

# Focal Therapy for Prostatic Carcinoma

Guest Editors: Eric Barret, Alberto Breda,  
and Scott E. Eggener





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Advances in Urology

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## Editorial

# Focal Therapy for Prostatic Carcinoma

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Medical therapeutics has solidly evolved in the last decades based on bright ideas and hard work. Thinking outside the box remains essential if one's idea is to make his/her specific fields move forward. Some years ago we were lucky to become part of the surgical evolution in radical prostatectomy; the development of laparoscopic radical prostatectomy followed by the robotic version of the procedure not only transformed the actual operation, but also brought up a minutely precise analysis of surgical outcomes. Prostate cancer remains one of the most rapidly evolving areas in medicine and perhaps after a massive application of surgical concepts to treat disease, we have come to the point to question ourselves about *overtreatment*. This is how the genius idea of active surveillance was born and the evolution of this approach has offered thousands of patients the logical option of a less aggressive approach to deal with a positive prostatic biopsy.

More recently, many of us have questioned both active surveillance and any other more aggressive treatment options, based on an oncological concept previously applied with success in other organs: partial treatment (partial mastectomy, partial nephrectomy, and partial cystectomy), meaning to treat only the diseased portion of an organ and not the whole thing.

Today, this is how we aim to make the field move forward in prostate carcinoma therapeutics; with focal therapy, a logical intermediate option to treat patients only was the positive biopsies are located aiming to obtain solid cancer control while maintaining quality of life.

We were pleased to guest this special issue, as we consider there is much to do in order to further improve this novel idea, that, as any other idea ever presented in medicine, remains a rather controversial issue where once again brilliant thoughts must be backed up with enormous effort to rapidly evolve beyond the proof of concept.

Focal therapy for prostate cancer should be established on three basic concepts: first, a reliable determination of cancer location within the prostate, second, a convenient type of energy providing safe and reliable intervention on the diseased portions of the organ, and third, a follow-up approach allowing physicians to objectively decide on further actions to control the disease. The mentioned concepts have not yet been completely defined and a great part of today's research is focused on the improvement of these elements.

We would like to highlight some of the manuscripts presented in the present special issue. To set up the ground for the subject, Al B. Barqawi et al. provide us with a rather solid review of epidemiological and screening studies, prostate cancer statistics, and information on patient outcomes. The manuscript presents the actual situation on prostate cancer therapeutics and how focal therapy will eventually define its role.

T. Nomura and H. Mimata present a summary of the recent data regarding focal therapy for prostate cancer and different energies have been deployed in this field. Moreover, they state today's limitations and the expectations we have for the future regarding the evolution of the technique.

Regarding available energies for Focal therapy, U. Maestroni et al. brought the analysis of their complications with high intensity focused ultrasound; 89 patients were analysed to confirm the oncological effectiveness of the procedure and the most related undesired events they observed in their experience.

P. Colin et al. performed a review on the role of laser energy in Focal Therapy and how the application of laser has been evolved from phase I assays until the future design of solid trials to objectively determine the oncologic efficacy in the long term.

In a rather interesting manuscript, A. K. Jain and R. D. Ennis introduce the approach of differential therapy where

the entire prostate is treated to a lower intensity and the tumor areas to high intensity. They review the available experience in the subject with external beam radiation, high-dose rate brachytherapy, and low-dose rate brachytherapy.

Finally, M. Morita and T. Matsuura present a very provocative paper featuring the application of old, good, and reliable transurethral resection of the prostate cancer treatment, with a subset of their population approached with a focal resection and featuring stable PSA between 0.007 and 0.4 ng/mL up to two-year followup and with a low complications rate.

Starting from the available knowledge and technology, Focal therapy is continuously developing from its infancy and a more mature era is awaiting. Technological development will be essential in the evolution of this approach; from imaging to tissue treatment, we must work together with technological scientists to bring to the patients side the tools on which we will base highly precise diagnosis, effective tissue treatment, and reliable oncological followup.

*Eric Barret*

## Clinical Study

# High-Intensity Focused Ultrasound for Prostate Cancer: Long-Term Followup and Complications Rate

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*Introduction.* As it is well known, High Intensity Focused Ultrasound (HIFU) is a minimally invasive procedure for prostate cancer. Many investigators reported their series of patients, demonstrating the effectiveness of the treatment. The most majority of Authors, however, do not report the side effects and the complications of the procedure, which is the aim of our study. The diagnosis and management of complications is discussed, and the oncologic outcome is reported in terms of quality of life. *Materials and Methods.* We report our experience in 89 patients, low-, intermediate-, and high-risk patients according with D'Amico classification. All data collected along the study were analyzed, including side effects and complications of the procedure. *Results.* Our series demonstrates the effectiveness of the procedure, in line with larger series reported in literature by other investigators. The most important side effects are sexual function impairment and transient incontinence in a minority of cases. Minor complications are reported as well as rare cases of major complications, which can require surgical treatment.

## 1. Introduction

Prostate cancer is considered one of the most important topics about male health with an important social impact on the quality of life. In Europe, it is the most common solid neoplasm with an incidence rate of 214 cases per 1,000 men [1]. The increasing life expectancy and the more and more widespread use of Prostate Specific Antigen (PSA) are probably the two most important reasons why more patients are diagnosed with prostate cancer [2, 3]. Radical surgery represents the treatment of choice in clinically localized prostate cancer and in >10 years life expectancy prostate cancer. Nevertheless, radical surgery itself can be considered a high-morbidity treatment [4].

Mini-invasive procedures development, such as three-dimensional external radiotherapy, brachytherapy, or cryotherapy, especially in old or anesthesiologically high-risk patients, represents a useful treatment in prostate cancer.

HIFU (High-Intensity Focused Ultrasound) is an alternative choice in localized and low-or medium-risk prostate cancer treatment. It is a noninvasive technique inducing complete coagulative necrosis of a target tumour, without

requiring surgical exposure or insertion of instruments into the lesion.

Since April 2006 we have been treating prostate cancer with HIFU [5]; we report our experience in 100 patients and we deal with oncological outcome and secondary side effects of the procedure itself.

## 2. Materials and Methods

After obtaining local institutional approval, HIFU was introduced in our department routine. Initial training was received by an approved Ablatherm (EDAP, Lyon, France) committee. Also, our first treatments were performed under EDAP supervision. 89 patients were treated between April 2006 and December 2010. The selection criteria were cancer localized to the prostate and local relapse after radiotherapy, clinical stage, PSA, comorbidity (including anaesthetic evaluation), age over 70. Exclusion criteria were anal stenosis, previous rectal surgery, prostate size (anteroposterior diameter of the prostate cannot be longer than 25 mm due to a technical reason), and coxofemoral ankylosis. All patients

TABLE 1: Complications and complication rate after HIFU treatment.

Complications	Patients	Patients rate
Grade I stress incontinence	4–7	5 to 11%
Grade II stress incontinence	3	4%
Grade III stress incontinence	0	—
Dysuria	7	10%
Impotence	67	90%
Bladder outlet obstruction	3	4%
Fistula	1	—

were given counselling about the investigational nature of the treatment and informed consent was obtained.

We included low-, intermediate-, and high risk patients in accordance with the classification of D’Amico [6]: low risk, clinical stage T1c or T2a, Gleason score  $\leq 6$ , and PSA  $\leq 10$  ng/mL; intermediate risk, PSA 10–20 ng/mL Gleason score 7 or clinical stage T2b; high risk, PSA  $\geq 20$  ng/mL, Gleason score  $>7$ , or clinical stage  $\geq T2b$ .

All patients were preliminarily unobstructed: 7 underwent Trans-Urethral Resection of Prostate (TUR-P) at the same time of the HIFU procedure; 44 underwent TUR-P two months before; others had previously unobstructed (9 underwent adenomectomy). Previous unobstruction also reduced duration of catheterization.

The characteristics of all patients are listed in Table 1. Tumours were staged using TNM staging system. None had metastatic disease.

To perform the treatment we used a Ablatherm device (EDAP, Lyon, France): it consists of a 3.0 MHz piezoelectric therapeutic applicator and a 7,5 MHz ultrasound scanner for treatment planning.

Ablatherm is a computerized surgical device (Figure 1) equipped with a treatment table, an ultrasound treatment system connected to an endorectal probe, a safety infrared ray detector, a refrigeration system keeping the rectal mucosa temperature below  $14^{\circ}\text{C}$ , and a monitor to set and control the treatment procedure through echographic screening (Figure 2).

All patients were regularly assessed based on post-HIFU PSA levels at 3, 6, 12 months and then every 6 months. Prostate biopsies (template) were performed 6 months after HIFU treatment, regardless of PSA. Prostate biopsies were also performed again during followup in cases of rise of PSA (three successive rises of PSA level).

The functional outcome was assessed using (IPSS) and (IIEF) scores: urinary symptoms and sexual potency were evaluated by IPSS—International Prostate Symptom Score, (0–7 mildly symptomatic; 8–19 moderately symptomatic; 20–35 severely symptomatic) and IIEF5—International Index of Erectile Function 5 (6–10 high erectile deficit; 11–16 moderate deficit; 17–25 low deficit; 26–30 no deficit). We collected IPSS and IIEF data before treatment and 6 months later. Incontinence data were collected from patient reported outcomes on leakage and pad usage.

Oncological failure was defined by several criteria: first of all, biochemical failure, assessed using Phoenix definition



FIGURE 1: HIFU computerized surgical device.



FIGURE 2: Monitor for setting and controlling the treatment procedure.

(PSA nadir + 2 ng/mL) [7]. Other criteria were starting salvage therapy, such as radiotherapy (RT) or androgen depriving therapy (ADT) and the presence of cancer on biopsy after treatment.

Data collected along experimentation was analyzed looking for risk factors.

### 3. Results

A total of 100 HIFU procedures were performed over a 4-year period (between April 2006 and December 2011). Twenty-six patients who underwent first-line treatment were excluded because of followup  $<1$  year as the procedure was performed in the last few months ( $n = 11$ ), because they had their followup elsewhere ( $n = 9$ ) or because they were not suitable for statistic evaluation, as they were not enough compliant to followup ( $n = 6$ ). Three patients were lost to followup.

Of the remaining 74 patients, the age ranged from 65 to 80 with a mean of 72,7 years.

The proportion in the high-, intermediate-, and low-risk categories of D’Amico [6] were 13,5%, 16,2%, and 70%, respectively, with a mean (SD) PSA level of 8,07 ( $\pm 8,17$ ) ng/mL. Particularly, mean PSA level was 18,2 ( $\pm 17,79$ ) ng/mL,

10,4 ( $\pm 5,04$ ) ng/mL, and 5,8 ( $\pm 2,56$ ) ng/mL in the high-, intermediate-, and low-risk categories. Seventeen patients (28,3%) had received neoadjuvant therapy (ADT) for three months and this was discontinued immediately after HIFU.

Only seven patients underwent TUR-P at the same time of HIFU procedure.

Mean catheterization time was 9,3 days ( $\pm 4,5$ ). On the whole, 3 patients required interventions for either a stricture or endoscopic removal of necrotic tissue within the prostate cavity.

The overall mean PSA nadir was 1.12 ng/mL ( $\pm 2,23$ ), with a median of 0,95 and was obtained within a mean range of  $3 \pm 2,3$  months. A nadir value  $\leq 0.2$  was obtained in 31.6%. The nadir value was  $\leq 1$  in 76.6%.

Using the Phoenix criteria for biochemical failure, HIFU failed in 26.6% during a mean followup of 29.9 months (median 15 months, range 9–40 months).

Stratification of failure by D'Amico criteria [6] was out of the 16 failures, 43.7% high-risk, 12.5% intermediate-risk, 43.7% low-risk. In the high risk group, failures were 87.5%, in the intermediate risk group 20% and in the low risk group 16.6%. Mean time to failure was 12.5 months, with a range of 3–40 months.

During the followup, 45 patients had prostate biopsies: 15.5% were positive. All these patients had biochemical failure.

At 3 months after HIFU, 13 patients complained of urinary incontinence (see Table 1). In 6 of these patients urinary incontinence was transient and solved in 6 months. In the other 7 patients it was still present after twelve months (2 pads/die). They were investigated with urodynamic evaluation: 5 were treated with anticholinergic drugs; 2 were diagnosed with sphincteric incompetence and required artificial sphincter AMS-800.

The mean change in IPSS was 4.18 ( $\pm 4,16$ ).

Sexual potency was defined according with the IIEF score system. 16 patients were potent before HIFU. Four men regained potency after HIFU. Four patients were partially impotent (a degree of erectile function was present but sexual intercourses were not possible) 6 months after HIFU. 5-phosphodiesterase treatment was proposed to these patients. IIEF score mean change was 11,6 ( $\pm 3,6$ ).

There was one rectovesical fistula. Diagnosis was provided by cystourethrogram and rectoscopy. This patient was managed with prolonged catheterization, as he declined any surgical procedure.

The procedure was well tolerated and no intraoperative or perioperative deaths occurred.

#### 4. Discussion

Nowadays, the management of localized prostate cancer offers different approaches. Traditional established interventions, such as Radical Prostatectomy (RP) and radiation therapy (EBRT) have undergone many technical refinements in the last few years, in order to improve the clinical outcome.

Madersbacher et al. reported the first localized prostate cancer successfully treated with HIFU in 1995 [8] and

Gelet et al. published the first series in 1996 [9]. Since then, HIFU is considered as a possible alternative choice in the management of localized prostate cancer.

In 2010, Crouzet et al carried out a multicentric study on 803 patients, reporting an overall survival rate of 83% and a cancer-specific survival rate of 98% in a mean followup of 6.4 years, but more efforts are needed to gain more knowledge about side effects of the procedure and oncological outcome predictive factors [10].

In the present study, HIFU resulted in local control in 73.4% of patients, which correlates well with the results reported for the other therapeutic options. Reportedly, the risk of progression after radical prostatectomy is about 20% [11]. Radiation therapy (EBRT) results in a higher rate of recurrence. Transperineal ultrasound-guided iodine-125 brachytherapy—with or without external beam irradiation—resulted in progression in about 20% of cases [12].

To define the biochemical failure after HIFU, Phoenix definition was used ( $2 + \text{PSA value}$ ). There is no common agreement as to what constitutes biochemical failure after HIFU. Different definitions have been proposed and used by other investigators for biochemical failure, such as Stuttgart definition [13]. However, in the largest reports to date of long-term oncological outcome after HIFU, Phoenix definition is used [10, 14].

In the present study, prostatic biopsy was also performed, as the use of combined criteria is certainly the best for evaluating the efficacy of HIFU treatment.

Our data show the oncological outcome of 74 patients after HIFU, with a mean followup of 29.9 months. As it is clearly reported in Table 1, the highest rate of biochemical failure was found in the high-risk group (87.5%), while the lowest rate was found in the low-risk group. The high rate of failure found in the high-risk group is also due to the small number of high-risk patients treated with HIFU. The most favourable outcome is reported in low- and intermediate-risk group. This correlates well with the results reported by many investigators.

The most common side effects of HIFU for prostate cancer include prolonged voiding dysfunction and retention caused by edema, necrosis, or bladder outlet obstruction. Combination therapy (TUR-P + HIFU) reduces these side-effects, thus improving the quality of life in the postoperative time [15].

The rate of adverse events is low (see Table 1). Grade I stress incontinence was observed in 5% to 11% of patients, grade II in up to 4% patients, and grade III incontinence is rare. Rectovesical fistula is a rare event, also. In our series only one case of fistula is reported.

The main consequence of HIFU treatment on quality of life is erectile function impairment. In this field, our results are in line with literature. Preservation of erectile function is dependent on the position of the tumoral lesion. Even if sparing the contralateral side for bundle preservation can improve potency, as reported by Poissonnier et al. [16], this results in a higher failure rate [17]. For this reason, in our series sparing technique was not performed.

The major complication of this treatment is rectovesical fistula, as reported in one case in our series. The addition of

the cooling system has dramatically decreased the incidence of this complication, which reportedly ranges between 0.5–1.2% [18].

In the most majority of cases, this complication can be managed with a conservative treatment, such as long-term catheterization. In selected cases major surgery is required.

Many investigators have confirmed the efficacy and effectiveness of HIFU treatment, but definitive data are not yet available, due to short followup and different definition of end points (by biochemical, disease-free survival rates), thus leading to difficulties and misunderstanding in results interpretation. Also, European guidelines for prostate cancer do not define a precise indication for HIFU treatment, which is still considered an alternative therapeutic option in patients diagnosed with localized prostate cancer. Our data contribute to demonstrate the positive oncological outcome in a four-year followup and to define the incidence of the most common complications.

