needles have been successfully used in combination with a directional transurethral applicator to coagulate large volumes of the canine prostate within 15 minutes without damaging the rectum [104]. Recent advances in integrating cooling within direct-coupled applicators has led to much higher power output capabilities (~40 W electrical power applied to 2.2 mm diameter x 10 mm long tubes), which can significantly shorten treatment times or allow larger highly perfused lesions to be treated. This has been demonstrated, for example, by the formation of coagulated lesions up to 15 mm radial depth within highly perfused *in vivo* liver for 5 min sonications and 9 mm depths of coagulation for 15 s sonications within moderately perfused in vivo thigh muscle [31]. These should allow thorough and fast thermal coagulation in the combination approach. We have also investigated using a peripheral implant of six directional (225°) CC applicators stereotactically placed around the periphery of the prostate gland using ultrasound guidance. All US energy can be directed inward toward the center of the prostate, away from surrounding bone and rectum. Figure 9 shows a picture such an implant and the midgland TRUS image with maximum temperatures overlaid after 10 minutes thermal coagulation. This strategy has not yet been implemented in the Clinic, but is near term. This may allow the use of thermal coagulation as an adjunct to interstitial HDR brachytherapy for locally recurrent disease.

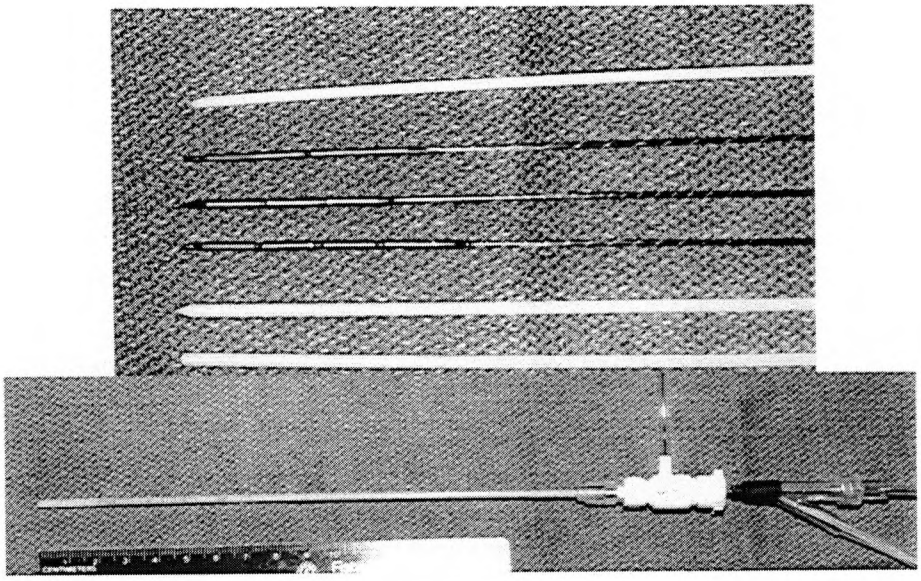

Fig. 7. Catheter-Cooled interstitial ultrasound applicators.

