Highlights from the 20th International Prostate Cancer Update

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OVERVIEW
Patterns of care in prostate cancer have changed tremendously in the past 20 years, altering the way patients with this tumor present and how they are evaluated before and after diagnosis. With the use of new and combined treatments, the frequency and variety of complications have differed from those previously reported. Advances have been made in prostate cancer imaging, in biopsy methodology, in understanding causative factors and disease, in treatment-related quality of life, and in predicting the behavior of individual tumors using risk strata. Despite these advances, no consensus has emerged regarding the optimal treatment for the most common patient with prostate cancer.

There is a need for both oncologists and urologists to understand the rationale behind targeted therapy for the treatment of advanced prostate cancer and how trial entry could improve the efficacy of drugs and decrease the toxicity. This activity seeks to educate urologists and other healthcare professionals about the latest advances in the prevention, screening, and treatment of prostate cancer. The International Prostate Cancer Update (IPCU) educational planning committee has identified the following educational gaps between recent research in prostate cancer and its integration into professional practice at the international, national, and community levels:

- Current best practices in prevention and screening of prostate cancer
- Promising therapies, issues, and economic concerns in the treatment of local disease
- Role of androgen deprivation therapy in 2010
- Emerging treatments for advanced and castration-resistant prostate cancer

LEARNING OBJECTIVES
This educational initiative aims to reach urologists, oncologists, and urologic oncologists. Upon completion of this activity, participants will be able to:

- Summarize the pathology of prostate cancer and corresponding prevention and screening strategies, including prostate-specific antigen (PSA) testing, the need for new biomarkers, and the watchful waiting option
- Compare and contrast the use of radiation and drug therapy for the management of localized prostate cancer
- Analyze the disease conditions that can affect bone health, including hypogonadism, androgen deprivation, and bone metastases
- Explain the role of hormone deprivation therapy, including benefits, complications, and the therapeutic approaches to the treatment of complications
- Identify the scientific rationale and clinical trial design of targeted agents for the treatment of advanced hormone refractory prostate cancer
- Define recent developments in prostate cancer surgery that improve patient oncologic and quality-of-life outcomes
- Compare and contrast the available treatment options and efficacy and safety of focal therapy

TARGET AUDIENCE
This activity has been developed and is intended for urologists, oncologists, urologic oncologists, and any medical professional who diagnoses or treats patients with prostate cancer.

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In this issue of *Grand Rounds in Urology*, we are pleased to provide readers with the highlights from the 20th International Prostate Cancer Update (IPCU), held January 27-30, 2010. This conference was the 20th anniversary of a meeting that began the year after prostate cancer became the most common cancer in American males and the second leading cause of death. Much has happened in the last 20 years with regard to diagnosis, surveillance, and prevention, as well as treatments for localized, advanced, and castration-resistant prostate cancer. This 3-day conference convened leading international experts to review the most recent advances.

Back at the beginning, we were in the era of simply switching over from the subcutaneous to the 1-month depots, the antiandrogens were just starting to break in, and a lot of exciting research was being conducted. Surgery also has come a long way. First we had retropubic and perineal surgery, which was followed by nerve-sparing surgery, after which we experienced the overtaking of the laparoscopic and robotic surgery options. In addition, the more recent options of focal therapy (high-intensity focused ultrasound and cryoablation) are being discussed at length. In terms of radiation therapy, the options have progressed from the pure external beam, from cobalt to the current intensity-modulated radiation therapy and treatment with gamma knives. Hormone therapy has evolved to the point where we now have an antagonist, there are now antiandrogens, and a vaccine therapy has been approved. Thus, there have been many changes regarding how to treat patients with prostate cancer. Each is discussed within the pages of this highlights publication, as are the improvements in testing and diagnoses.

A discussion of clinical trials has been a hallmark of *IPCU* meetings, and this year was no exception. The clinical trials discussed included the Cancer and Leukemia Group B study, which is a phase III trial of bevacizumab for prostate cancer; data on sipuleucel-T, which will be the first immunotherapeutic drug available for treatment; and a report on a recently completed phase III trial involving abiraterone, a cytochrome P450 enzyme inhibitor that is also the focus of another ongoing phase III trial with chemotherapy.