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## Clinical Study

# Management of Localized Prostate Cancer by Focal Transurethral Resection of Prostate Cancer: An Application of Radical TUR-PCa to Focal Therapy

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**Background.** We analyzed radical TUR-PCa against localized prostate cancer. **Patients and Methods.** Seventy-nine out of 209 patients with prostate cancer in one lobe were studied. Patients' age ranged from 58 to 91 years and preoperative PSA, 0.70 to 17.30 ng/mL. In other 16 additional patients we performed focal TUR-PCa. Patients' age ranged from 51 to 87 years and preoperative PSA, 1.51 to 25.74 ng/mL. **Results.** PSA failure in radical TUR-PCa was 5.1% during the mean follow-up period of 58.9 months. The actuarial biochemical non-recurrence rate was 98.2% for pT2a and 90.5% for pT2b. Bladder neck contracture occurred in 28 patients (35.4%). In 209 patients, pathological study revealed prostate cancer of the peripheral zone near the neurovascular bundle bilaterally in 25%, unilaterally in 39% and no cancer bilaterally in 35%, suggesting the possibility of focal TUR-PCa. Postoperative PSA of 16 patients treated by focal TUR-PCa was stable between 0.007 and 0.406 ng/mL at 24.2 months' follow-up. No patients suffered from urinary incontinence. Bladder neck contracture developed in only 1 patient and all 5 patients underwent nerve-preserving TUR-PCa did not show erectile dysfunction. **Conclusion.** Focal TUR-PCa was considered to be a promising option among focal therapies against localized prostate cancer.

## 1. Introduction

Current standard radical surgery [1–3] against localized prostate cancer (PCa) has possible risks to disturb urinary continence or erectile function because they target the whole prostate. Many operative procedures [4–6] were introduced to improve the recovery of postoperative sexual function and urinary incontinence, such as bladder neck suspension or reconstruction, reconstruction of the rhabdosphincter, periurethral suspension of the dorsal vein complex/urethral complex and preservation of the neurovascular bundle to preserve erectile function [7]. But all these have failed to solve the problems completely until now. Irradiation therapy such as brachytherapy [8], three-dimensional conformal radiation therapy 3D-CRT [9], or intensity-modulated radiation therapy (IMRT) [10] cannot completely prevent urinary

incontinence, intestinal damage, or erectile dysfunction as well.

As the number of patients with low-volume, low-grade localized prostate cancer increased after the introduction of PSA into health check-up program, less invasive focal therapy has been proposed because of possible advantages of both cancer control and quality of life. Cryotherapy [11, 12] and high-intensity focused ultrasound (HIFU) [13, 14] are current main procedures of focal therapy but are still considered experimental.

We previously reported that radical transurethral resection of prostate cancer (RTUR-PCa) could be a radical therapy against localized prostate cancer [15]. We then referred to the possibility of focal transurethral resection of prostate cancer (FTUR-PCa), the procedure in which we mainly resected the affected lobe of the prostate [16]. We

made a retrospective analysis of RTUR-PCa against localized prostate cancer to evaluate whether FTUR-PCa could be a valid focal therapy. We here report our result of FTUR-PCa, too.

## 2. Patients and Methods

**2.1. Cases of RTUR-PCa as a Database to Estimate FTUR-PCa.** Between December 2003 and July 2009, a total of 261 RTUR-PCa were performed under spinal anesthesia in 209 patients with localized prostate cancer. Clinical stages were determined according to the UICC TNM staging system of 1997. We performed bone scintigraphy and computerized tomography for the purpose of metastatic workup in patients who had initial PSA levels of 20 ng/mL or more. And we recommended the patients who had PSA level between 10 and 20 ng/mL and higher Gleason score to undertake such examinations with some of them having refused to take. We informed the patients that the procedure was not a standard radical surgery, and those who refused this procedure were excluded from the study. We also excluded patients who might not tolerate standard transurethral resection of the prostate (TURP). Patients who gave the written informed consent were eligible for the study in the order they were given a diagnosis of localized prostate cancer. Institutional review board approved the TUR-PCa program after a preliminary study.

**2.2. Retrospective Analysis to Evaluate the Efficacy and Safety of FTUR-PCa.** We thought that the most appropriate indication of focal therapy should be localized prostate cancer in one lobe. We reviewed RTUR-PCa cases to find patients to match such criteria. Seventy-nine of the above 209 RTUR-PCa patients diagnosed to have prostate cancer in one side of the lobes were included in the present study. In 74 out of these 79 patients, cancer was detected by ultrasound-guided transrectal needle biopsy, and in the other 5 patients prostate cancer was incidentally detected after TURP for benign prostate hyperplasia (BPH). We obtained a total of 14 biopsy samples per case from the peripheral and transition zone including far lateral part, dividing the prostate into base (2 cores), upper middle part (2 cores), lower middle part (6 cores), and apex (4 cores), and we marked at the dorsal end to obtain tumor maps. In the patients underwent TURP; after resecting most of the transition and central zone, we made a slightly deeper resection dividing the residual thin transition zone and peripheral zone into 6 parts and collected the resected specimens separately to identify the affected sites by pathological examination (advanced TURP) [15].

We performed 93 RTUR-PCa in 79 patients under spinal anesthesia. Patients ranged from 58 to 91 years old (mean  $\pm$  SD, 73.9  $\pm$  6.6; median, 74.0) and preoperative PSA, 0.70 to 17.30 ng/mL (mean  $\pm$  SD, 5.77  $\pm$  3.51; median, 4.57). Chlormadinone acetate was administered for a mean period of 4.6 months in 52 patients.

**2.3. Focal TUR-PCa.** Between July 2007 and September 2011, we performed FTUR-PCa in 16 patients. FTUR-PCa includes

two different procedures: in one procedure we radically resect the affected one lobe with unaffected lobe being resected as advanced TURP for BPH (one lobe radical TUR), and in the other procedure we radically resect both lobes except for the prostate tissues near the neurovascular bundle (nerve sparing radical TUR) based on the tumor mapping. Patients ranged from 51 to 87 years old (mean  $\pm$  SD, 68.9  $\pm$  9.6; median, 70.0) and preoperative PSA, 1.51 to 25.74 ng/mL (mean  $\pm$  SD, 7.87  $\pm$  6.35; median, 6.19). Chlormadinone acetate was not administered in this group.

**2.4. Surgical Procedure and Followup.** One urologic surgeon (M. Morita) performed all operations. We used a standard TURP setup with an irrigation pressure of 80 cm H<sub>2</sub>O and an irrigation rate of 250 mL/min using D-sorbitol solution. After resecting almost all the transition and central zone, we tried to resect and fulgurate the peripheral zone completely especially where cancer was detected by biopsy. The resection was performed as deep as adipose tissue was identified and as distal as the external sphincter was identified. But we did not resect prostate tissues until adipose tissue was exposed all around the operative field. We aggressively fulgurated the area adjacent to where adipose tissue was exposed because the remaining prostate tissue could be considered a thin layer. We especially paid attention not to distend the bladder too much to prevent a high irrigation pressure and resultant TUR syndrome. Special attention was also paid to avoid injury to Santorini's plexus and the rectum. The procedure was started from the 12 o'clock position, dividing the prostate into 6 parts, and resected specimens were separately collected from each part to examine the distribution of cancer. The seminal vesicle was partially resected at its attached part to the prostate between the 4 and 8 o'clock positions to determine the invasion of cancer. Finally the verumontanum was resected to achieve the complete resection of prostate tissue. A bag catheter was removed on the third postoperative day.

Postoperative PSA was measured every two months starting two months after the operation. PSA failure was suspected when PSA levels showed a consecutive rise over 0.2 ng/mL. But when the PSA level reached a plateau between 0.2 and 1.0 ng/mL, we did not immediately think that the patients were in a treatment failure. This was also applied to the indication of the second RTUR-PCa. We evaluated stress urinary incontinence by asking patients the postoperative status of urinary leak on a cough or a sneeze and needs for urinary pads.

## 3. Results

**3.1. Retrospective Analysis Based on the Results of Radical TUR-PCa.** The mean follow-up period of 79 patients was 58.9  $\pm$  17.0 months (mean  $\pm$  SD; median, 60.5; range, 15–88). The operation time ranged between 65 and 120 minutes (mean  $\pm$  SD, 79.9  $\pm$  15.2; median, 80.0), and the resected tissue weight was between 5.0 and 37.0 grams (mean  $\pm$  SD, 13.3  $\pm$  6.4; median, 12.0). The preoperative PSA value was

5.77 ± 3.51 ng/mL (mean ± SD; median, 4.57; range, 0.70–17.3). Clinical stages were as follows: T1b, 28 cases; T1c, 47; T2, 4; and pathological stages: pT2a, 56 cases; pT2b, 21; pT3, 2 (Table 1). Gleason scores were: 4, 3 cases; 5, 3; 6, 27; 7, 28; 8, 12; 9, 6 (Table 2).

One patient died of cerebrovascular accident 15 months postoperatively with a low PSA value of 0.012 ng/mL. No patients died of prostate cancer. Sixty-four patients had stable PSA after the first operation. The second operation was required in 14 patients after a mean period of 16.4 months (mean ± SD, 16.4 ± 7.5; median, 16.0; range, 6.4 to 30.5) due to rising PSA levels. Resected tissue weight was between 5.0 and 12.0 grams (mean ± SD, 6.9 ± 1.6; median, 12.0). No cancer was detected by pathological examination in 3 patients. The second operation was required in 10 (40.0%) out of 25 patients before April 2006 but in only 4 (7.0%) out of 54 patients after that time, suggesting that there seemed to be a learning curve for the operative technique.

At the final followup, there were 75 (94.9%) patients with stable PSA levels: PSA ≤ 0.01, 40 cases; ≤0.02, 12; ≤0.03, 5; ≤0.04, 5; ≤0.1, 5; ≤1.0, 8. PSA failure developed in 4 (5.1%) of the studied patients. Clinical stages were as follows: T1b, 1 case; T1c, 2; T2, 1; pathological stages: pT2a, 1 case; pT2b, 2; pT3, 1. In all cases studied, the actuarial biological non-recurrence rate was 96.4% for the clinical stage T1b and 95.7% for T1c at 58.9 months (Figure 1). PSA failure developed in one of 4 patients with stage T2 cancer. The actuarial biological non-recurrence rate was 98.2% for the pathological stage pT2a at 88 months and 90.5% for pT2b at 84 months (Figure 2). One of 2 patients with stage pT3 cancer developed PSA failure. Nonrecurrence rate of each risk group according to The D’Amico classification [17] is shown in Figure 3. PSA failure did not develop in the low-risk group (stage T1c, T2a, and PSA level ≤ 10 ng/mL and Gleason score ≤ 6) of 32 patients. Biological non-recurrence rate was 96.4% in the intermediate-risk group (stage T2b or Gleason score of 7 or 10 < PSA level ≤ 20 ng/mL) of 28 patients and 84.2% in the high-risk group (stage T2c or PSA level > 20 ng/mL or Gleason score ≥ 8) of 19 patients, respectively.

To evaluate the distribution of prostate cancer near the neurovascular bundle, we studied the result of pathological examination of resected samples in 209 RTUR-PCa patients. Cancer was detected at the 4 to 6 o’clock position in 44 patients (21%), at the 6 to 8 o’clock position in 38 patients (18%), bilaterally (at the 4 to 8 o’clock position) in 74 patients (35%) and was not detected bilaterally in 53 patients (25%).

**3.2. Result of FTUR-PCa.** Concerning the 16 patients underwent FTUR-PCa, the follow-up period ranged from 3 to 53 months (mean ± SD, 24.2 ± 15.4; median, 22.0), operation time 80 to 120 minutes (mean ± SD, 92.5 ± 11.6; median, 90.0), and resected tissue weight 12 to 30 grams (mean ± SD, 21.0 ± 4.9; median, 20.0). Postoperative PSA was stabilized between 0.07 and 0.406 ng/mL (mean ± SD, 0.119 ± 0.111; median, 0.090). The Gleason scores were as follows: 5, 1 case; 6, 4; 7, 8; 8, 1; 9, 2. Clinical stages were T1c in all patients, and

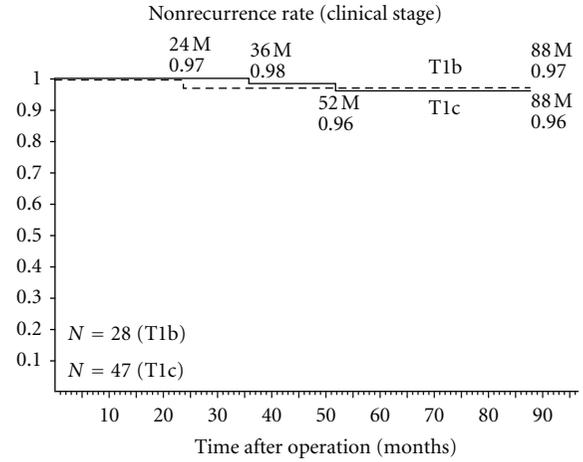


FIGURE 1: Actuarial biochemical non-recurrence rate of each clinical stage.

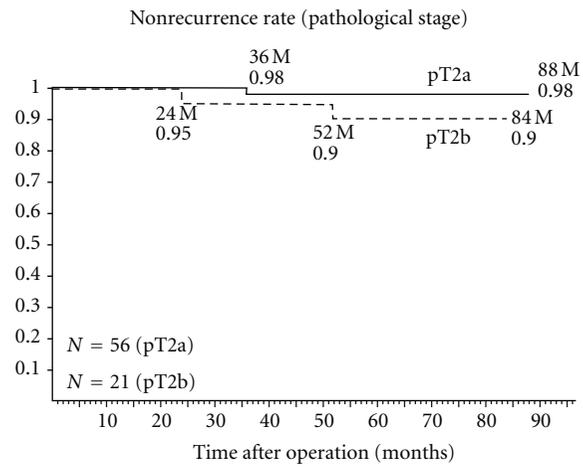


FIGURE 2: Actuarial biological non-recurrence rate of each pathological stage.

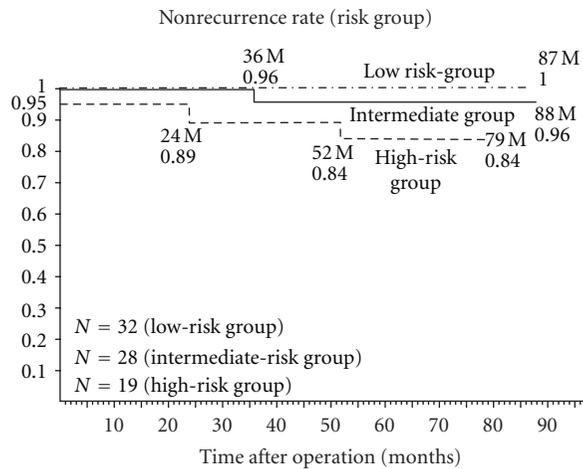


FIGURE 3: Actuarial biological non-recurrence rate of each risk group.

TABLE 1: Results of RTUR-PCa grouped by pathological stage.

Pathological stage	Total patients		Patients treated with 1 operation				Patients treated with 2 operations			
	No. of patients	Preop PSA Mean (SD) Median (range)	No. of patients	No. of patients with stable PSA after TUR	Latest PSA Mean (SD) Median (range)	No. of PSA failures	No. of patients	No. Patient	Latest PSA Mean (SD) Median (range)	No. of PSA failures
pT2a	56	5.68 (3.42) 4.55 (0.70–17.30)	46	46	0.087 (0.191) 0.010 (0.001–0.897)	0	10	9	0.040 (0.078) 0.013 (0.003–0.258)	1
pT2b	21	5.44 (3.10) 4.33 (1.55–14.90)	17	17	0.019 (0.019) 0.010 (0.001–0.074)	0	4	2	0.001–0.008 (Range)	2
pT3	2	7.41–16.36 (Range)	2	1	0.001	1	0	—	—	0

TABLE 2: Results of FTUR-PCa grouped by Gleason's score.

Gleason score	Total patients		Patients treated with 1 operation				Patients treated with 2 operations				
	No. of patients	Preop PSA Mean (SD) Median (range)	No. of patients	No. of patients	Latest PSA Mean (SD) Median (range)	No. of PSA failure	No. of patients	Latest PSA Mean (SD) Median (range)	No. of PSA failure	No. of patients	Latest PSA Mean (SD) Median (range)
4	3	4.59 (0.85) 4.41 (3.65–5.70)	3	3	0.064 (0.074) 0.016 (0.008–0.168)	0	0		0		
5	3	5.01 (2.85) 3.96 (2.17–8.90)	3	3	0.009 (0.006) 0.009 (0.002–0.016)	0	0		0		
6	27	4.52 (2.38) 4.33 (1.55–11.54)	24	24	0.096 (0.184) 0.017 (0.001–0.685)	0	3	0.010 (0.008) 0.008 (0.001–0.021)	0	3	0.010 (0.008) 0.008 (0.001–0.021)
7	28	6.64 (3.76) 4.80 (2.01–16.36)	21	21	0.065 (0.192) 0.006 (0.001–0.897)	0	7	0.009 (0.005) 0.010 (0.001–0.016)	1	6	0.009 (0.005) 0.010 (0.001–0.016)
8	12	5.54 (3.53) 4.52 (0.70–12.40)	10	10	0.038 (0.102) 0.002 (0.001–0.344)	0	2	0.025	1	1	0.025
9	6	8.84 (4.55) 7.77 (3.50–17.30)	4	3	0.027 (0.011) 0.033 (0.011–0.036)	1	2	0.258	0	1	0.258

pathological stages were as follows: pT2a, 10 cases and pT2b, 6. There were 11 cases underwent one lobe radical TUR and 5 cases underwent nerve sparing radical TUR. Eight (72.7%) out of 11 patients underwent one lobe radical TUR had the postoperative pathological stage of pT2a.