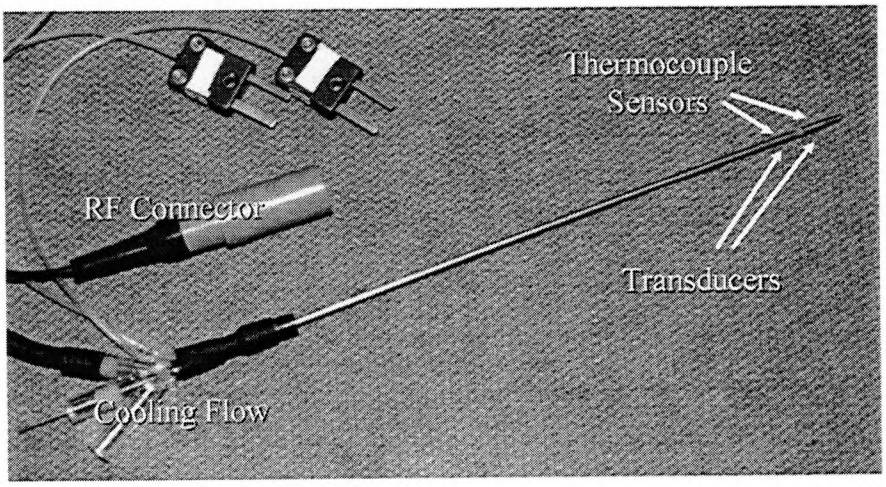

Fig. 8. Direct-Coupled interstitial ultrasound applicators.

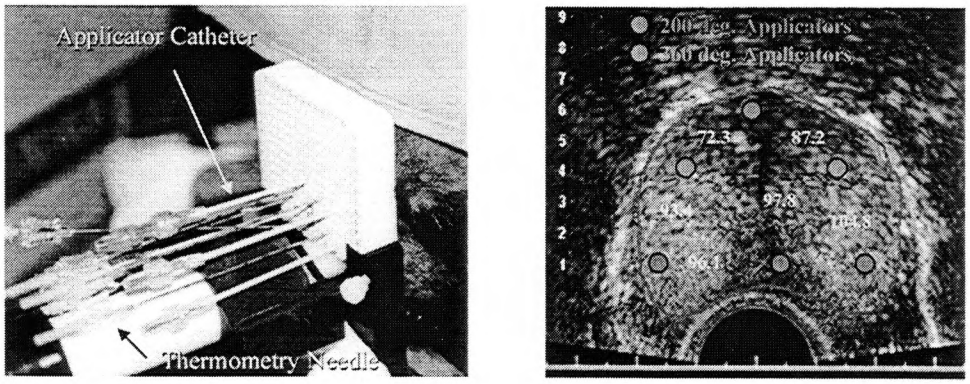

Fig. 9. *In vivo* canine prostate heating using a peripheral implant of catheter-cooled interstitial ultrasound applicators with all energy directed inward.

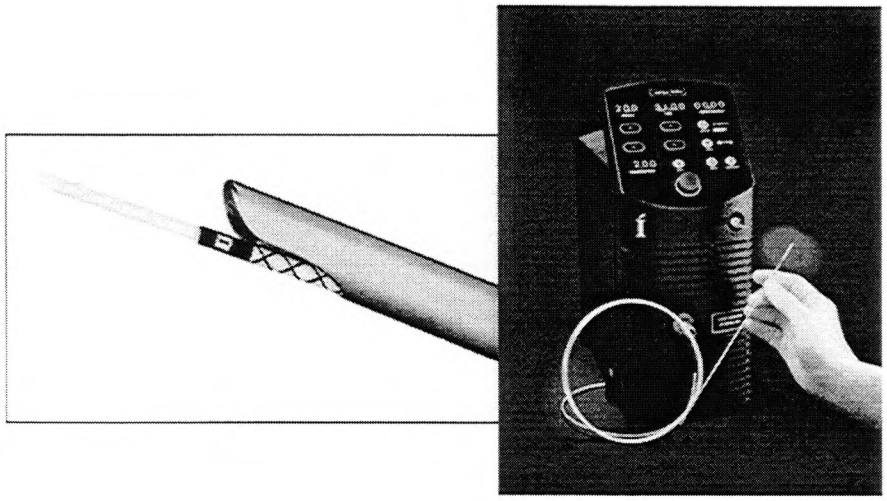

Fig. 10. Cylindrical diffusing tip laser fiber in a cystoscope and the Indigo system (Courtesy of Indigo Medical).