Some of the disappointments in research over the past year were also discussed in January. They include the US Food and Drug Administration (FDA) decision not to more favorably review toremifene. This drug, a selective estrogen receptor modulator, or SERM, has potential in prostate cancer treatment as a side-effect drug (eg, for osteoporosis, hot flashes, and many of the estrogen-like side effects of androgen deprivation). The submitted study on toremifene was positive, yet the FDA did not grant their blessing for approval. Nor did they grant approval for denosumab, a RANK ligand that also is an exciting drug. Denosumab has been approved for osteoporosis and is on hold for treating prostate cancer pending further review.

Another aspect of treatment I think in need of discussion is the cost of therapy in this whole system. We hope to soon publish a retrospective analysis of the economic and clinical burden of prostate cancer. The bottom line is that prostate cancer costs money, with or without active treatment. In addition, the rates of both surgery and radiation therapy have increased, whereas the use of hormone therapy has declined. The average costs have increased, and so there has been some watchful waiting. There is probably still not a lot, but with an aging population, this concept will continue to grow.

Finally, the main focus of the annual *IPCU* conference is to gather multidisciplinary specialists to discuss and determine the future landscape for diagnosing and treating prostate cancer. We hope you enjoy reading the expert opinions in this issue and that you use the discussion as a guideline in determining the best courses of treatment for your patients.

Sincerely,

E. David Crawford, MD
The use of prostate-specific antigen (PSA) as serum marker of prostate cancer risk has evolved over recent years. In 1987, Stamey and colleagues defined 3 thresholds for total PSA that correlated with increasing prostate cancer risk: total PSA <4.0 ng/mL (<2%), total PSA 4.0 to 10 ng/mL (25%), and total PSA >10 ng/mL (67%) [1]. In 2 major papers published in 1997 and 1999, respectively, Catalona and colleagues refined the lowest-risk category, showing definitively that men with PSA levels of approximately 2.5 to 4.0 ng/mL had a higher probability of prostate cancer (15% to 20%) than those with PSA levels <2.5 ng/mL (<2%) [2,3]. Most recently, the lowest-risk category was further divided based on data from the 2003 Prostate Cancer Prevention Trial, resulting in the algorithm that is currently used to define the relationship between PSA level and prostate cancer risk (Figure 1) [4].

Despite the widespread use of PSA, investigators are searching for better markers of prostate cancer risk. The main limitation of elevated serum PSA level is its relatively low specificity for prostate cancer, given that increased PSA could be symptomatic of other prostatic conditions such as benign prostatic hyperplasia. Promising diagnostic and prognostic markers with improved sensitivity and specificity for prostate cancer include those harvested from serum, urine, and prostate tissue.

SERUM TESTS

Researchers have identified disease-specific isoforms of free PSA that exist in prostate tissue and in serum. One of these isoforms, the precursor protein for PSA (proPSA), is a promising serum biomarker for the prediction of early prostate cancer detection [5-7]. The National Cancer Institute Early Detection Research Network (EDRN) evaluated the predictive values of 6 potential serum assays for prostate cancer detection: PSA, benign PSA (BPSA), free PSA, proPSA, proPSA/BPSA, and testosterone. In men with PSA levels between 2 and 10 ng/mL, proPSA had the greatest area

**Figure 1.** Prostate Cancer Prevention Trial: 7-year prostate cancer risk by prostate-specific antigen (PSA) level [4].
under the curve (AUC = .73), with 90% sensitivity and 41% sensitivity for prostate cancer detection (Figure 2) [8]. EDRN investigators are continuing to evaluate proPSA as an individual marker and as part of multi-marker panels for prostate cancer detection.