**3.3. Operative Complications.** TUR syndrome (systolic hypotension or electrolyte abnormality which needs repeated correction to keep vital signs stable) and perioperative bleeding (bleeding during the procedure or bladder tamponade that requires blood transfusion) did not develop.

As for the postoperative complication of RTUR-PCa, urinary incontinence was seen in about half of the patients when a bag catheter was removed on the third postoperative day. Incontinence soon improved until the third postoperative week, and no patients complained of stress urinary incontinence at all after the third postoperative month. Bladder neck contracture developed in 28 patients (35.4%; Grade IIIa by Clavien's classification) mostly three to four months postoperatively. Other complications included one pubic osteitis (1.3%; Grade II) and one acute epididymitis (1.3%; Grade II). Erectile function was preserved after the operation in 9 (50.0%) of the evaluated 18 sexually active patients.

In FTUR-PCa, bladder neck contracture developed in only 1 out of 16 patients. We experienced no stress urinary incontinence, and erectile function was preserved in the all 5 patients underwent nerve-sparing TUR.

## 4. Discussion

**4.1. Limitations of the Accuracy of Preoperative Staging.** Out of 79 patients with the clinical stage of T2a, 56 (70.9%) patients were finally diagnosed to have the pathological stage of pT2a disease with PSA non-recurrence rate of 98.2% at a mean follow-up period of 58.9 months. These results may support that FTUR-PCa is a promising procedure. But it may be desirable to make the cancer distribution in the prostate more accurate to select proper candidates of the procedure. Only 27.3% to 35.1% of patients with unilateral cancer on biopsy are reported to have cancer in one lobe on radical prostatectomy samples [18, 19]. Crawford et al. report that the concordant rate of laterality could be 76% on saturation biopsy using a template [20]. And accuracy of biopsy is reported better in transperineal approach with a template than transrectal biopsies [21]. From the result of pathological studies in our 209 RTUR-PCa, bilateral preservation of the neurovascular bundle was thought to be possible in as many as 25% of the patients and unilateral preservation in 39%. Current biopsy procedures may be insufficient to predict cancer foci near the neurovascular bundle. Neurovascular bundle reserving TUR, unilateral or bilateral, is worth trying based on biopsy information, because TUR-PCa is possible to repeat if postoperative PSA tends to rise gradually.

**4.2. Comparison with Other Focal Therapies and Rationales of FTUR-PCa.** The number of patients with low-volume, low-grade localized prostate cancer has increased after the

introduction of PSA into health check-up program [18, 22]. Ablation of only main cancer lesion (index cancer) in one lobe by HIFU or cryotherapy is reported not to affect the prognosis as much [23, 24] because the second lesion, if it exists, is usually as small as less than 0.5 mL [25, 26]. But these procedures have some serious drawbacks concerning the selection of patients. Current methods of biopsy cannot always predict another lesion to be treated, and followup PSA criteria have not been established yet. Furthermore, pathological samples cannot be obtained, resulting in the inadequate final pathological diagnosis. On the other hand, FTUR-PCa is possible to search the second cancer focus after the radical resection of main index cancer in one lobe and advanced TUR in another lobe [27], resulting in the accurate diagnosis of Gleason scores and the pathological stage. And the second TUR may be possible, when necessary, using PSA as an indicator of postoperative follow-up and cancer recurrence. We therefore consider that FTUR-PCa could be another possible procedure of focal therapy against prostate cancer overcoming the drawbacks of HIFU and cryotherapy. Our present result of FTUR-PCa seems satisfactory in cancer control, urinary continence, and erectile function, though the follow-up period is as short as 24.2 months in a very small number of patients.

It is still controversial to support or not a mass screening of prostate cancer because screening may lead to overdiagnosis and overtreatment. Active surveillance policy or watchful waiting, which is an ultimate noninvasive procedure, is then accepted to care for the patients with low-risk cancer [28, 29]. But active surveillance seems still difficult to select a suitable patient, and the patient may feel anxiety about cancer progression. Focal therapy is less invasive compared to current standard treatment procedures such as radical prostatectomy or irradiation therapy and may be a treatment option with satisfactory cancer control and quality of life. FTUR-PCa can expand the possibility of focal therapy, and we think it is one of the feasible procedures to solve the problems of overdiagnosis and overtreatment caused by PSA screening of prostate cancer.

**4.3. Possible Risk of FTUR-PCa and Some Other Considerations.** Dissemination of cancer cells may occur during TUR, but the effect on the clinical outcome is controversial [30–32]. Our previous report could not find any adverse effects on the prognosis of the studied patients [15, 16]. RTUR-PCa can eradicate cancer cells like other current standard radical therapy because repeated TUR is possible, and improvement of the surgical results will be expected.

Extravasation of irrigation fluid is sure to occur during the operation, but there were no patients in whom water intoxication developed with the lowest irrigation pressure, and postoperative serum electrolytes were kept normal. At present much safer operation is possible with the use of a bipolar TUR system. The most frequent postoperative complication was bladder neck contracture occurred in 35.4% of patients 3 to 4 months after surgery. This had been anticipated because of aggressive bladder neck resection to achieve radicality. It was easily treated by optical urethrotomy

under caudal block on a day-surgery basis. In FTUR-PCa, occurrence of bladder neck contracture is expected to be low because it is a radical procedure in only one affected lobe with advanced TUR in the other lobe.

The effect of chlormadinone acetate on postoperative PSA must be considered in the present study. We could not find any reports that describe the duration of the suppressive effect of chlormadinone acetate in patients with prostate cancer. But in patients with prostate hyperplasia 50 mg/day of chlormadinone acetate given for 16 weeks, PSA levels are reported to return to the baseline levels 32 weeks after discontinuation [33]. In the present study the effect of preoperative hormonal therapy on the most recent PSA levels, therefore, can be minimal or negligible.

## 5. Conclusion

We could get a satisfactory cancer control with less invasive procedure of RTUR-PCa and FTUR-PCa. Although the results of long-term followup with more cases need to be studied, the procedure we report here could be a potential option of focal therapy against localized prostate cancer with minimum adverse effect on urinary continence and erectile function.

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## Review Article

# Focal Therapy, Differential Therapy, and Radiation Treatment for Prostate Cancer

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Focal and differential therapy represent an approach to improve the therapeutic ratio of prostate cancer treatments. This concept is a shift from treating the whole gland to intensely treating the portion of the gland that contains significant tumor. However, there are many challenges in the move towards focal approaches. Defining which patients are suitable candidates for focal therapy approaches is an area of significant controversy, and it is likely that additional data from imaging or detailed biopsy methods is needed in addition to traditional risk factors. A number of methods have been suggested, and imaging with multiparametric MRI and transperineal template mapping biopsy have shown promise. The approach of differential therapy where the entire prostate is treated to a lower intensity and the tumor areas to high intensity is also discussed in detail. Radiation therapy is a well suited modality for the delivery of differential therapy. Data in the literature using external beam radiation, high dose rate brachytherapy, and low-dose rate brachytherapy for differential therapy are reviewed. Preliminary results are encouraging, and larger studies and randomized controlled trials are needed to validate this approach.

## 1. Introduction

Prostate cancer is the most common malignancy in men in the US, with an estimated 241,740 cases to be diagnosed in the US in 2012 [1]. The widespread acceptance and implementation of PSA screening beginning in the early 1990s have also led to a shift to a greater number of cases diagnosed with earlier stage disease. From 1989 to 1992 the percentage of cases diagnosed with low-risk disease in the US was 29.8%, and this increased to 45.3% from 1999 to 2001 [2]. While many men with low-risk disease are well managed by surveillance [3], a large number of patients need or choose treatment. Definitive treatments such as brachytherapy, external beam radiation therapy, or radical prostatectomy generally provide high success rates with biochemical control and disease specific survival of 80–90% or higher for low-risk disease [4–6]. However, these procedures are associated with sexual, urinary, and rectal side effects that may impact patient quality of life and overall satisfaction of treatment outcome [7].

Focal therapy represents an approach to improve the therapeutic ratio by maximizing tumor control while minimizing side effects. Whereas traditional therapies typically treat the entire prostate gland, this concept is a shift towards intensely treating the portion of the gland that contains significant tumor. This targeted treatment strategy has the potential to reduce the chance of injury to adjacent organs and resultant side effects while maintaining excellent oncologic outcomes. However, there are many challenges in the move towards focal therapy including identifying appropriate candidates, methodology of identifying intraprostatic tumor, and whether the remaining prostate gland should receive some form of treatment.

## 2. Candidates for Focal Approaches

Defining which patients are suitable candidates for focal therapy approaches is an area of significant controversy. Patients in the low-risk group, with the excellent outcomes

described above, would appear to be the most logical choice for deintensification of treatment. Strict low-risk criteria were used by Katz et al. (Gleason < 7, PSA < 10, <T2b, only 1 biopsy core positive, no larger than 80% of a single core, no perineural invasion noted) to attempt to identify patients who could adequately be treated by focal therapy [8]. However, when 56 patients with these characteristics underwent radical prostatectomy, 12 (21%) were found to have significant bilateral secondary tumor, and thus the authors concluded that these criteria alone could not be used to select for focal therapy candidates. A consensus panel of international experts at the 2nd International Workshop on Focal Therapy and Imaging in Prostate and Kidney Cancer has issued recommendations on candidate selection for focal therapy [9]. They recommended that candidates for focal therapy should be limited to patients of low or moderate risk, and any patients with dominant Gleason 4 or clinical stage T2b or greater should be excluded. In addition, to these traditional risk factors, they also recommended that patients should undergo transperineal template mapping biopsies or multiparametric MRI with TURP biopsy. These recommendations underscore the fact that the clinician who is considering focal therapy must be able to define the anatomic location and extent of disease. As newer methods of identifying intraprostatic tumor evolve, these will be incorporated into both patient selection and treatment planning for focal therapy.

### 3. Identifying Intraprostatic Tumor

The current standard of care for prostate biopsy is to use transrectal ultrasound (TRUS) guidance to take 6–12 transrectal needle biopsies throughout the prostate in a systematic fashion. Although a reasonable approach when whole gland treatment is being considered, a comparison with prostatectomy specimens has shown that this method misses a number of clinically significant cancers and is inadequate to identify candidates for focal therapy [10]. Increasing the number of cores as in the saturation biopsy method still misses clinically significant cancer in 31% of patients [11]. Three-dimensional transperineal prostate mapping biopsy using a template grid is one way of providing a more accurate mapping of the prostate using biopsy. Preliminary studies using this method have shown good results [12], although detailed studies comparing it to radical prostatectomy are still lacking. A major drawback of this method is that it is an invasive procedure with associated complications including ecchymoses, temporary erectile dysfunction, as well as acute urinary retention [13].

Newer imaging modalities offer a noninvasive method of identifying tumor foci. Ultrasonic tissue type imaging based on spectrum analysis of radiofrequency signals has been developed by Feleppa et al., to help identify prostate cancer. When compared to biopsy data, this method has shown a receiver-operator characteristic curve (ROC) of 0.87 [14, 15]. This ultrasound imaging carries the advantage of being easily incorporated into prostate biopsies and in situ cancer treatments like brachytherapy, high-intensity

ultrasound (HIFU), and cryotherapy, which are ultrasound based.

Magnetic resonance imaging (MRI), with the inclusion of diffusion and dynamic contrast, has shown even more promise in identifying intraprostatic tumors. Multiple studies have shown significant correlation between MRI abnormalities and radical prostatectomy specimens for determining size and location of cancer foci [16–19]. Cancer location and contour have been shown to have significant agreement with MRI [16, 17]. For example, in one study, MRI has been shown to have sensitivity of 86%, specificity of 94%, and receiver-operating characteristic curve of 0.874 for identifying cancer foci >0.5 mL on radical prostatectomy [18] and has in fact been shown to be accurate in detecting cancer foci as small as 0.2 cc [19]. The addition of MR spectroscopy (MRS) may improve accuracy even further, as Yamamura et al. found a sensitivity of 91.9% and specificity of 98.3% for detecting prostate cancer when using the combination of MRS and diffusion weighted imaging and comparing results to biopsy data [20]. MRS may also provide information on cancer aggressiveness, as combinations of metabolite ratios have been shown to correlate with Gleason score [21].

### 4. Limitations of Pure Focal Treatment and Rationale for Differential Therapy

A major dilemma in the implementation of focal therapy is whether the shift from treating the entire gland uniformly to purely treating the tumor only (*pure* focal therapy) is too drastic and risks missing biologically significant tumor. Prostate cancer can be multifocal in up to 87% of patients, and the prostate often contains three or more foci of cancer, and sometimes as many as twelve, on radical prostatectomy specimens [22–24]. Pretreatment risk factors have not been reliably able to predict multifocality [23], so advanced biopsy or imaging methods, as described above, are needed to define anatomic distribution of tumor. Bilaterality is also common and was seen in 80% of radical prostatectomy specimens in a series from the Duke Prostate Center, although pretreatment Gleason score and percentage of tumor involvement were found to be predictive [25]. With bilateral disease, it is doubtful that any significant gland sparing could be achieved if all tumors are adequately treated. In addition, the question of what constitutes a clinically significant tumor is a matter of controversy. Due to the long doubling time of prostate cancer, tumor size is likely to play a role in this determination. Analysis of prostate cancers, found incidentally at cystoprostatectomy by Stamey et al. suggests that cancers less than 0.5 cc are not clinically significant [26]. However Cheng et al., found 16% of cancers less than 0.5 cc found on radical prostatectomy contained Gleason pattern 4 and might, therefore, ultimately have become clinically significant [27].

Another drawback of focal therapy is that there is a lack of data on an accurate way to follow these patients. With a large portion of the gland left untreated, traditional definitions of PSA failure are not likely to be reliable. A European

consensus panel suggested that oncologic efficacy would be best achieved by interval posttreatment biopsy [9]. Multiparametric MRI may also be helpful in this situation, for diagnosis or to target biopsies [28, 29]. The management of local recurrence after focal therapy also presents a challenging clinical problem—the effect of focal therapy on subsequent focal or whole gland treatments remains largely unknown.

To address the concerns of multifocality and minimize the chances of local recurrence, an alternative approach is desirable. One such approach is to decrease the intensity of the treatment to the whole prostate gland to eradicate any small foci missed by the imaging or biopsies, while simultaneously increasing the intensity to the identified tumor; an approach we term *differential* therapy. This approach, theoretically, will still improve the therapeutic ratio compared to standard whole gland treatment by decreasing the exposure of the surrounding normal tissues to the treatment.

## 5. Pure Focal Therapy

The limited data that has been published thus far using focal therapy for prostate cancer has primarily been using HIFU, cryotherapy, and laser ablation [30–32]. Results in highly selected patients have shown excellent control rates and low toxicity, but followup has been short. All of these methods are pure focal therapies with no treatment delivered to the remainder of the prostate gland. This is an inherent limitation of these techniques, since treatment intensity is “all or nothing.” Therefore, by themselves, these treatments are not well suited for differential therapy. Instead, these therapies need to be combined with another therapy to achieve the differential therapy goal. Possible additions to these purely focal therapies include low-dose external beam radiotherapy or an oral 5-alpha reductase inhibitor.

## 6. Radiation and Differential Therapy

Radiation therapy is especially well suited to differential therapy because the treatment intensity can be varied. With modern technology and treatment planning techniques, the capability exists to deliver a high dose to the tumor region while simultaneously giving a lower dose to the remainder of the prostate gland and adjacent organs. A dose response relationship for prostate cancer has been well established for both external beam radiation therapy and brachytherapy, with higher radiation doses to the prostate resulting in higher rates of tumor control [33–36]. Likewise, a dose response relationship exists for adjacent normal tissues such as bladder, rectum, and urethra with lower doses to these organs correlating to a decreased incidence of side effects after radiation treatment with either external beam radiotherapy or brachytherapy [37–40]. These dose relationships support the hypothesis that differential therapy using radiation therapy may improve outcomes while decreasing toxicity. In addition, radiation treatment planning is image based, and the information from MRI and ultrasound for intraprostatic

tumor identification can easily be incorporated to develop a treatment plan to achieve the differential therapy goals.