2.4 Laser Heating Technology

Transurethral Laser Heating Devices

Laser energy can be delivered transurethrally by inserting a 600 μm fused silica optical fiber through a 21 Fr cystoscope. "Side-firing" fibers are incorporated with a gold-plated reflector or glass-on-glass refractive mechanism to direct laser energy at an exit angle of approximately 90° (35°-105° depending on the manufacturer) from the fiber to the prostatic urethra. Throughout the 1990's, side firing laser delivery systems were commercially available from such manufacturers as Bard (Covington, GA), LaserSonics (Milpitas, CA), Myriadlase (Forest Hill, TX), and Laserscope (San Jose, CA) for laser prostatectomy.

The advantage of a free-beam coagulative procedure is the ability to perform the surgery in the clinic, on an out-patient basis, under local or epidural anesthesia. Initially the Nd:YAG laser was used since laser energy at a 1,064nm wavelength is poorly absorbed by water or blood constituents. This allows laser energy to penetrate more deeply into tissue before generating char, which limits optical penetration. However, diode lasers have also begun to play a role in laser prostatectomy. Diode laser with wavelengths between 800-1000 nm are now being used for coagulation and immediate vaporization of tissue, and offer the potential advantage of being smaller, more cost effective than the Nd:YAG, or KTP lasers. With power levels of 30-60 W, the laser energy is directed at various points around the urethra to coagulate tissue. Although there are many variations of this, a typical coagulative treatment strategy would be 40-60 W for 60-90 seconds applied to the lateral lobes at the 2, 4, 8 and 10 o'clock positions to create a circumferential series of lesions approximately 1 cm distal to the bladder neck [135]. A second set of circumferential lesions just proximal to the verumontanum might be required for larger prostates.

Scanning or "painting" of the prostatic urethra is an alternative treatment strategy. The beam is held stationary at the 2 o'clock position near the bladder neck for a 3 second dwell time. The beam is then scanned along the urethral surface from the bladder neck to the verumontanum at a rate of 1 mm/sec [136]. The beam is then relocated to the bladder neck at the 3 or 4 o'clock positions, and the procedure is repeated until the entire urethral surface blanched.

In the early 1990's, a device was developed for transurethral ultrasound guided laser induced prostatectomy (TULIP, Intrasonics, Burlinton, MA). Here, a side-firing fiber was encased in a balloon which, when inflated with degassed water to 2 atm held the laser fiber a constant distance from the urethral surface. Ultrasound transducers mounted on either side of the laser window allowed for visual guidance of the procedure. The laser fiber could be retracted at a constant 1 mm/sec rate during treatment while the balloon was in place [137] [138]. Clinical results using this device are considered poor compared to TURP, or other laser modalities [139].

The efficacy of transurethral coagulation of prostate tissue compared to TURP has been a topic of debate. Although improvement in voiding may be evident after 4-6 weeks, maximum voiding outcome may not be realized until 3 months post-operatively [140]. In some cases, the free-beam approach has been abandoned for contact laser probes in which tissue is removed at the time of the procedure giving the patient immediate relief

from obstructive systems. Nevertheless, there seem to be fewer complications than those observed with TURP, and laser coagulation may remain the preferred treatment for some patients.

Interstitial Laser Heating Devices

Although introduced in the early 1980's for non-thermal applications, interstitial lasers have recently found a use for laser induced thermotherapy (LITT) of the prostate. Commercial systems such as the Indigo 830e (Indigo Medical, Cincinnati, OH), and the Dornier fibertom (Kennesaw, GA) are currently available and have seen some clinical use (Fig. 10). Two basic types of fibers can be used, a "bare-tip" fiber, and a cylindrically diffusing fiber. The bare-tip fiber generates a conical lesion emanating from the fiber tip. The cylindrically diffusing fiber, on the other hand, produces a uniform ellipsoidal lesion. The lesions produced by most of these fibers are limited to approximately 1 cm diameter. The interstitial fibers can be introduced into the prostate transperineally, transrectally, or transurethrally.