The observation of misshapen nuclei in tumor cells led to the discovery of the early prostate cancer antigen (EPCA)-2, a nuclear matrix protein that is highly specific to prostate cancer cells. Indeed, EPCA-2 is far more specific than any other marker of prostate cancer identified to date, including PSA, suggesting several potential applications for an EPCA-2 assay [9]. For example, EPCA-2 appears to be effective in distinguishing between patients with organ-confined disease and those with more aggressive disease. EPCA-2 also improves risk-stratification algorithms by identifying individuals with elevated PSA levels and/or positive digital rectal examinations (DREs) who will have prostate cancer on subsequent biopsy. In patients who have been diagnosed with prostate cancer, EPCA-2 may also serve as a biomarker of disease progression and as a marker of therapeutic response [9]. EPCA-2 is currently undergoing evaluation as a serum marker for prostate cancer in a multicenter clinical trial with a target enrollment of approximately 700 patients [10].

Assays of GSTP1 methylation may be particularly effective in reducing unnecessary repeat biopsies in men with initial negative biopsy and high-risk features, such as elevated PSA level (≥8.0 ng/mL), elevated PSA density (≥0.2 ng/mL/cc), low prevalence of free PSA (≤10%), or the presence of high-grade PIN or atypia. In a prospective study of 86 men with histologically negative biopsies and high-risk features, investigators compared GSTP1 and adenomatous polyposis coli (APC) methylation patterns on initial biopsy tissue versus methylation patterns in tissue from repeat biopsies that were performed within 24 months [16]. Both GSTP1 and APC gene methylation showed high negative predictive values and high sensitivity for repeat biopsy outcomes (Table 1) [16]. If these findings are validated in larger prospective studies, GSTP1 and APC methylation assays may help to determine which men can avoid unnecessary repeat prostate cancer biopsies.

**URINE TESTS**

The prostate cancer gene 3 (PCA3) is a new molecular marker that has shown promise for improving the diagnosis of prostate cancer. PCA3 is a prostate-specific, noncoding mRNA that is overexpressed 60- to 100-fold in prostate tumors. For use as a predictive marker, the overexpression of PCA3 mRNA can be quantified and expressed relative to the PSA gene. The PCA3/PSA mRNA ratio is also called the PCA3 score [17].

In a retrospective study of 225 patients with persistently high PSA levels and at least 1 negative biopsy, PCA3 expression was a better predictor of biopsy result than PSA. With a cutoff of 35, the PCA3 score showed a specificity of 72% and sensitivity of 58% for prostate cancer [18]. The PCA3 score also strongly predicted positive biopsy outcomes in men with initial negative biopsies and high-risk features [16].

<table>
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<th>Methylation Assay</th>
<th>Negative Predictive Value</th>
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<td>APC</td>
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<td>0.96</td>
<td>0.95</td>
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*GSTP1 indicates glutathione-S-transferase-pi gene; APC, adenomatous polyposis coli gene.
in a prospective study of 570 men who were scheduled for a prostate biopsy, standardized DRE, and urine collection [19]. Incorporated into a nomogram that also included PSA, prostate volume, and DRE finding, the PCA3 score significantly improved prediction of biopsy outcome compared with PSA or PCA3 score alone (Figure 3) [19].

Currently, PSA testing remains the gold standard for prostate cancer screening and diagnosis. Ongoing studies will determine whether new serum, tissue, and urine biomarkers can supplant or enhance traditional PSA assays to improve the accuracy of prostate cancer detection.

**Expectant Management: The Johns Hopkins Program Experience**

Alan W. Partin, MD, PhD

Active surveillance is a practical option for managing appropriate patients with localized prostate cancer. Unlike palliative care, which is reserved for patients who are too old or too ill to benefit from treatment, or for cancer that is too far advanced to cure, active surveillance is conducted with curative intent. Over the past 2 decades, only a small proportion of patients with low-risk prostate cancer (10% to 15%) have been managed with active surveillance. The majority of patients with low-risk, localized disease are managed with surgery, radiation therapy, drug therapy, or a combination of these modalities, which may represent overtreatment for some [20]. Other studies have also shown that overtreatment of prostate cancer with low-risk characteristics is common, particularly among older men [21,22].