With the use of custom immobilization and image-guided or stereotactic methods for external beam radiotherapy, the accuracy of treatment delivery is within a few millimeters. The combination of these techniques is an exciting platform for the delivery of differential therapy with external beam radiation. This approach has thus far been explored in two ways: Miralbell et al. delivered 64 Gy external beam radiation to the entire prostate, followed by an external beam stereotactic boost of two fractions of 5–8 Gy each to the dominant tumor region of the prostate in 50 patients [41]. The tumor region was identified based on rectal examination, biopsy findings, and T2 MRI images. Treatment was delivered with a customized body cast and external markers for stereotactic guidance. They found that the technique was feasible with a 5 yr biochemical control of 98%, and 5 yr Grade 2 or greater urinary toxicity of 17.8% and rectal toxicity of 27.8%. The FLAME randomized controlled multicenter phase III trial which is ongoing in Europe is also using external beam radiotherapy for differential therapy [42]. Intermediate or high-risk patients receive 77 Gy to the entire prostate, and the experimental arm receives a simultaneous boost of 95 Gy to the area of macroscopic tumor. Multiparametric MRI is used to delineate intraprostatic tumor, and implanted fiducial markers are used for treatment set-up. The primary endpoint is to evaluate whether the addition of an “ablative microboost” to the macroscopic tumor within the prostate increases the five-year freedom from biochemical failure rate compared to the current standard of care. Secondary endpoints are treatment-related toxicity, quality of life, and disease-specific survival. 50 patients were registered as of October 2010, and accrual is ongoing.

Brachytherapy is also very well suited for differential therapy. The manual implantation of radiation sources in combination with the rapid falloff in dose as the distance from the seeds gives the physician great flexibility to vary the treatment dose to different parts of the prostate gland. In addition, there are intrinsically very high doses of radiation within a few millimeters of each source. These areas, termed “hotspots,” contain radiation doses 2–3 times the prescription dose, which allows for a creation of a higher dose gradient with brachytherapy than with external beam radiotherapy. Therefore, increasing the dose directed to the tumor while decreasing dose to the remainder of the gland with brachytherapy offers a promising method of optimizing outcomes while limiting side effects and has been used in a few preliminary studies in the literature.

High-dose-rate (HDR) brachytherapy has been used as part of a differential therapy approach, by Schick et al., to boost the dominant intraprostatic tumor in 77 patients [43]. The patients received 64 Gy external beam radiation therapy and then HDR brachytherapy to the tumor-bearing regions. Tumor was identified using information from MRI, rectal examination, and biopsy, and HDR brachytherapy was delivered with Iridium-192 source and MRI guidance. In this series, there was a subset of twenty patients who received only a boost to one side of the gland only due to

presence of unilateral tumor. The five-year biochemical relapse free survival was 79.7% versus 70.5% ( $P = 0.99$ ), for unilaterally boosted versus bilaterally boosted patients; however grade 4 toxicity was seen only in patients who had bilateral brachytherapy boost (5/57, 8.8%). The authors concluded that hemi-irradiation of the prostate with HDR brachytherapy could be considered when patients have rectal examination, MRI, and biopsy findings that suggest unilateral involvement only. Differential therapy using purely HDR brachytherapy has been investigated by Pouliot et al. at UCSF in a treatment planning study with 10 patients [44]. MRI and magnetic resonance spectroscopy (MRS) data was used to identify dominant intraprostatic lesions. HDR brachytherapy treatment plans were devised to escalate the dose to the dominant lesions while maintaining the prostate at prescription dose and minimizing doses to adjacent normal organs. They found that they could escalate the dose to the dominant intraprostatic lesion to a minimum of 120% of the prescription dose without increasing dose to adjacent organs. Further dose escalation was feasible but resulted in slightly higher doses delivered to the rectum and urethra.

Low-dose-rate (LDR) brachytherapy is also an effective method for differential radiation therapy. Todor et al. suggested dual-isotope seed implants as a technique to vary the dose throughout the prostate gland [45]. They used MRI/MRS datasets to identify disease foci within the prostate and generated nine LDR brachytherapy plans using Iodine-125, Palladium-102, and Cesium-131 alone and in combination. They found that with the combination implant plans, they were able to increase the biological effective dose to the tumor regions while achieving a reduction in dose to the urethra. Gaudet et al. performed LDR brachytherapy dose escalation to the dominant intraprostatic lesion and reported clinical results in 120 patients [46]. The location of the lesion was determined by sextant biopsy information, and the involved sextant was boosted to 150% of the prescription dose. They compared the results with 70 patients who received LDR brachytherapy with standard treatment plans. There were no differences in acute and late toxicities between the two groups. When comparing the dose escalation plans to the standard plans, they found that urethral and rectal dose parameters were lower in the group that received higher dose to the tumors. The study demonstrated the feasibility of differential therapy with LDR brachytherapy without any increase in urinary, rectal, or sexual side effects. However, the use of sextant biopsy to determine the location is limited compared to either more extensive biopsies, or imaging methods such as ultrasound spectrum analysis or MRI.

Ultrasound spectrum analysis as a method for identifying intraprostatic lesions is particularly attractive for brachytherapy. Most brachytherapy is ultrasound based, and images can be acquired at the time of the procedure and readily incorporated into the treatment plan [47]. At our institution, we are completing a phase I prospective trial to evaluate the safety and technical capability of ultrasound spectrum analysis to guide differential dose prostate LDR brachytherapy. Thus far, 14 patients have been enrolled, and we have found that the technique was feasible in all but

2 patients for a technical success rate of 86%. The tumor regions are identified on the intraoperative ultrasound spectrum analysis, and a brachytherapy treatment plan is devised to treat the tumors to 200% of the prescription dose. Standard plans were also created for each patient for comparison. Preliminary clinical and dosimetric results of the trial in the first 9 patients have also been encouraging [48]. The differential dose LDR brachytherapy plans successfully escalated the dose to the tumors compared to what would have been accomplished with a standard brachytherapy plan. A mean of 98% of the tumor volume received at least 200% of the prescribed dose compared to only 55% with the standard plans ( $P \leq 0.0009$ ). In addition, consistent with the previously mentioned studies, there was statistically significant reduction in dose to the prostate gland outside the tumors seen with the differential dose brachytherapy. The experimental brachytherapy has been very well tolerated, as no grade 3-4 toxicities have been noted with a followup range of 4–16 months.

## 7. Conclusion

Pure focal and differential therapy represents exciting approaches to improve the therapeutic ratio of prostate cancer treatment by decreasing complication risks while maintaining or perhaps even improving cancer control rates. Newer imaging modalities offer accurate and noninvasive methods for identifying intraprostatic tumors and can be incorporated into treatment planning. Radiation therapy is well suited for differential therapy, where treatment intensity is increased towards the tumors and decreased in the remaining prostate. Preliminary data using external beam radiotherapy, HDR brachytherapy, and LDR brachytherapy for differential therapy have been encouraging and shown that these techniques are feasible and safe. Further areas of study include defining the optimal degree of dose escalation to the tumors and dose reduction to the prostate that provide the most favorable outcomes for patients and refining the technical procedures used to deliver this dose. In addition, the possibility exists for using low-dose radiotherapy as an adjunct to HIFU, cryotherapy, and other focal treatment techniques. Additional clinical studies, and ultimately, large randomized controlled trials are needed to validate these approaches.

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## Review Article

# Focal Laser Ablation of Prostate Cancer: Definition, Needs, and Future

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Current challenges and innovations in prostate cancer management concern the development of focal therapies that allow the treatment of only the cancer areas sparing the rest of the gland to minimize the potential morbidity. Among these techniques, focal laser ablation (FLA) appears as a potential candidate to reach the goal of focusing energy delivery on the identified targets. The aim of this study is to perform an up-to-date review of this new therapeutic modality. Relevant literature was identified using MEDLINE database with no language restrictions (entries: focal therapy, laser interstitial thermotherapy, prostate cancer, FLA) and by cross-referencing from previously identified studies. Precision, real-time monitoring, MRI compatibility, and low cost of integrated system are principal advantages of FLA. Feasibility and safety of this technique have been reported in phase I assays. FLA might eventually prove to be a *middle ground* between active surveillance and radical treatment. In conclusion, FLA may have found a role in the management of prostate cancer. However, further trials are required to demonstrate the oncologic effectiveness in the long term.

## 1. Introduction

Prostate cancer is the most frequent cancer among men over 50 years old in industrialized countries. With PSA screening, development of new prostate biopsies protocols, and MRI, the accuracy of detection and localization has increased. Also, today a growing number of small-volume and low-grade cancer foci are diagnosed in young healthy men. Standard treatments for prostate cancer such as surgery or radiation involve the whole gland, even if the tumor is localized. Despite their oncologic efficiency, radical treatment modalities are associated with significant morbidity (urinary and sexual dysfunction) and may be linked to useless overtreatment, which affects quality of life of patients diagnosed with very low development of potential small localized tumors.

Today, 94% of low-risk cancers are treated with radical treatment. In 2009, the ERSPC study has proven the value of screening [1]. A gain of survival of 27% among screened men aged 55 to 69 was demonstrated, with an average follow-up of

9 years after diagnosis. But this gain of survival was associated with a high rate of overdiagnosis and overtreatment.

Active surveillance can be an alternative to radical treatment in this indication. However, this strategy induces important psychological stress for patients, and it is often difficult for clinicians to propose this management option to young men with long life expectancies.

Today, a new treatment concept is emerging and is termed *focal therapy*. The challenge of current focal therapy techniques is to treat only localized tumors sparing the rest of the prostate to minimize the potential morbidity.

To be effective, focal therapy must be (1) guided by imaging (to define the exact location of cancer area), (2) able to target only the desired area (dosimetric planning), and (3) followed by surveillance of the untreated areas.

Different energy sources are being developed for this indication, and some are currently under clinical protocols such as cryotherapy, high-intensity focus ultrasound (HIFU), or vascular photodynamic therapy (VTP).

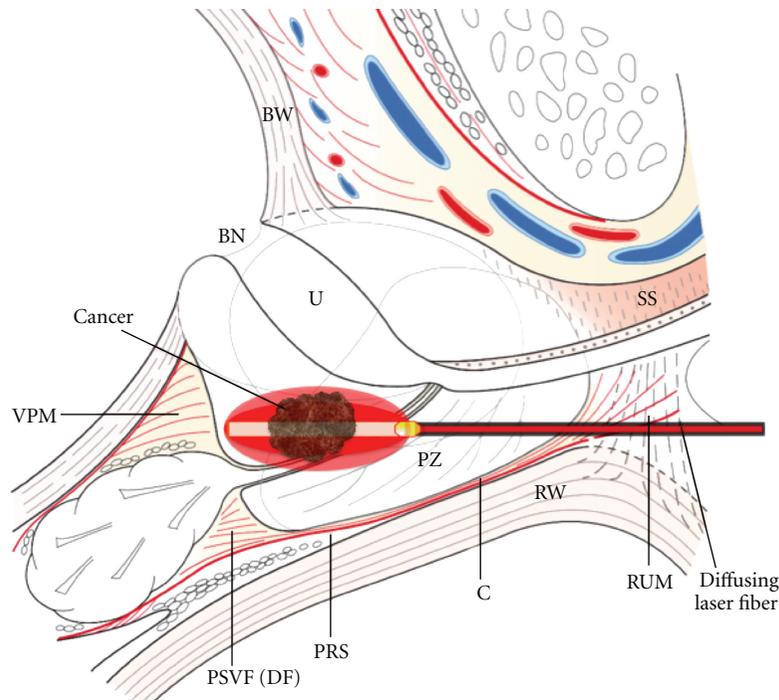


FIGURE 1: Principle of FLA. The diffusing laser fiber was introduced by transperineal way (schematic midline sagittal section of prostate, bladder, urethra, and striated sphincter). BW: bladder wall; BN: bladder neck; U: urethra; SS: striated sphincter; RUM: rectourethral muscle; RW: rectal wall; PZ: peripheric zone; C: capsule of prostate; DF: Denonvilliers' fascia; VPM: vesicoprostatic muscle; PSVF: posterior seminal vesicle fascia; PPF: posterior prostatic fascia.

Focal laser ablation (FLA) by interstitial thermotherapy could be another modality for prostate cancer focal therapy. This technique presents the following benefits: an ease of use, low cost, and less cumbersome workstation. This paper describes the mechanisms, history, and components of FLA with an account of current clinical experience for prostate cancer. The principle of transperineal FLA is illustrated in Figure 1.

Relevant literature was identified using MEDLINE database with no language restrictions (entries: focal therapy, laser interstitial thermotherapy, prostate cancer, focal laser ablation) and then by cross-referencing from previously identified studies. Articles were selected by their relevance to the topic. Current clinical trials concerning FLA were found using the database clinical trials conducted in the USA and around the world (<http://www.clinicaltrial.gov/>).

## 2. FLA Mechanisms and Components

**2.1. FLA Mechanisms.** FLA is defined as the thermal destruction of tissue by laser. For prostate cancer, this denomination is preferred to the other names such as photothermal therapy, laser interstitial tumor therapy, and laser interstitial photocoagulation because it describes both the intention and the treatment [8].

FLA action is based on a photothermal effect. The thermal action results from the absorption of radiant energy by tissue receptive chromophores inducing heat energy in a very short time (few seconds) [18]. This increased

temperature may cause irreversible damages and remotely *in vivo* destruction. The thermal effect depends on the amount of heat energy delivered but also on the depth of light distribution. Consequently, the deep tissue damage is dependent on the wavelength of the laser in action. Due to weak absorption by water or hemoglobin, wavelengths between 590 and 1064 nm are classically used to obtain a deeper tissue penetration.

The extension of thermal tissue damage depends on both temperature and heating duration. Cell viability is in relation with thermostability of several critical proteins. Irreversible protein denaturation may occur around 60°C [19]. While over 60°C, coagulation is quasi-instantaneous, between 42 and 60°C, a thermal damage is obtained with longer heating periods. The area submitted to supraphysiological hyperthermia less than 60°C will develop coagulative necrosis in 24 to 72 h after treatment [6, 20]. Macroscopic appearance of coagulation areas of FLA corresponds to well-demarcated foci of necrosis surrounded by a small rim of hemorrhage with no viable glandular tissue (benign or malignant) after vital staining, based on immunoreactivity with cytokeratin [9, 21].

### 2.2. FLA Material

**2.2.1. Computed Dosimetric Planning.** Pretreatment dosimetric planning of FLA requires three steps to predict the extent of the coagulated necrosis [18]. An optothermal model of FLA consists in calculating light distribution,

temperature rise, and the extent of thermal damage. Light distribution could be obtained using the Monte Carlo simulation to estimate photons distribution in irradiated tissue. This process is based on tissue optical properties at the used laser wavelength.

Absorption of light in tissue causes a local elevation in temperature. Tissue heat transfer due to the energy of light deposited is described by the bioheat transfer equation (Pennes' equation).

Thermal damage in cells and tissue can be described mathematically by a first-order thermochemical rate equation, in which temperature history determines damage. Damage is considered to be a unimolecular process, where native molecules are transformed into a denatured/coagulated state through an activated state leading to cell death. It is calculated from the Arrhenius law [22].

Previous theoretical models of prostate treatment have generally assumed threshold damage temperatures of 50°C. These values are based on studies involving exposure durations of about seconds or greater. For instance, histological evaluation performed by Peters et al. showed that the thermal-injury boundary can be predicted from a threshold-maximum temperature of approximately 51 degrees °C [3, 20, 23].

**2.2.2. Laser Sources.** As it was reported above, wavelengths in the range of 590 to 1064 nm are the most adequate to induce a maximal photothermal effect in human tissue. At the beginning of interstitial laser coagulation development, Nd:YAG laser (1064 nm) was used. This laser source allowed deep penetration into the tissue (10 mm); however, this kind of material is cumbersome due to the need for cooling systems.

In 1998, with the development of laser for benign prostate hypertrophy (BPH) treatment, small diode lasers appeared allowing interstitial laser coagulation at 830 nm with transurethral application of diffusing fibers [24, 25]. Thereafter, these diode lasers were used for hepatic and brain tumors treatment in near-infrared (800–980 nm) [26]. With these wavelengths, while tissue penetration is weaker (5 mm) in comparison with Nd:YAG laser, these diodes present an excellent energy efficiency permitting the minimization of their cooling system. Improvements in the design of high-power diode laser sources have made medical laser systems smaller, more portable, more powerful, and less expensive than previous generations. Since 2011, diode laser emitting at 1064 nm  $\pm$  10 nm has been proposed and could replace the Nd:YAG laser.

**2.2.3. Optical Fibers.** Light is delivered via flexible quartz fibers of diameter from 300 to 600  $\mu$ m. Conventional bare-tip fibers provide a spherical lesion of about 15 mm diameter at their ends, but have been largely replaced by interstitial fibers consisting of cylindrical diffusing tips of 10 to 40 mm of length. These needles provide larger ablative area of up to 50 mm [27, 28].