For the transurethral approach, a 9 Fr cystoscope is used to visualize the prostatic urethra, and deliver the laser fiber. The fiber is then inserted at an angle (approximately 30°) into the prostate. An initial power setting of 15-20 W is used until the temperature at the applicator reaches a preset limit, typically 85° C to prevent carbonization of the tissue surrounding the applicator. A temperature feedback system then regulates the power level in order to maintain this preset temperature limit. After approximately 3 minutes, the fiber is withdrawn and inserted in another location approximately 5-10 mm from the adjacent lesion. The number of fiber placements required to treat the entire gland is dependent on the prostate volume. Unlike transurethral coagulation techniques, the coagulated tissue undergoes atrophic fibrotic disintegration rather than being sloughed and cleared in the urine, thus relieving obstructive symptoms. If immediate relief of obstructive symptoms is required, interstitial coagulation may be combined with incision of the bladder neck, producing similar results to TURP[141].

For older patients, patients in general poor health, or patients with very large prostates (>50 cc), a transperineal approach may be used. An advantage of a transperineal approach is that the location of the fiber can be imaged using transrectal ultrasound. Additionally, the prostatic urethra is left intact thus avoiding some post-operative complications associated with transurethral approaches[139]. This also allows MRI monitoring of thermal lesions during treatment[142].

2.5 Hot-Source Heating Technology

Interstitial Hot-Source Techniques

Thermal conduction or hot source technologies do not radiate heating energy directly into the tissue, but rely on thermal conduction and blood perfusion to spread the energy from the surface of the applicator, which is the location of maximum temperature. Typically, these devices can use circulating hot water, electric currents through resistive wire, or ferromagnetic seeds to generate the temperature elevation [88]. In general, since there is no direct power deposition into the tissue, the penetration from each source is rather limited. Advantages include the simplicity of most techniques, plus the knowledge of the

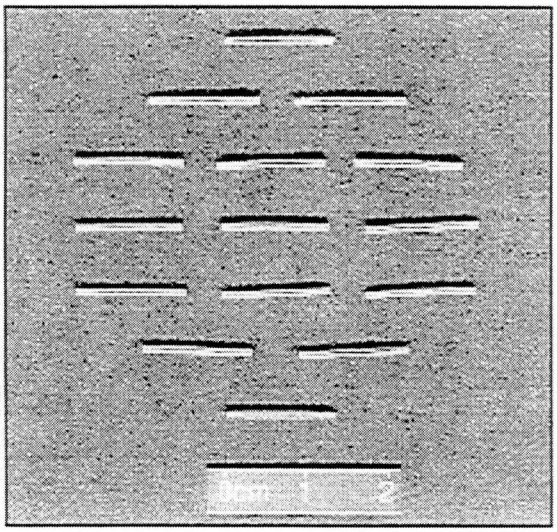

Fig. 11. Ferromagnetic seeds for prostate thermal ablation (Courtesy of Ablation Technologies, San Diego, Calif.)

location and value of the maximum temperature. Conductive heating catheters using resistive wire elements of controllable length have been used for hyperthermia as an adjunct to simultaneous radiation brachytherapy in treating prostate cancer [143]. The catheters are hollow so that the radiation sources can be left in place during the heating, maximizing the biological effect of hyperthermia. This and other studies have indicated that the response to this simultaneous approach has been more dramatic than to sequential hyperthermia protocols. A single interstitial conductive source has been designed for prostate ablation, which uses an electrically heated ceramic tip [144].

Recently ferromagnetic seed implants have been proposed for prostate thermal ablation in the treatment of prostate cancer by Ablation Technologies (San Diego, Calif.). For this approach, a large number of strings of ferromagnetic seeds are surgically placed within the prostate similar to permanent seed brachytherapy implants (Fig. 11). These seeds have a diameter approaching that of an 18-g needle. Once in place, the pelvic region/prostate is exposed to a strong RF magnetic field generated within a chair or bed. The seeds absorb the energy and heat. The permeability of the ferromagnetic seeds sharply change as a function of temperature, and have been designed to regulate at 50-60°C.

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