According to the American Urological Association (AUA) guidelines for the management of localized prostate cancer, all patients should be informed about the option of active surveillance [23]. Those who are most likely to benefit from surveillance, however, are patients with a shorter life expectancy and/or low grade tumor. Thus, the first step in developing an active surveillance program is identifying appropriate candidates, primarily men who harbor a cancer with a low probability of progression.

Traditional definitions of insignificant prostate cancer are arbitrary and may not reflect the underlying tumor biology or the true risk of progression. Other criteria used to identify small-volume (<0.5 cc), low-grade tumors—such as PSA <10 ng/mL, Gleason score ≤5, and clinical stage T1 or T2A—may result in misclassification. Approximately 10% of patients initially classified as having small-volume tumors based on these criteria are found with further studies to have larger volume, high-grade cancers [24]. Therefore, a wider set of criteria should be used to select potential candidates for active surveillance. These include patient age, as it relates to life expectancy and the duration of follow-up treatment, disease stage, needle biopsy findings, and PSA features, such as PSA density, the proportion of free PSA, and PSA kinetics such as doubling time and velocity.

Active surveillance programs must also formulate a follow-up plan designed to identify disease progression and allow intervention during a window of curability. At minimum, this may involve monitoring every 6 to 12 months with a PSA measurement and DRE. Some centers also include surveillance prostate biopsies at defined intervals of every 12 to 18 months, and others incorporate periodic imaging studies. Surveillance programs must also define triggers for intervention, such as local progression, higher Gleason score, evidence of perineural invasion, or certain PSA kinetics (eg, PSA velocity of 1-2 ng/mL per year in patients with a baseline PSA level of 4-10 ng/mL).

Although a PSA doubling time of <4 years is associated with the need for treatment during active surveillance, the value of PSA kinetics for triggering intervention during a window of curability remains unknown [25]. Other factors associated with intervention include younger age, higher baseline PSA, higher clinical stage at baseline, higher Gleason score, higher percentage of positive biopsy cores, and positive repeat biopsy findings.

**JOHNS HOPKINS EXPECTANT MANAGEMENT PROGRAM**

Two prospective studies have provided important insights on the use of active surveillance, also called expectant management, in the PSA era. The first program, based at Johns Hopkins University and led by H. Ballentine Carter and colleagues, has enrolled more than 1400 patients since 1995. Enrollment is based on predictive...
The Johns Hopkins surveillance algorithm includes PSA and DRE at 6-month intervals, as well as annual biopsy, for all patients up to age 75 (Figure 4). Men with evidence of disease progression are recommended for curative interventions. With a cumulative follow-up period of approximately 12 years, 52% of men in the program continue to be managed with active surveillance, while 35% have gone on to curative treatment. The remaining participants have withdrawn (7%), were lost to follow-up (4%), or died from a non-prostate cancer cause (2%).

Among the patients who progressed to unfavorable pathology during follow-up, 18% showed a grade change from Gleason score ≤6 to Gleason score ≥7. Most of these patients were upgraded to Gleason score 7 (91%); only 8% progressed to Gleason score 8 disease. Slightly more than half (54%) of Gleason score upgrades occurred within the first 24 months of follow-up, and the 3-year risk of grade progression was 20%. Over time, the prognosis appears to be improving. For patients enrolled between 1995 and 1999, the 3-year risk of intervention was at least 27%, whereas fewer than 16% of patients enrolled between 2000 and 2007 have required intervention to date.

Investigators at Johns Hopkins were able to identify factors that predicted an eventual trigger for curative intervention among patients who met the entry criteria. According to a multivariate analysis, older age at diagnosis (risk ratio [RR], 1.08; \(P = .006\)) and steeper PSA slope (RR, 1.27; \(P = .021\)) were associated with an increased risk of disease progression. PSA density was also an independent predictor of intervention; for every .01 unit change in PSA density, the risk of intervention increased by 11% (RR, 1.11; \(P = .29\)). Among potential protective factors, only year of diagnosis was associated with a reduced risk of intervention (RR, 0.88; \(P = .003\)).