#### 2.2.4. Temperature Monitoring

*Two Different Temperature Monitoring Set-Ups Are Proposed.*

(i) Thermocouples placed at the laser probe are used to control the laser power in the adaptive monitoring mode. Usually, the initial laser power is set at 15 W for each fiber and the control temperature is set at 100°C. As the temperature measured by the laser fiber probe quickly increases to 100°C, the power delivered by the laser fiber quickly decreases and stabilizes at about 2 W [11].

(ii) Fluoroptic temperature probes used to control the temperature of specific structures. Due to their technology these probes (Model 3100, Luxtron Corp., Santa Clara, California) are insensitive to the magnetic fields. These probes can be used to validate the measurements performed by MR thermometry. Usually, they are placed at the expected ablation boundary to ensure that therapeutic temperatures (55°C or greater) are reached at the target borders and to control that near-critical structures remain unaffected by heat (by maintaining temperatures less than 42°C) [29].

**2.2.5. Real-Time MRI Control.** Multiparametric MRI devices are valuable tools for laser fiber guidance and control of coagulative necrosis after FLA [3, 11]. As previously demonstrated for other organs, the extent of tissue necrosis is visible in MRI (T1 weighted spin echo and FLASH sequences) [29, 30]. During the procedure, real-time 3D temperature maps could be obtained using the proton resonance frequency (PRF) shift. For MRI thermometry, a gradient-recalled echo pulse sequence is rapidly repeated during FLA procedure. With dedicated software, the acquired MR images are analyzed in real time to estimate the thermal changes; computation of the ablation zone maps was done using the Arrhenius model of thermal tissue ablation.

### 3. Experimental Trials

**3.1. Primary Development.** The use of lasers to coagulate tumors was first proposed in 1983 by Bown [31]. Application for prostate ablation started in 1993-94 [2, 12].

With development of laser treatment for BPH, feasibility of FLA was established in canine model with a Nd:YAG laser (1064 nm) [2]. Johnson et al. reported an immediate well-demarcated area of acute coagulative necrosis surrounding each laser fiber pathway. A continuous and progressive enzymatic tissue liquefaction led within days to the development of central necrotic cavities.

Amin et al. reported the first clinical application of FLA for local recurrence of prostate cancer after external radiotherapy [12]. The procedure was performed under intravenous sedation with 805 nm diode laser. Laser fibers were inserted transperineally using 18G needles under US-guidance and CT-scan control. A bladder and urethral cooling was performed using continuous saline solution perfusion with triple-lumen urinary catheter. Procedure was well tolerated by patient with hospital discharge 24 h after treatment. A nonenhancing zone corresponding at ILC area was visible in CT-scanning control at 10 days. Control

biopsies at 3 months confirmed presence of coagulative necrosis in treated area and revealed cancer cells in other untreated area. A second laser treatment was performed without major side effect [2, 12]. At that time, development was limited by accuracy to localize the cancer areas on preoperative evaluation, computer dosimetric planning, and imagery follow-up.

**3.2. Preclinical Developments.** Table 1 summarizes the different preclinical publications dealing with FLA.

In 2000, Peters et al. described MRI-guidance and real-time thermometry for FLA in an *in vivo* canine prostate model [3]. They used an 830 nm diode laser (Indigo, Ethicon EndoSurg) with a quartz-clad diffuser at the end of laser fiber. Developments in MR imaging allowed accurate fiber positioning and obtaining quantitative 3D maps of *in vivo* temperature during the photothermal treatment. Animals were sacrificed at 4 and 24 h after the procedure. On histologic sectioning, the necrotic area was surrounded by hemorrhage and acute inflammation. In light microscopy, intact viable cells were described in the necrotic area of animal sacrificed after 4 h.

As previously described, these tissue areas exposed to supraphysiological hyperthermia (between 42 and 60°C) take from 24 to 72 hours for the full extent of lethal thermal damage to be revealed by necrosis. The cells appeared intact at this 4 hr time point because their intrinsic lytic enzymes have been thermally denatured and will likely persist until new blood vessels bring inflammatory cells to invade and digest the necrotic tissue. Consequently, on posttreatment dynamic MRI control, the visible margins of thermal necrosis were smaller than the histological finding. The authors concluded that thermal damage planning using MRI thermometry was needed.

In another study, after *ex vivo* calibration, Fuentes et al. performed FLA at 980 nm under MRI in canine prostate model (2 animals) [4]. They realized 1.5 Tesla MRI real-time thermometry, heat shock protein (HSP) expression, and cellular damage planning. The laser procedure consists in heating at 5 Watts for 90 seconds.

The objective of obtaining a visible necrosis over 12 mm of diameter was reached on immediate histopathologic examination. The authors concluded there was good correlation between planning and histopathologic observations. These findings were confirmed by Stafford et al. working on a canine model (5 dogs with healthy prostate and 2 immunosuppressed dogs with prostate cancer) [5]. Different levels of energy were used at 980 nm. This study demonstrated the feasibility of MRI laser fiber guidance with template. The laser fiber was placed in target site with accuracy (mean standard deviation = 1.1 mm  $\pm$  0.7). The correlation ratio between planning and histopathologic findings was about 0.94.

More recently our research group prove reproducibility of FLA in rat model with heterotopic tumor for one energy level [6]. The volume of visible necrosis in MRI was significantly different between 1 hour and 48 hours after FLA procedure ( $P < 0.001$ ). This difference was explained by the

existence of a noncoagulated degenerative zone surrounding the coagulative necrosis zone in the acute phase, which developed coagulative necrosis after 48 hours as previously described. Histological analysis showed a correlation with the mean necrosis volume obtained by MRI at 48 h ( $r = 0.87$ ). Histopathologic findings were in accordance with cellular damage planning.

In order to get a realistic model with materials presenting optical properties values closer to those of human prostate, Lindner et al. described a prostate phantom gel [10]. This allows the implementation of the FLA under ultrasound, CT, or MRI. The MR thermometry was validated with this model by temperature measures correlation obtained by fluoroptic thermometry (Luxtron Model 3100 optical probes were placed *in situ* in the phantom and could determine the temperature in real time).

In another study, Woodrum et al. have tested FLA at 980 nm on cadaveric model with MRI thermometry and damage planning (Visualase system) [11]. They concluded that MRI real-time thermometry and transperineal fiber guidance thru a template is technically feasible.

## 4. Clinical Trials

Table 2 summarizes the different clinical publications on FLA.

Several clinical studies in North America have recently been reported [9, 13–15]. An initial phase I study (NCT00448695, <http://www.clinicaltrial.gov/>) was published by the team of Professors Trachtenberg and Haider in Toronto who used a laser diode of 830 nm already used for the treatment of prostatic hyperplasia (Indigo Laser) [13]. After planning on MRI, the laser fibers were placed by a transperineal way; the monitoring of real-time processing was achieved by contrast-enhanced ultrasonography (CEUS). Necrotic lesions were visible on this examination (hypovascular zone), and the volumes obtained were consistent with those obtained on the control MRI.

Postoperative morbidity was negligible. Adverse events reported most frequently consisted of a perineal discomfort (25%) and mild hematuria (16%). Seventy-five percent of patients treated could leave hospital the day after the procedure. At 6 months, there was no significant decrease in erectile dysfunction score (IIEF-5) or worsening of urinary symptoms assessed by the International Prostate Symptom Score (IPSS).

On six-month biopsies, the authors reported short-term oncological results with 67% of patients without recurrence of tumor in the treated area [14]. These results described in phase I trial need to be pondered: the goal of this study was to assess the technical feasibility of FLA procedure. Also, short-term oncologic results could be considered as interesting but still limited by technical problems: in case of residual cancer cells in the ablated zone (33% of patients), the failure of treatment was explained either by poor overlap between pretreatment planification and posttreatment MRI results or by extraprostatic tumour extension to which MRI did not allude on pretreatment or posttreatment scan.

TABLE 1: Preclinical publications concerning focal laser ablation.

Reference Year	Type of preclinical model	Wavelength Type of laser source	Energy (Joules) Power (Watt) Time (seconds)	Type of imagery control	Delay between procedure and histopathologic examination	Dimension of thermal necrosis	Conclusions
Johnson et al. 1994 [2]	Dog (x9)	1064 nm (Neodymium YAG)	3000 J 10 W 300 sec	No imagery control	3 hours to 35 days	13–20 × 17–25 mm (median: 15 × 23 mm)	Immediate coagulation > 60°C Progressive coagulation 42–60°C
Peters et al. 2000 [3]	Dog (x2)	830 nm (diode laser)	449–751 J 10–15 W 180–300 sec	1.5 T MRI control (thermometry)	4 hours and 24 hours	120–260 mm <sup>3</sup>	Feasibility of MRI guidance and thermal monitoring
Fuentes et al. 2009 [4]	Dog (x2)	980 nm (diode laser)	450 J 5 W 90 s	1.5 T MRI control (thermometry, cellular damage, HSP production and cell viability planification)	immediately after	>12 × 12 × 12 mm	Good correlation between cellular damage planification and histopathology
Stafford et al. 2010 [5]	Dog (x7) 5 without tumour 2 with orthotopic tumour	980 nm (diode laser)	462–3460 J 4–14.3 W 40–524 s	1.5 T MRI control (thermometry, cellular damage planification)	immediately after	12.4–26.7 × 11.4–15.5 mm (median: 19–13.7 mm)	Accuracy of MRI template guidance Excellent correlation of planification with histopathology
Colin et al. Marqa et al. 2011 [6, 7]	Rat (x10) with heterotopic tumour	980 nm (diode laser)	375 J 5 W 75 s	7.0 T MRI control (cellular damage planification)	48 hours	923–1125 mm <sup>3</sup> (median: 974 mm <sup>3</sup> )	Reproducibility for one level of energy Good correlation of planification and histopathology
Fuentes et al. 2009 [4]	<i>Ex vivo</i> canine prostate in 1% agar gel	980 nm (diode laser)	240 J 8 W 30 s	1.5 T MRI control (thermometry, cellular damage planification)	—	—	MRI calibration for <i>in vivo</i> experiments
Lindner et al. 2010 [10]	Gelatine phantom With tumour target of 5 cm <sup>3</sup>	980 nm (diode laser)	—	1.5 T MRI control (thermometry, ultrasonography CT scan Fluoroptic temperature probes)	—	—	MRI, US, CTS compatible phantom Good correlation between MRI and fluoroptic thermometry
Woodrum et al. 2010 [11]	Cadavers (x5) 3 fixed in Formaldehyde 2 fresh	980 nm (diode laser)	1800–3600 J 15–30 W 120 s	3.0 T MRI control (thermometry and cellular damage planification)	—	22–27 × 23–28 mm	Feasibility of transperineal 3.0 T MRI guidance and real-time control

TABLE 2: Clinical trials concerning focal laser ablation of prostate cancer.

Reference Year	Number of patients	Wavelength Type of laser source	Number of fibers	Energy (Joules) Power (Watt) Time (seconds)	Type of real-time imagery control	Adverse events	Visible dimension of thermal necrosis	Carcinologic results or conclusions
Amin et al. 1994 [12]	1 patient	805 nm (Diomed diode laser)	3	3000 J 2 W 500 sec	US and CT scan	Mild dysuria	Unknown	Feasibility of FLA Biopsies at 10 days: necrotic tissue in targeted area, cancer cells in other areas
Atri et al. 2009 [13]	12 patients	830 nm (Indigo diode laser)	1 or 2	2880 J 2–15 W (temperature control at 100°C) 720 sec	CEUS and fluoroptic temperature probes 7-day follow-up 1.5T MRI	Perineal discomfort (3 patients) Mild hematuria (2 patients) Hematospermia (2 patients) Fatigue (1 patient)	300–4000 mm <sup>3</sup>	Biopsies at 6 months: 67% of patients free of tumour in the targeted area 50% of patients free of disease
Raz et al. 2010 [15]	2 patients	980 nm (Visualase diode laser)	≥2	Unknown	3D 1.5 T MRI control (thermometry, cellular damage planification) and CEUS just after procedure	No adverse event	Unknown	Feasibility of immediately repeated therapy
Lindner et al. 2010 [8, 9]	4 patients	980 nm (Visualase diode laser)	2 or 3	3260–5900 J	15-day follow-up 1.5T MRI CEUS and fluoroptic temperature probes 7-day 1.5T MRI control followed by radical prostatectomy	Not described	2500–4500 mm <sup>3</sup>	Strong correlation between MRI findings and vital stain histopathology images (Pearson's correlation index = 0.89)
Lindner et al. 2011 [16]	2 patients	980 nm (Visualase diode laser)	Unknown	Unknown	3D robotic 1.5 T MRI control (thermometry, cellular damage planification)	Improvement of IPSS score (1 patient) No change of IIEF-5 score	8700–9300 mm <sup>3</sup>	Safe and precise robotic guidance of laser fiber Possible oblique insertion angles to provide adequate dose
Woodrum et al. 2011 [17]	1 patient with local recurrence of prostate cancer after prostatectomy	980 nm (Visualase diode laser)	2	Unknown	3 T MRI control (thermometry, cellular damage planification)	No change of potency or continence	Unknown	Feasibility of FLA for local recurrence of prostate cancer

Thus, these limitations came from the poor visualization of the tumor and the difficulty of fiber guidance to the target previously defined. These same limitations also apply for other interstitial techniques (cryotherapy or photodynamic therapy). Advances in MR imaging and those of fiber guidance (nonrigid registration between MRI and ultrasound, real time guidance under MRI, robotic) should resolve these technical gaps.

Two other studies demonstrate the feasibility of focal treatment of cancer by MRI-guided FLA system at 980 nm with Visualase system (NCT00805883 and NCT01094665) [11, 28]. In the phase I trial NCT00805883 including 4 patients, the laser fiber guidance was performed as previously reported [9]. A radical prostatectomy was performed one week after the FLA procedure. Analysis of surgical specimens concluded for good correlation between the volumes of thermal damage visible on MRI and those actually recorded on the vital stain histopathological parts set (Pearson's coefficient  $R = 0.89$ ). In the thermal ablation zone, lack of viable tumor cells seen after immunostaining for cytokeratin 8 validates the scientific relevance of this minimally invasive treatment modality [9, 21].

In phase I trial NCT01094665, Raz et al. described fiber guidance under 3D MRI reconstruction by transperineal approach in 2 patients. MRI thermometry and thermal damage planning were calculated using Visualase system. Transrectal CEUS was realized immediately after the FLA procedure, and in case of residual vascularized target tissue, another procedure with new fibers position was performed. The patients were discharged home within 3 h, and no adverse event or complication was noted at  $\leq 1$  month following treatment [15]. The same research team described feasibility of robotic MRI-guided FLA in one case [16].

Recently, Woodrum et al. reported the case of one patient with locally recurrent prostate cancer after radical prostatectomy treated by FLA under 3T MRI guidance [17]. Authors reported no change in continence or potency after the MRI-guided FLA procedure.

Today, three phase I trials are recruiting in Canada (NCT01094665) and the USA (NCT01192438 and NCT01377753), and many American centers are already equipped with the Visualase system and have started to publish on the FLA technique for focal treatment. In Europe, a pilot study will open soon.

## 5. Discussion

Focal therapy for prostate cancer is recent and controversial in the urological community.

Showing a high rate of overdiagnosis and overtreatment concerning men with low-risk cancers, the results of international studies led to increased interest in alternative strategies and treatment options [1]. Also in selected patients, focal therapy could be an interesting alternative between radical treatment and active surveillance [32, 33]. Although the idea of focal treatment is simple (ablating a specific and previously defined area sparing uninvolved tissue), the application for prostate cancer met some difficulties: criteria

of patient's selection for focal therapy, precise localization, visualization and characterization of significant cancer foci, accuracy guidance of ablative energy in the area to be treated, oncologic efficacy evaluation, and finally surveillance modalities.

Nowadays, we are witnessing the concomitant development of the means of detection and the treatment modalities of these small significant cancers. Also, different energy sources are being tested for this indication. If limited short-term oncologic results of prior focal trials concerning cryotherapy or HIFU are encouraging, other ablative modalities such as VTP or FLA have only demonstrated technical feasibility to date [32].

FLA is an underdevelopment minimally invasive technique for *in situ* destruction of solid-organ tumors. Based on the use of low-power laser, which delivers luminous energy using an adapted optical system, FLA produces a coagulative necrosis zone with a controlled volume, reducing the risk of healthy adjacent structures damage (nerves, blood vessels, sphincter) [6, 9, 13–15].