To evaluate the value of active surveillance as a tool for cancer control, Warlick and colleagues compared outcomes of 38 patients managed in the Johns Hopkins active surveillance program who underwent delayed surgical intervention at a median of 26.5 months after diagnosis with a group of 150 similar patients who underwent immediate surgical intervention at a median of 3.0 months after diagnosis [26]. In the active surveillance group, 9 of 38 patients (23%) were diagnosed with incurable disease, defined as adverse pathology associated with less than 75% chance of remaining biochemically disease free at 10 years. By comparison, 24 of 150 patients in the immediate intervention group had incurable cancer. These findings suggested that delayed prostate surgery as part of an active surveillance strategy does not compromise curability in men with small, lower-grade prostate cancer [26].
TORONTO ACTIVE SURVEILLANCE PROGRAM

Investigators from the Toronto Active Surveillance Program have also reported prospective data on outcomes of active surveillance. One analysis included 299 men with stage T1c to T2b disease, Gleason score ≤7, and PSA ≤15 ng/mL [27]. During the median follow-up of 64 months, 34% of men came off surveillance to receive curative intervention for reasons including a PSA doubling time of less than 2 to 3 years (15%), patient preference (12%), histologic progression (4%), and clinical progression (3%). Of 24 men who were treated surgically, 58% were shown upon pathological examination to have progressed to stage pT3a-c disease, and 8% had positive lymph nodes. Disease-specific survival was favorable, with just 2 patients dying of prostate cancer in the first 5 years of follow-up. Overall, the 8-year disease-specific survival was 99% [27,28].

Canadian investigators have initiated the phase III START trial to compare radical intervention and active surveillance in approximately 2320 patients with stage T2b or earlier prostate cancer, Gleason sum ≤6, and PSA <10 ng/mL (Figure 5). The primary endpoint is disease-specific survival [29]. Findings from the START trial may provide further evidence supporting the use of active surveillance as a strategy for managing small-volume, lower-risk prostate cancer.

In summary, providing immediate curative treatment for all men with low-risk prostate cancer will result in unnecessary treatment for most patients. Active surveillance with curative intent is a rational alternative for carefully selected men with low-risk prostate cancer. As ongoing prospective observational studies refine the selection criteria and follow-up schemes for active surveillance programs, this strategy may become increasingly attractive to physicians and patients who wish to avoid the risks of overtreatment.

The Economics and Effectiveness of HIFU and Robotics

James A. Eastham, MD

High-intensity focused ultrasound (HIFU) is a type of anticancer therapy in which ultrasound energy is focused at a specific location in the body. At that location, or focal point, the temperature rapidly rises to almost 90°C (195°F), and any tissue at the focal point is destroyed. HIFU is currently not approved in the United States for the treatment of prostate cancer, although it is a popular modality in other areas of the world. Indeed, several recent studies of HIFU have been reported by European investigators, reflecting its predominance as a treatment option for localized prostate cancer in Europe.

In a long-term follow-up study from Germany, Blana and colleagues showed that transrectal HIFU is an effective minimally invasive procedure for patients with localized prostate cancer [30]. The study included 140 men with cT1–T2 NxM0 disease, a baseline PSA level <15 ng/mL, and a baseline Gleason score <7. Patients were treated with a first-generation HIFU device between 1997 and 2001. The primary endpoint was treatment failure, defined as biochemical failure or positive biopsy.

In this series, the rate of biochemical failure-free survival (PSA ≤0.5 ng/mL) was 66% at 5 years and 59% at 7 years, with similar outcomes in low-risk versus intermediate-risk patients (Figure 6) [30]. Patients experienced a range of adverse events that negatively affected quality of life, including the risk of urinary tract infection (7%), urinary obstruction (14%), urinary incontinence (6%), and pelvic pain (6%). Among those who were potent prior to HIFU therapy, 57% experienced significant erectile dysfunction (ED) following treatment [30].