Before the generalization of this concept, many issues have to be addressed. First, accurate localization of the tumor is required. MRI technology is emerging as the most important imaging tool for identifying low-volume prostate cancers, characterizing tumours, helping in patient-risk stratification, and allowing targeted use of biopsy [33, 34]. Accuracy of MRI as just imaging modality was reported in our previous work with radical prostatectomy histopathology correlation in which MRI sensitivity and specificity for identification of significant cancer foci ( $>0.5$  cc) were 86 and 94%, respectively [35]. Other teams also reported similar results. Besides identification, information concerning location and contours of lesions is important to consider an ablative technique. Important knowledge on modelling of cancer morphology such as zone of origin and intraprostatic patterns of spread of organ-confined prostate cancers at histopathology was made available for imaging interpretation and treatment planning decision [36, 37]. In a study by Dickinson et al., when the location is depicted by biopsy and the tumour is visualized by MRI, it accurately denotes the specific location 83% of the time in the peripheral zone for tumors larger than 4 mm in diameter [38]. It should be nevertheless noted that MRI application requires a degree of discipline in its conduct, reporting, and evaluation to obtain homogenous results among centers as emphasized by a recent European consensus meeting [39]. If MR imaging still lacks a strong validation, nowadays it remains the most important available imaging tool for identifying early prostate cancers and enabling focused use of energy ablative modalities.

The second issue concerns the ability to place precisely the laser-diffusing fiber within the target area. Using a brachytherapy-stabilizing apparatus with modified template grid and VariSeed system, Atri et al. were able to target in transrectal ultrasonography a suspicious area visible in MRI after rigid body registration [13]. Also, to compensate prostate deformation using transrectal sonography, the authors planned a target volume four times higher than the MRI suspicious area. In Phase I NCT00448695, Lindner et al.

described the same transperineal technique using 3D US and deformable registration for MR images fusion [14]. The authors concluded that improved deformable registration techniques might be able to minimize registration error and improve targeting. The development of such commercial devices with integrated laser is now achieved (e.g., Echolaser by Esaote), but no data are available concerning FLA of prostate application to the best of our knowledge.

Then, to enhance accuracy and facilitate real-time assessment of lesion size, the same team performed fiber placement manually under MRI procedure [15]. They used an MRI-compatible template grid and multiplanar images to obtain virtual 3D representation of the template with insertion paths and fiber placement within the prostate. Accuracy of MRI-template-based manual targeting was tested in a preclinical study concluding to standard deviation of  $1.1 \pm 0.7$  mm in fiber placement [5]. Now emerges the possibility of robotic guidance under MRI. In recent years, robotic MR-guided biopsy of the prostate has been reported to be of technical safety and a high degree of accuracy in the biopsy needle placement [39, 40]. Lindner et al. described first case of robotic MRI-guided FLA [16]. Moreover the accuracy to place the diffusing part of the laser fiber within the prostate cancer can be improved: the authors demonstrated that the robot can be used to produce oblique insertion angles to provide adequate dose coverage of low-volume tumors or with difficult location (anterior). This placement technology could be used for FLA under 3D-CEUS too but has not been described with this energy source to the best of our knowledge [41].

The third issue is the treatment planning required to optimize therapy parameters to ensure the optimal coverage of the area while sparing surrounding tissue. This issue is challenging and still needs the development of dedicated dosimetric tools as it was the case for radiotherapy and brachytherapy. Recent key advances in MRI allowed us to open some technological locks in FLA monitoring and guidance. With computer modeling development for thermal damage and multiplanar MR temperature imaging, it is now possible to accurately determine the expected thermal necrosis in region of interest and to control in real time the photothermal effect on homogeneous tissue [5, 7, 42]. Commercialisation of integrated system (laser source and fiber, computerized planning, and monitoring solution) has made MRI-guided FLA clinically relevant [14, 15]. However some limits are still present. Principal variability observed between predicted and obtained ablation areas is due to tissue heterogeneity. This heterogeneity is in relation firstly with own relaxation properties of the tissue (dependant on zonal anatomy, presence of tumor, vascularization, etc.) and secondly with changing of the tissular thermal conductivity during temperature increasing. New nonlinear calibrated computational model of the bioheat transfer may provide a reasonable approximation of the laser-tissue interaction, which could be useful for treatment planning in heterogeneous areas such as prostate cancer [4, 7]. Another limitation for thermal necrosis prediction is related with cooled applicators. To avoid charring or photovaporization, most teams are using cooled applicators to maintain a

temperature between 60 and 100°C during the heating phase. The use of these types of applicators necessitates computer modeling of the rise in temperature of the *in situ* fluid to reduce systematic errors [4, 43].

In order to reduce morbidity for healthy adjacent structures and reinforce specificity of FLA for cancer cells, recent preclinical development have been described using nanoparticles [44–46]. The goal of this technique is to produce photothermal coagulation in prostate tissue containing nanoparticles by near-infrared (NIR) activation. Although this is not shown specifically for prostate adenocarcinoma cells, the preferential accumulation of nanoparticles in cancer cells compared to healthy tissue has been suggested (passive diffusion in tumour neovasculature by enhanced permeability and retention effect). Also, if this theoretically selective accumulation was confirmed, the NIR illumination could activate a specific coagulation of the cancer cells. Thus, photoactivation of nanoparticles may occur at power levels that do not generate significant damage to healthy tissue. However the absence of toxicity of these nanoparticles must first be proven before considering an application in clinic.

In conclusion FLA is a potential tool for focal therapy of low-risk prostate cancer. Precision, real-time monitoring, MRI compatibility, and low cost of integrated system are principal advantages of this minimal invasive therapy. Feasibility and safety of this technique have been reported in phase I assays. Further trials are required to demonstrate the oncologic effectiveness in the long term.

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## Review Article

# Current Challenges in Prostate Cancer Management and the Rationale behind Targeted Focal Therapy

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Among men, prostate cancer has a high prevalence, with relatively lower cancer-specific mortality risk compared to lung and colon cancer. Prostate-specific antigen (PSA) screening has increased prostate cancer awareness since its implementation as a screening tool almost 25 years ago, but, due to the largely indolent course of this disease and the unspecific nature of the PSA test, increased incidence has largely been associated with cancers that would not go on to cause death (clinically insignificant), leading to an overdiagnosis challenge and an ensuing overtreatment consequences. The overtreatment problem is exacerbated by the high risk of side effects that current treatment techniques have, putting patients' quality of life at risk with little or no survival benefit. The goals of this paper are to evaluate the rise, prevalence, and impact of the overdiagnosis and ensuing overtreatment problems, as well as highlight potential solutions. In this effort, a review of major epidemiological and screening studies, cancer statistics from the advent of prostate-specific antigen screening to the present, and reports on patient concerns and treatment outcomes was conducted to present the dominant factors that underlie current challenges in prostate cancer treatment and illuminate potential solutions.

## 1. Background

Accounting for 29% of all cancers in men, prostate cancer is the most common cancer among men behind nonmelanoma skin cancer and is the second highest cause of cancer death among men of all races [1, 2]. Over 2 million men currently alive in the United States have had prostate cancer, and it is estimated that 16.48% of men will be diagnosed with prostate cancer at some point during their lives [3]. Estimates of newly diagnosed prostate cancer cases hover near 240,000 for 2011 [4].

However prevalent, the incidence and mortality of prostate cancer present very differently. It is estimated that 1 in 6 men will be diagnosed with prostate cancer but only 1 in 36 are expected to die because of it [5]. This may be because it is predominantly diagnosed in more senior adults, and, with a generally favorable outlook, men usually die before any symptoms appear [1, 5]. To be sure, there are tens of thousands of individuals who suffer the symptoms of aggressive prostatic cancer, but, in terms of the larger picture of prostate cancer, these men are well in the minority.

The question remains, why, for such a largely symptomless condition, do so many incidental or nonmortal cancers get diagnosed, and what does a diagnosis of cancer mean at this clinically insignificant stage? The purpose of this paper is to understand the trends that made such a predominantly hidden cancer become so noticeable, highlight the burden that this now markedly prevalent cancer places on healthcare, and illuminate current developments that may hold promise for easing that burden.

## 2. PSA Test Increases Incidence

The primary reason for such a high rate of diagnosis for so often a symptomless condition is most likely the result of prostate-specific antigen (PSA) screening practices which came about in the late 1980s following studies which seemed to demonstrate the value of PSA as a biomarker for prostate cancer [6–8]. The 1987 study by Stamey and colleagues was perhaps the most dominant one due to its citation prevalence in Medline [9, 10]. In 2004, however, Stamey and colleagues

maintained that PSA was only an accurate reflection of prostate cancer circa 1985 and that it was only demonstrated a relation to benign prostatic hyperplasia throughout the five years preceding their newer study [11]. Moreover, Thompson and colleagues demonstrated in 2005 that there was no single PSA cutoff that could yield both high sensitivity and specificity [12].

Nevertheless, early studies of PSA testing exhilarated the scientific community by offering the prospect of early detection of prostate cancer, a disease so often diagnosed late in its development due to its often symptomless progression [13, 14]. The use of PSA screening increased rapidly in the United States after 1987, resulting in a dramatic change in annual prostate cancer incidence and, in turn, a sharp increase in prostate cancer treatment both in the United States and abroad [15–17]. But while more cancers were being found and treated, the prostate cancer specific mortality rate only modestly decreased until 1993, after which little change was seen [15, 18]. Figure 1 from the National Cancer Institute shows this rising incidence of prostate cancer in contrast to the relatively unchanged mortality rate from 1975 to 2007. The disparity continues today, where the number of newly discovered prostate cancers is over seven times the number of prostate cancer related deaths [2].

### 3. PSA Test Creates Stage Migration

What may account for this is the fact that, while helping to discover mortal cancers, PSA testing also often led to the discovery of nonmortal cancers, or those which would never have been given notice in the absence of screening [19]. Given that 20–50% of asymptomatic men are found to harbor prostate cancer upon autopsy, it follows that the PSA test, with only a 24.1% positive predictive value, leads to a much greater detection of cancers, both mortal and nonmortal [20–23]. It is also possible that widespread PSA testing and treatment may have slowly weeded out the more dangerous prostate cancers from the population. Whether from increased testing, increased treatment of dangerous cancers, or some combination of the two, more cancers were being found at lower stages from 1986 to 1993, with tumors often being low grade, clinically localized, and/or organ confined. From 1993 to 2003, there was a 75% reduction in the proportion of metastatic diagnoses for prostate cancer [24]. The link between PSA testing and stage migration was documented in Austria during a large-scale PSA testing study and again later in the United States [24–26]. This seems to indicate that as PSA testing continues, prostate cancer will also continue to be diagnosed at clinically insignificant stages.

### 4. Overdiagnosis Ensues

Given the propensity of PSA testing to detect cancers both mortal and nonmortal, overdiagnosis was a probable outcome. Overdiagnosis due to PSA testing has been documented extensively through epidemiological studies and computerized models, at rates which range from 29% in

specific regions to an estimated 80% should all men in the United States be screened [7, 27, 28]. Progress has been made in investigating different biomarkers and variations of PSA testing for early detection of mortal prostate cancer, but, despite its flaws, the PSA test still remains the best screening tool currently available, suggesting continued overdiagnosis [29–31].

### 5. Uncertainty Leads to Treatment

The corollary of the overdiagnosis problem is an overtreatment problem. While active surveillance (AS) might seem the best course of action for many due to the relatively low mortality rate and exceedingly high 15-year survival rates of prostate cancer, working against that is a lack of consensus on what the inclusion criteria should be for AS, what the optimal follow-up schedule should be, or even how to best define progression [32]. For instance, the Epstein criteria is one common method of establishing whether or not a cancer is clinically insignificant, and this relies on a third or less of biopsy cores being positive, 50% or less involvement of any 1 core, and a PSA density of less than 0.15 ng/mL. However, the D'Amico criteria, also widely used, calls for a Gleason score of six or less, a PSA of less than 10 ng/mL, and a T1 clinical stage. Studies have shown highly favorable results for certain criteria, like the 100% 10-year prostate cancer-specific survival rate documented by researchers who took patients off AS based on PSA doubling time [33]. Other studies suggest that PSA kinetics are not reliable for AS inclusion/exclusion criteria [34]. In yet another study, researchers found that prostate specimens fitting six different inclusion criteria for clinically insignificant disease would have been misclassified 14–27% of the time based on Gleason 8 findings [35]. Research continues to refine AS criteria, but a clear understanding of how to define clinically insignificant disease has not been reached.

The lack of consensus and the thought of harboring a cancer with an unpredictable progression leads to feelings of uncertainty in the patient, in turn arousing high levels of emotional distress, anxiety, and depression [36]. While support services can assist in ameliorating the psychological distress, men with prostate cancer tend to avoid disclosure and are unlikely to utilize health and psychological support services [37]. At the same time, doctors tend to underestimate the psychological morbidity of men with prostate cancer, leading to a lack of provider referral [38].

With a lack of social support, motivation to seek it out, or provider referrals to address the psychological discomfort associated with prostate cancer, most newly diagnosed men suffer the full psychological burden of living with an unpredictable cancer. This proves too much to bear, as rather than learning to live with what is most likely a nonmortal cancer, men elect various courses of treatment to escape the mental anguish of uncertainty. In a study of the reasons for undergoing various treatment types, Gwede et al. found that 44% of men chose radical prostatectomy primarily because they believed it to be their best chance to be cured [39].

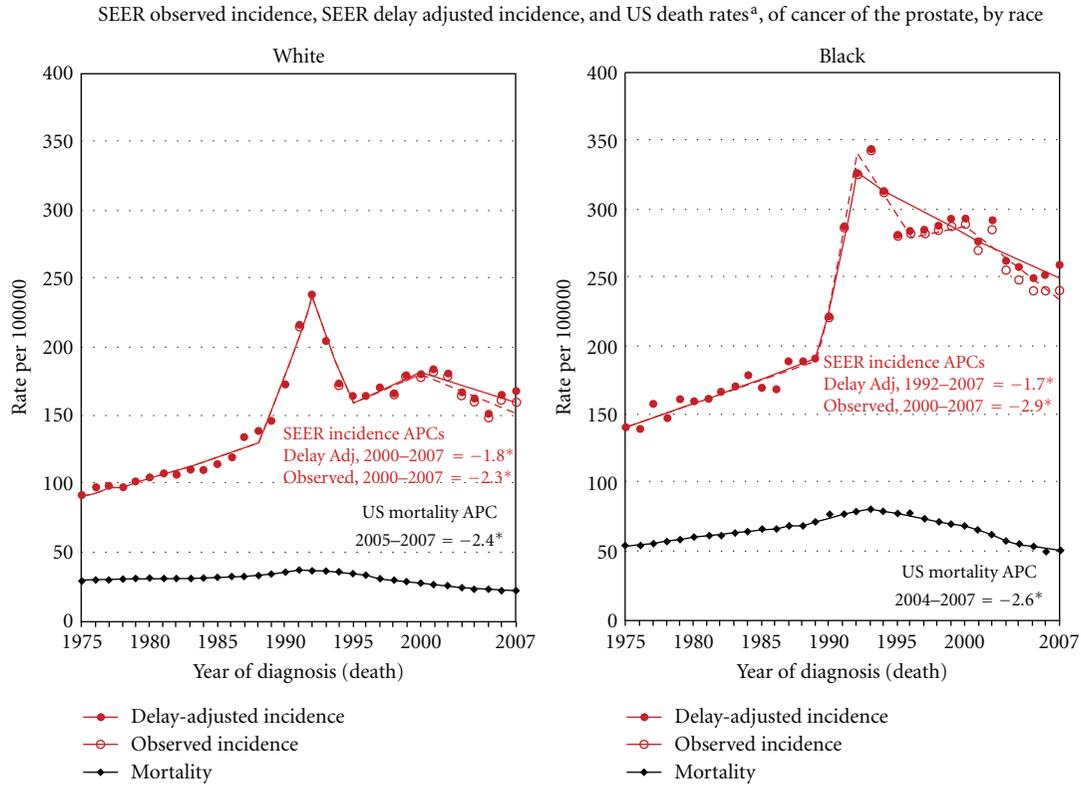


FIGURE 1: Change in prostate cancer incidence and mortality from 1975 to 2007 documented by the National Cancer Institute. <sup>a</sup>rates are age adjusted to the 2000 US Std Population (19 age groups—Census P25-1103). Regression lines and APCs are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute. The APC is the annual percent change for the regression line segments. The APC shown on the graph is for the most recent trend. The APC is significantly different from zero ( $P < 0.05$ ).

Denberg et al. found that a group of men underwent surgery due to the belief that it was the most certain, expeditious, and tangible option and that, even though it might reveal that a tumor escaped the prostate, it would at least eliminate some uncertainty. These same men found no other option appealing because they dealt with acting on a hidden and unseen cancerous organ. Even those who did not choose surgery in the Denberg study were motivated by uncertainty, in their case, they were trying to avoid the uncertainties associated with surgery. It should also be noted that half of their patient sample avoided seeking second opinions due to delay, prolonged uncertainty, and feelings of increased anxiety [40]. Similar findings were reported in England, Scotland, and Wales, where a study of 50 men with early-stage prostate cancer found reasons for prostatectomy ranging from frustration with the lack of concrete information and consensus over what to do, to the explicit desire to fix the problem [41].

The uncertainty and anxiety of having prostate cancer are certainly a formidable driver for treatment instead of AS, and researchers have documented it as a valuable predictor of treatment receipt [42, 43]. Watchful waiting (often synonymous with AS) is often used in other countries but rarely in the United States, especially for younger men with early-stage prostate cancer for whom treatment is often advocated [44]. When briefed with specific cancer statistics

and information on the side effects of treatment, most patients place little weight on side effects when there is even a chance of prolonged survival [45]. Mazur and Hickam showed that even when attempting to bias patients against surgical therapy by explicitly naming surgical complications and presenting rates of those complications higher than what was typically in the literature, most patients still preferred surgical treatment over AS for localized prostate cancer [46]. Research shows that, on the whole, only 18.5% forgo active treatment for watchful waiting, all in the face of a cancer that is lethal in only 1 in 32 cases [47].

## 6. Prevalence of Overtreatment

The amount of treatment received is certainly disproportional, and studies clearly indicate that a substantial proportion of treatments do not go on to prevent death from prostate cancer. The European Randomized Study for Prostate Cancer (ERSPC) reported, for instance, that 1410 men needed to be screened and 48 treated to prevent 1 cancer death [48]. Results from the Randomized Scandinavian Prostate Cancer Group Study show that an estimated 15 patients needed to be treated to avert one death at 15 years and that, for adjuvant radiation therapy, the number of patients needed to be treated to avert one death at 12.6 years

was 9.1 [49]. Perhaps the most favorable results were found in Quebec, where out of an estimated 100 men with screen-detectable prostate cancer, an average of 16 could have their lives extended by surgery (should those men be found by way of extensive screening efforts) [50]. However, the most recent data comes from the Prostate Cancer Intervention versus Observation Trial (PIVOT), which reports that, after 12 years of followup, overall prostate cancer mortality was only 3% lower for men having radical prostatectomy. In fact, men with low-risk prostate cancer were actually shown to have a 2.4% better survival rate with watchful waiting than with surgery. PIVOT reports that, even when looking exclusively at cases of intermediate risk, radical prostatectomy still only achieves a 4.8% better survival rate [51].

The statistics from these studies also do not take into account the copious amounts of unnecessary biopsies that would have to be performed to find these cancers in the first place, as in order to detect even 83.4% of cancer cases by PSA testing, a calculated 61.1% of men without cancer would need to be subjected to prostate biopsy, a procedure that is in itself not without consequence to quality of life [12].

In an effort to quantify the amount of overtreatment stemming from prostate cancer, Welch and Albertsen used Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute and statistics from the US Census to estimate that from 1986 to 2005, 1,004,800 of an additional 1,305,600 overdiagnosed cancers received treatment, with 571,000 excess prostate-cancer-related surgeries, and 477,400 excess prostate-cancer-related radiation treatments [10].

## 7. Side Effects of Treatment

Excess treatment brings excess side effects, and, in the case of prostate cancer, they are not uncommon. Overtreated patients run several risks, especially when it comes to radical prostatectomy and/or radiation therapy, the most dominant treatment options. The US Preventative Services Task Forces reviewed the most common side effects of treatment from 1994 to 2002, bringing the problems associated with overtreatment to light. Long-term adverse effects of radical prostatectomy, for instance, were sexual dysfunction (20–70%) and urinary incontinence (15–50%). For electron beam radiation therapy, approximately 45% could expect erectile dysfunction, 2–16% urinary dysfunction, and 6–25% bowel dysfunction. For Androgen Deprivation Therapy (ADT), approximately half of patients who were sexually active beforehand were not sexually active afterward, 5–25% had breast swelling, and 50–60% had hot flashes along with other potential long-term complications like anemia and osteoporosis. For brachytherapy, a majority of men reported having distressing urinary symptoms, 21–36% reported decreased erectile function, 18% diarrhea, and 19% persistent rectal bleeding [52].

The primary concern of most men undergoing radical prostatectomy is preservation of potency, and, to that end, bilateral nerve sparing techniques in younger cohorts (median age 57) have yielded a potency rate as high as 86%,

with more typical results hovering around 44–76% [53]. The second most dominant concern is urinary continence, but data on that is difficult to generalize given the changing definition of continence which various studies employ. When urinary continence is defined as not needing protection to keep outer garments dry, 93% of men followed for more than 18 months recovered continence, but, when using total urinary control as a benchmark, only 32% of men were continent at 24 months [53]. Among patients in the Rotterdam section of the ERSPC who underwent radical prostatectomy, as much as 80–90% reported erectile dysfunction and 39–49% reported urinary incontinence [54]. Studies analyzing even the most advanced minimally invasive prostatectomy techniques (robotic and/or laparoscopic) find continence ranging 68.0–94.7%, potency 33.3–65.3%, and progression-free survival 84.1–92.0% [55].

In more recent findings, these problems are still prevalent. In a comparison of 1938 men who received minimally invasive radical prostatectomy and 6899 men who received open retropubic radical prostatectomy, investigators found incontinence rates of 15.9 and 12.2 per 100 person-years, respectively. Sexual dysfunction was higher, however, with rates of 26.8 and 19.2 per 100 person-years, respectively [56]. Another large-scale study of 1,201 patients treated with surgery, brachytherapy, or EBRT found erectile dysfunction rates two years posttreatment of 57%, 31%, and 35%, respectively [57, 58].

## 8. Focal Therapy Offers a Solution

The aforementioned statistics indicate that the majority of these treatments will infer no survival benefit in the first place, so the amount of men who go on to suffer such side effects is certainly unwarranted. However, without an established and reliable way to distinguish mortal from nonmortal cancers and the overwhelming preference by both patients and providers to pursue treatment options in the face of such uncertainty, it seems treatment will continue to be the dominant option. Fortunately, focal therapy techniques developing since the 1990s are now showing promise as a method of treatment which is not associated with such arresting rates of side effects. These techniques avoid the costs that other techniques would require in order to reduce side effects to comparable levels while still being effective [59].

Clinical trials have demonstrated the feasibility of focal ablative methods using high-intensity focused ultrasound and cryosurgery [60], and focal techniques are expected to improve as imaging techniques allow for better pathological assessments [61–63]. Successful focal therapy demands stringent selection factors, and this requires an imaging modality which can accurately characterize the location, extent, and grade of a patient's prostate cancer [64]. In this effort, a brachytherapy template-guided transperineal saturation biopsy technique (3DMB) was described and tested by Crawford et al. on prostate autopsy specimens in 2005, which demonstrated both feasibility and increased accuracy over sextant biopsies [65]. In evaluating the potential of 3DMB in

vivo, Barqawi et al. compared previous TRUS results of 215 patients to those obtained using 3DMB, finding new cancer foci in 82 patients and higher Gleason scores in 49 patients, demonstrating a potentially significant improvement in the way prostate cancer can be evaluated [66]. While long-term results have not been disseminated as of yet, we are currently anticipating the publication of 5-year follow-up data on patients treated with focal cryoablation in conjunction with 3DMB.

While promising results continue to be seen, there are still hurdles to overcome, such as the issue of gland stabilization during treatment, or how to work around large prostates when employing 3DMB [67]. In addition, wide variability in patient selection, disease characterization, and treatment protocols still exist. A preferred ablative energy for focal therapy has also not been conferred (cryosurgery, high-intensity focused ultrasound, vascular-targeted photodynamic therapy, brachytherapy, radiotherapy, or tomotherapy), yet it seems that one of the dominant concern for those investigating this approach has to do with standardizing follow-up protocols and creating reliable and meaningful outcomes measures to evaluate it, as the PSA measurements so often relied on to assess other forms of treatment are not only unreliable as mentioned, but also tend to take on different meaning when larger portions of the organ are left intact, as is the case with focal therapy [68, 69]. While biochemical disease-free status using American Society of Therapeutic Radiation Oncology or Phoenix criteria seems to be the dominant means of evaluating focal treatment, standardized algorithms for determining success would be of significant benefit to researchers pursuing long-term follow-up studies on focal therapy. Standardization should be a primary focus of future follow-up studies and will serve greatly in conferring the efficacy of different methods and identifying areas for improvement.

## 9. Conclusion

While procedural advances and screening efforts continue to report improvements, the PSA test is still the best screening tool currently available, and this suggests a continuing trend of overdiagnosis based on historical data. Early detection of prostate cancer is possible, but early discrimination is not, leading to a great deal of uncertainty as to whether or not a particular patient's prostate cancer will become aggressive. The psychological burden that comes with this uncertainty more often than not leads to treatment regardless of patients' understanding of high risks of side effects and low survival benefit rates. Whether or not improved screening or imaging techniques will be able to better distinguish nonmortal from mortal cancers remains to be seen, as well as what role that will play in regards to the psychological distress that comes with being diagnosed with prostate cancer.

With overwhelming evidence, the root of overtreatment and the unnecessary side effects that ensue lie in the psychological burden of dealing with uncertainty and with the lack of emotional support or the motivation to seek it out, the vast majority of newly diagnosed men undergo

serious treatment efforts regardless of the potential for harmful side effects. Solutions to the overtreatment problem may come from enhanced screening and imaging efforts or the delivery and implementation of psychological care for those diagnosed with localized cancer. More likely, solutions will come from improvements in treatment methodology. Focal therapy appears to be a promising avenue in this regard as it is noninvasive, has fewer side effects, and remains more cost-effective than side-effect reducing advanced radiation and robotic techniques. Moreover, focal therapy does not exclude the possibility of more radical options and does not necessarily replace traditional techniques. Enhanced methods to evaluate focal therapy and standardized protocols to assess outcomes measures will help progress this emerging practice as improvements in imaging modalities help practitioners realize its assumed potential.

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## Review Article

# Focal Therapy in the Management of Prostate Cancer: An Emerging Approach for Localized Prostate Cancer

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A widespread screening with prostate-specific antigen (PSA) has led increased diagnosis of localized prostate cancer along with a reduction in the proportion of advanced-stage disease at diagnosis. Over the past decade, interest in focal therapy as a less morbid option for the treatment of localized low-risk prostate cancer has recently been renewed due to downward stage migration. Focal therapy stands midway between active surveillance and radical treatments, combining minimal morbidity with cancer control. Several techniques of focal therapy have potential for isolated ablation of a tumor focus with sparing of uninvolved surround tissue demonstrating excellent short-term cancer control and a favorable patient's quality of life. However, to date, tissue ablation has mostly used for near-whole prostate gland ablation without taking advantage of accompanying the technological capabilities. The available ablative technologies include cryotherapy, high-intensity focused ultrasound (HIFU), and vascular-targeted photodynamic therapy (VTP). Despite the interest in focal therapy, this technology has not yet been a well-established procedure nor provided sufficient data, because of the lack of randomized trial comparing the efficacy and morbidity of the standard treatment options. In this paper we briefly summarize the recent data regarding focal therapy for prostate cancer and these new therapeutic modalities.

## 1. Introduction

Prostate cancer is one of the most common cancers in the developed countries [1]. Statistically it has overtaken lung and colon cancers to be the most common cancer in male. One of the most important advances in prostate cancer management in recent years is the discovery of prostate-specific antigen (PSA) as a tumor marker [2]. A 75% decrease in metastatic prostate cancer and a 91% increase in localized disease with patients diagnosed annually have been observed since 2002 [3]. That is, the PSA screening has resulted in an increased detection rate of prostate cancer with stage migration towards lower stage, leading to overdiagnosis and overtreatment of prostate cancer by at least 30% [4, 5]. A dramatic diagnostic paradigm shift has forced urologists to reevaluate the role of traditional radical therapies such as external beam radiotherapy and prostatectomy. Maintaining quality of life is as important as

prostate cancer eradication. Thus, it is no longer acceptable to just cure prostate cancer patients by aggressive treatments in downward grade and stage migration as well as declining age of prostate cancer diagnosis. Because radical treatments carry significant morbidity with operative complications (hemorrhage, pain, etc.) and long-term toxicity (incontinence, impotence, rectal problems, etc.), there has been a great need for developing ablative therapies that attempt to reduce treatment burden with assuring good cancer control and avoiding the psychological morbidity associated with active surveillance. In addition, it seems reasonable that interest has been considerable in adapting focal methods because the prostate is easily accessible by way of the rectum, urethra, or perineum. Partial surgery of the prostate is impossible due to the location of the cancer in the periphery of the prostate gland, which to access necessitates the almost same morbidity as removing the whole gland. Therefore, focal therapy using energy modalities offers generally

accepted only solution for partial treatment of the prostate gland.

Focal therapy has been introduced as middle ground alternative between active surveillance and radical treatments with effective early cancer cure or control. The terms “focal therapy” and “organ-preserving therapy” may be defined as complete selectively ablation techniques of clinically significant cancer foci within prostate in a focal or subtotal manner with the overall objective of minimizing lifetime morbidity without compromising life expectancy. That is to say, the energy modalities must be easily delivered to the prostate and be capable of destroying cancer cells. The obvious benefit of focal therapy is preservation of the uninvolved surround healthy tissues such as the sphincter, the neurovascular bundles, and normal prostate gland using a minimally invasive technique [6]. And there may be a potential to repeat focal therapy or use another treatment modality in case of persistent cancer. On the other hand, the main issue of prostate cancer is multifocal localization of cancer foci [6]. The patients with unifocal, unilateral, or low volume prostate cancer are most suitable for focal therapy; however, we found a great deal of difficulty in identifying patients with multifocal clinically significant cancer foci who require aggressive whole gland therapy from those with clinically focal cancers who may benefit from organ-sparing treatment. It has been reported that the oncological outcome was similar between the unilateral or bilateral cancer groups in patients with low-risk prostate cancer, suggesting that the limiting factor for focal therapy is clinical risk stratification, not laterality of cancer [7]. Indeed prostate cancer has long been recognized as characteristically multifocal, but it may present as true unifocal or volume-limited multifocal disease in the era of widespread PSA screening and early detection. Therefore, improved imaging techniques and mapping biopsy protocols in patient selection are needed to fully support focal therapy.

In this paper we briefly discuss the evidence for a variety of ablative energy modalities available for use in focal therapy of localized prostate cancer including cryotherapy, high-intensity focused ultrasound (HIFU), and vascular-targeted photodynamic therapy (VTP).

## 2. Cryotherapy

The first report describing cryotherapy of benign prostate hyperplasia appeared in 1966 [8], and an attempt to destroy prostate cancer by using a transperineally introduced cryoprobe was reported in 1972 [9]. Although cryotherapy did not achieve wide usage initially due to incomplete eradication of the tumor or high recurrent rate of cancer [10, 11] and high complication rates including urinary retention, incontinence, urethrorectal or urethrocutaneous fistulas, stricture, chronic rectal or perineal pain, and loss of erections, advantages of the procedure were recognized [12]. In particular, use of transrectal ultrasound (TRUS) for real-time monitoring of the freezing process, improved cryoprobe system, and a urethral warmer using a continuous irrigation system could popularize cryotherapy as an effective

and technically feasible treatment for prostate cancer [13]. Finally, cryotherapy was approved as treatment for prostate cancer by Centers for Medicine and Medical Services in 1999 [14].

Cryotherapy is the localized destruction of tissue by low temperature and thawing, which causes direct injury to cells as well as secondary injury from the inflammatory response of the body. Current technology uses argon gas or liquid nitrogen circulating through hollow needles to freeze the prostate and helium gas to warm the urethra via the Joule-Thompson effect. There are three treatment parameters correlated with cancer cell destruction: the cooling rate, the lower temperature, and the duration of the freeze cycle. Complete cell death is likely to occur at temperatures lower than  $-40^{\circ}\text{C}$  for two cycles. After reaching a tissue temperature of less than  $0^{\circ}\text{C}$ , the extracellular fluid starts to crystallize and formation of crystals causes hyperosmotic pressure of the unfrozen portion of the extracellular fluid compartment, leading to water shifting from the intracellular space to the extracellular space. The cell water loss induces intracellular dehydration and pH change. This is followed by cell shrinkage and denaturing of cellular proteins. With further drops in temperature less than  $-15^{\circ}\text{C}$  intracellular crystallization takes place and cell metabolism begins to fail. This mechanically breaks the cellular membrane and the cell apoptosis is also induced after thermal injury. The apoptotic cells are observed primarily in the peripheral zone of the cryogenic lesion outside the killing zone, where the temperature is not fully decreased to kill all the cells [15]. As temperatures rise, extracellular fluid shifts back again into the intracellular space, leading to cellular bursting. The vasodilation around the targeted tissue occurs after thawing causing hyperpermeability of the vessel wall. This leads to endothelial damage and microthrombi formation resulting in regional tissue hypoxia and secondary necrosis of the tissue [14, 16].

A significant current development is the introduction of cryotherapy probes that use argon gas rather than liquid nitrogen. Argon gas can rapidly cool the probe tip to  $-187^{\circ}\text{C}$  and can be rapidly exchanged with helium gas at  $67^{\circ}\text{C}$  for an active thawing phase, producing a faster response to operator input and significantly speeding 2-cycle treatment [17]. Moreover, argon-based probes have a much smaller diameter. Thus, they permit direct, sharp transperineal insertion using transperineal placement of ultrathin probes through a brachytherapy template, avoiding the need for tract dilation and facilitating more conformal cryosurgery by allowing placement of more probes [18].

## 3. Patient Selection

This modality can be used in any tumor grade of prostate cancer with clinical stage T1c-T3 disease. In general, primary cryotherapy is suitable for patients with low-risk group (clinical stage T1c-T2a disease, Gleason grade 6, and PSA  $< 10\text{ ng/mL}$  who are not potent or not interested in maintaining their potency). Patients with intermediate

risk group (Gleason grade 7, PSA between 10 and 20, or clinical T2b) are also effective for the procedure. Because of the minimally invasive therapeutic modality, cryotherapy may have specific advantages in selecting patients with certain comorbidity including those who cannot tolerate radical prostatectomy or radiation therapy (e.g., persons with previous pelvic radiation or pelvic surgery, irritable bowel disease, cardiac disease, extreme obesity) [14]. Contraindication to cryotherapy includes the presence of tumor foci near the urethra because the urethral warming catheter will preclude complete eradication of disease [16]. In addition, this therapy is generally contraindicated in patients with the presence of tumor foci near the neurovascular bundles if patients are potent or interested in maintaining their potency [16]. Patients with severe lower urinary tract symptoms or large prostate are also poor candidates for cryotherapy, and a previous transurethral resection of the prostate (TURP) is generally considered a contraindication. If the prostate size exceeds 50 mL, neoadjuvant hormone therapy is needed to reduce the prostate volume because complete freezing of the prostate is difficult [14, 19]. However, there is no evidence whether neoadjuvant therapy or combination therapy with androgen deprivation influences postcryotherapy cancer control [14].

#### 4. Clinical Outcomes

There were a lack of consensus on how recurrence was defined and no accepted biochemical definition of PSA failure after primary cryotherapy. The PSA value rises immediately after cryotherapy due to release of intracellular PSA from cellular necrosis and PSA nadir is usually achieved more than 3 months after the procedure [20]. Serum PSA levels are unlikely to reach undetectable levels because some PSA-producing periurethral prostatic tissue will remain. Commonly, in order to assess local control patients who have been treated with cryotherapy have undergone repeat prostate biopsy 6 to 12 months after cryotherapy in several series. The positive biopsy rate after the procedure ranges from 7.7% to 23% [13, 19, 21, 22]. These studies are including focal targeted cryoablation, hemiablation, and radical cryoablation. Higher initial PSA levels and clinical T stage were positively associated with a risk of positive biopsy rate after cryotherapy. In 860 patients treated with focal cryotherapy included in the Cryo On-Line Data (COLD) Registry, 5-year biochemical disease-free rates ranged from 77.6% to 82.4% according to the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria of three consecutive PSA rises after the posttreatment nadir and 58.0% to 74.9% according to the Phoenix criteria of PSA nadir plus 2. For this series, 21% had evidence of cancer at postcryotherapy biopsy [23]. Taken together, results of recent reports indicate that 5-year biochemical disease-free survival rates range from 60% to 90% for patients with low- and intermediate-risk groups [24–27]. A recent randomized trial to compare external beam radiotherapy to cryotherapy for patients with localized prostate cancer receiving neoadjuvant

antiandrogen therapy indicated cryotherapy to be noninferior to external beam radiotherapy in disease progression (23.9% in cryotherapy versus 23.7% in radiotherapy) at 36 months and 5 years overall (89.7% versus 88.5%) and disease-specific survival at 5 years (96.4% versus 96.1%) [28].

#### 5. Complications

Erectile dysfunction and impotence after cryotherapy are common. Some series have reported impotence rates ranging from 50% to 92% [27, 29]. This is probably because of the use of multiple freeze-thaw cycles and the extension of the damage beyond the prostate, into the area of the neurovascular bundles; however, complete ablation of the neurovascular bundles is necessary to ensure eradication of cancer at the periphery of the prostate. Interestingly, impotence rates after hemiablation ranged from 10% to 29% and potency made a recovery within 1 year, although subtotal or focal cryotherapy should be investigational [30, 31]. A recent randomized trial reporting on quality of life outcomes showed that cryotherapy was associated with poorer sexual function comparing with external beam radiotherapy. Patients who wish to increase their odds of retaining sexual function may be better to choose other modalities over cryotherapy [32]. Cryotherapy is associated with more acute urinary dysfunction, which resolves over time [32]. The reported incidence of urinary incontinence ranges from 3.7% to 4.8% [26, 27, 29]. The causes of incontinence include sphincter muscle destruction, disruption of the pudendal nerve, and urethral sloughing.

There are some complications specific to cryotherapy including tissue sloughing, urethral stricture, pelvic and rectal pain, rectourethral fistula [33], and penile numbness [19]. Penile and scrotal swelling within several weeks after cryotherapy is reported as a rare complication. Hydronephrosis or small bowel obstruction as uncommon complications results from the extensive freezing and deep insertion of cryoprobe [34]. The risks of these complications have decreased with advances in technology, such as urethral warming techniques, and improved patient selection.

#### 6. High-Intensity-Focused Ultrasound (HIFU)

The first report describing HIFU using the transrectal probe of benign prostate hyperplasia appeared in the mid-1980s [35], and an attempt to treat localized prostate cancer was reported in 1995 [36]. Diagnostic ultrasound usually uses frequencies in the range of 1 to 20 MHz, but transrectal HIFU uses sound waves with frequencies of 0.8 to 3.5 MHz and can achieve coagulative necrosis and the destruction of the targeted tissue through hyperthermia in two ways. The two mechanisms of tissue damage are by the conversion of mechanical energy into heat and inertial cavitation. Firstly, ultrasound energy is concentrated and tissue absorption of the focused ultrasound wave generates temperatures that

exceed 80°C, which denature proteins and destroy lipid-based membranes, and this process finally results in instantaneous and irreversible coagulative necrosis. Secondly, the alternating cycles of compression and rarefaction develop inertial cavitation effect causing additional damage to the prostate and periprostatic tissue. Histologically, homogeneous coagulative necrosis developed in the damaged tissue with an inflammatory response that follows leading to formation of granulation [37]. Currently, two systems including Sonoblate-500 produced by Focus Surgery (Indianapolis, IN) and Ablatherm produced by EDAP TMS (Lyons, France) for delivery of HIFU are available. The treatment area is heated for 3 seconds and cooled for 6 seconds with real time images. The energy decreases sharply outside the target zone; thus the surrounding tissues are minimally affected. Days to months are required for necrosis and cavitation to occur, and the prostate gland shrinks a small size over 3 to 6 months after the procedure. Due to the limits of the ultrasound wave, there is the difficulty in ablating the whole prostate gland, especially in a large prostate (>40 mL) and the difficulty in ablating anterior cancers [38]. Hormone therapy or transurethral resection of the transitional zone may be useful in overcoming the difficulty of reaching the anterior zone.

## 7. Patient Selection

In general, primary HIFU is suitable for older patients (over 70 years) with low- and intermediate risk groups. HIFU may be used to treat prostate cancer, either as a primary or as salvage therapy. There is an upper limit to prostate gland size of 40 mL due to focal length of the probe. In this case, a TURP before HIFU can be of benefit to reduce prostate size and can also reduce morbidity and indwelling catheter time. In general, the prostate with highly calcifications (>1 cm) should be contraindication because these will obscure ultrasonographic visualization. In some cases TUR of large calcifications may be performed before HIFU. As with cryotherapy, HIFU may have specific advantages in selecting patients with certain comorbidity including those who cannot tolerate radical prostatectomy or radiation therapy.

## 8. Clinical Outcomes

As the data on HIFU as salvage therapy were limited, we focused on HIFU as primary therapy. The combination of PSA value and prostate biopsy is used to define recurrence after HIFU. A multicenter trial with the results of using the Ablatherm was reported in 2003 [39]. Although 28% of the patients required two treatment sessions, 87% of the patients had a negative biopsy with 92%, 86%, and 82% in the low-, intermediate-, and high-risk groups, respectively. Mean PSA nadir in the low-, intermediate-, and high-risk groups was 1.3 ng/mL, 1.4 ng/mL, and 3.1 ng/mL, respectively, and a median PSA nadir of 0.4 ng/mL was achieved at a minimal follow-up of 6 months. Gelet et al. reported the long-term results in patients with low-risk disease. Patients with

preoperative PSA less than 10 ng/mL demonstrated negative biopsy of 78% and 5-year disease-free survivals of 83%. For those with intermediate- and high-risk groups, the disease-free survival rate was 53% and 36%, respectively [40]. Blana et al. also analyzed a large cohort in patients with low- and intermediate- risk disease. The 5-year disease-free probability was 66%, and 28% of the low-risk disease developed treatment failure [41]. The negative biopsy rate after the procedure ranges from 55% to 100% in recent trials including clinical T1 to T3 stages. Higher clinical T stage and larger prostate size were positively associated with a risk of both PSA failure and positive biopsy rate after HIFU [39, 42–44].

## 9. Complications

Transient urinary retention arising from swelling of the prostate after HIFU is the common complication, which may require prolonged catheterization or cystostomy drainage [39]. Prolonged retention ranged from 6% to 32% [39, 42–44]. A high degree of urethral stenosis near the verumontanum and bladder outlet obstruction was seen, which are late complications of HIFU. The recent reported incidence of urethral stenosis ranged from 2% to 17% [39, 42–44]. De novo erectile dysfunction and impotence were also known to occur at 24%–77% of those who were potent preoperatively. The use of a pulsed-wave Doppler ultrasound system to visualize the neurovascular bundles during treatment may improve this outcome. Mild to moderate stress incontinence rates after HIFU ranged from 6% to 14% of patients in earlier series, but this has decreased over the years with next-generation HIFU devices [39, 42–44]. Severe incontinence developed in 1%–5% requiring intervention [39, 42–44]. Stress incontinence, urethral stenosis, and bladder outlet obstruction were reported to be decreased by TURP before HIFU [45]. Therefore, TURP may be indicated before HIFU; however, TURP appears to have no effect on cancer control including PSA nadir, negative biopsy rate, and biochemical failure. There were some serious complications specific to HIFU including rectal wall burn and rectourethral fistula before the use of the rectal cooling device and robotic control system of rectal distance [46]. Current results report on the complications seen with HIFU as whole gland therapy; however, one can expect lower rates of complications with HIFU as targeted focal therapy.

## 10. Vascular-Targeted Photodynamic Therapy (VTP)

VTP is an investigational ablative technology which employs the use of photosensitizing properties that is selectively taken up by prostate cancer cells and produces radical oxygen species upon exposure to light of a specific wavelength which results in the destruction of the tissue. The first report describing photodynamic therapy for prostate cancer with light-sensitive agent (either hematoporphyrin derivative or polyporphyrin photofrin) using a transurethral approach

appeared in 1990 [47]. The photosensitizers have taken a long time to be cleared from the body and accumulated in the skin. To avoid sunburn-like reaction patients must have been covered from sunlight for a several weeks after treatment [48]. Recent advances in photodynamic therapy have led to improvements of the synthesis of new generation photosensitizers with more excellent stability and shorter half-lives with faster metabolism. The rapid clearance of these new agents from the circulation and then from the liver could negate the need to avoid exposure to sunlight for long periods. Vascular acting photosensitizers currently under investigation are Tookad (WST09: padoporfin; palladium bacteriopheophorbide) and its water-soluble derivative WST11 (padeliporfin; palladium bacteriopheophorbide monolysotaurine) produced by Steba Biotech (The Netherlands), which are the most widely used new generation photosensitizers. Both WST09 and WST11 remain confined to the vascular bed [49].

A photosensitizer is injected intravenously and is distributed throughout the body during treatment. Under ultrasound guidance, small energy-delivering probes can be positioned in the prostate using a needle placement grid developed for brachytherapy. VTP usually uses an intravenously administered WST09 that absorbs light in the visible near infrared wavelength with maximum light energy absorption at 763 nm. This long light absorption wavelength allows for a deeper light penetration into tissues. A photosensitizer enhances sensitivity of the tumor vasculature to light energy. Damage to the vascular endothelium is followed by platelet aggregation and vascular coagulation round the tip of the fiber with subsequent localized tissue necrosis [50].

## 11. Clinical Outcomes

A first multicenter phase I/II clinical trial reported the safety and efficacy of VTP using WST09 in patients with recurrent localized prostate cancer after external beam radiotherapy including clinical T1 and T2 stages. VTP-treated lesions were generally ellipsoidal on MRI and repeat target biopsies at 6 months, which correlated with devascularized zones on MRI, showed fibrosis, and were devoid of cancer [51–53]. In contrast, no effective areas on MRI included the presence of cancer. Since VTP did not attempt to ablate whole prostate gland in this trial, the PSA changes only reflect the destruction of prostate tissue and not necessarily of prostate cancer. There were no serious adverse events including cutaneous photosensitivity, and neither urinary nor erectile function was compromised in the long-term follow-up up to 6 months after the procedure. In general, VTP using WST09 was performed safely and well tolerated with no serious adverse events including incontinence, tissue sloughing, and rectal injury [51]. This safety may be a result of VTP using the vascular targeting nature of WST09 of the limited light exposure of the urethra and rectum. In contrast, a patient with meso-tetra-hydroxyphenyl chlorine (mTHPC, Foscan) developed a rectourethral fistula after assessing abnormal rectal mucosa by a rectal biopsy [54]. And other

side effects including urinary retention, temporary stress incontinence, and urethral stricture were noted in VTP using mTHPC [54].

## 12. Up-to-Date Biopsy Technique and Imaging Modality

The success of focal therapy is obviously dependent on the ability to detect the extent of prostate cancer and then accurately target it. The problem is that we have lack of agreement on candidate selection protocols for focal therapy. This point derives from the lack of an adequate biopsy techniques and imaging modality that could reliably detect prostate cancer foci. There is no clear answer as to what is the optimal biopsy strategy to be used to evaluate potential candidates for focal therapy. However, biopsy is the only accurate method for prostate cancer laterality. There are insufficient data on standard sextant biopsy to assure correct localization of prostate cancer foci [55]. Even extended TRUS-guided saturation biopsy has appeared to be inadequate in the proper selection of patients for focal therapy [56]. At present, transperineal 3D mapping biopsy has been proposed as a way to more accurately predict prostate cancer focality [57, 58]. In this approach, samples are taken every 5 mm throughout the volume of the prostate using a brachytherapy template grid under TRUS guidance. Using transperineal 3D mapping biopsy, 61.1% of patients with unilateral cancer on TRUS biopsy were positive bilaterally, and 22.7% were upstaged by Gleason scores [58]. Therefore, transperineal 3D mapping biopsy may provide the most accurate cancer localization information and appear essential for proper patient selection for focal therapy. The chief objection to this type of procedure is time demand and cost involved. Thus, an alternative imaging technology for tumor detection and localization must be considered. MRI is the gold standard over the past decade. Improvements in functional MRI techniques include MR spectroscopy (MRS), diffusion-weighted imaging (DWI), and dynamic contrast enhanced MRI (DCE). Each of these three techniques has improved tumor detection compared with standard T2-weighted imaging (T2WI) alone [59–61]. The combined diagnostic accuracy of T2WI, DCE, and MRS enabled tumor detection with significant independent and additive predictive value [62]. Multiparametric MRI (MpMRI) is currently considered the state of the art for prostate imaging with reasonable sensitivity and specificity values.

## 13. Conclusion

The recent downward stage migration favoring early disease has revealed new treatment options for patients with localized prostate cancer. And the therapeutic dilemma between active surveillance and radical therapy and the significant morbidity associated with radical therapy have led to development of minimally invasive focal therapy such as cryotherapy, HIFU, and VTP. Cryotherapy and HIFU emerged as pioneers in focal therapy showed a lot of promise

but still need a long-term follow-up for assessing quality of life and cancer-specific and overall survival before the indications for primary or salvage therapy can be expanded. VTP as an investigational therapy needs careful patient specific planning since significant variability in the dose distribution and consequent tissue response. The goal of focal therapy is to selectively ablate known disease, while minimizing lifetime morbidity without compromising life expectancy. To reduce the side effects and maintain a favorable quality of life after focal treatment, we must pursue alternative techniques such as a subtotal gland treatment, hemiablation, or focal targeted ablation. The ideal patients for focal therapy appear to be ones with low-grade, low-volume disease that can be easily characterized. In addition, focal therapy may be potentially useful in salvage therapy. Since prostate cancer is commonly a multifocal disease, standard or extended biopsy techniques are not capable of reliably identifying all existing cancer. Therefore, the technical innovations such as 3D-mapping prostate biopsy, histoscan, and MpMRI are applied to accurately detect prostate cancer foci. A further novel imaging tool for identifying individuals is desirable in careful preoperative patient selection.

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