In 2009, Ahmed and colleagues reported findings from a series of 172 men treated with HIFU in the United Kingdom (UK) between 2005 and 2007 [31]. Across the mean follow-up of 346 days, there were no reports of rectal toxicity or recto-urethral fistulae. Following HIFU treatment, patients showed a good and durable PSA response. The mean preoperative PSA was 8.3 ng/mL, dropped to 0.33 ng/mL at 3 months, and remained under 1.0 ng/mL throughout the 24-month follow-up period. Using the same definition of biochemical failure-free survival (PSA ≤0.5 ng/mL) the German and UK studies showed a similar pattern of prolonged disease-free survival after HIFU therapy (Figure 6) [31].

In the UK series, post-HIFU prostate biopsy was recommended if PSA did not achieve a nadir <0.5 ng/mL or if PSA level increased in 2 consecutive treatments. Thirty-one patients received a post-HIFU prostate biopsy, of which 13 (42%) were positive for prostate cancer, suggesting that patients with apical disease may not be the best candidates for HIFU. The most commonly reported morbidity after HIFU was urinary tract infection (UTI) or dysuria (24%), followed by intervention for necrotic tissue (18%), dilation for stricture (16%), bladder neck incision (11%), epididymitis (8%), and grade 1 (8%) or grade 3 (0.6%) stress urinary incontinence (SUI). Two-thirds (67%) of patients who reported potency at baseline also reported potency at 12 months [31].

In a systematic review of literature, Rebillard and colleagues reported additional insights about PSA responses following HIFU [32]. Investigators searched the Medline and Embase databases for HIFU literature published through July 2007, and reviewed abstracts presented at the 2005 to 2007 annual meetings of the European Association of Urology (EAU) and American Urological Association (AUA). A total of 37 publications, all of them case series, were selected for review. Across all series, the negative prostate biopsy rates was 89% in patients who achieved a PSA nadir <0.2 ng/dL, 54% in those with a PSA nadir between 0.2 and 1.0 ng/dL, and 52% in patients whose PSA nadir was higher than 1.0 ng/dL [32].

Rebillard also showed the safety and efficacy benefits of conditioning with transurethral resection of the prostate (TURP) prior to HIFU. In Europe, more than 95% of prostate HIFU treatments are performed in combination with TURP in an effort to condition the prostate for treatment. This can be accomplished in men with total prostate volume up to 40 cc, provided that HIFU is combined with TURP. Compared with men who were treated with HIFU alone, those who underwent TURP and HIFU have a lower risk of SUI and UTI and were less likely to require postprocedure TURP. In another study, Thueroff and colleagues also showed a reduction in the risk of obstruction and/or stenosis, obstruction time, incontinence, UTI, fistula, and sloughing in patients who received both TURP and HIFU compared with those who received HIFU alone [33].
Experience with HIFU to date suggests that the treatment can be given safely. Modest outcomes in terms of cancer control and quality of life have tempered enthusiasm for the procedure, but these outcomes may improve with better equipment and with the routine use of pre-HIFU TURP. Ongoing clinical trials in the US will likely reveal strategies for the best use of HIFU, perhaps as a treatment modality best suited for focal therapy.

ROBOT-ASSISTED LAPAROSCOPIC PROSTATECTOMY

Preliminary evidence suggests that minimally invasive radical prostatectomy, also called robot-assisted laparoscopic prostatectomy (RALP), has the potential to achieve excellent results in treating prostate cancer with a low risk of sexual or urinary morbidity. Despite the lack of prospective randomized trials to support its widespread use, RALP is projected to account for 80% of radical prostatectomy procedures performed in the US within 5 years.

Open prostatectomy and minimally invasive radical prostatectomy both have potential benefits and limitations. Most surgeons have considerable experience with open prostatectomy, and the procedure achieves excellent cancer control with well-defined clinical outcomes. Limitations of open prostatectomy include incisional pain, higher blood loss, and difficulty visualizing nerves. By comparison, minimally invasive prostatectomy is associated with shorter recovery, less blood loss, lower use of pain medications, earlier catheter removal, and magnified images that aid in nerve visualization. Minimally invasive surgery is more technically challenging than open prostatectomy, and has limited mature outcome data to demonstrate long-term cancer control.

In 2009, Hu and colleagues reported findings from a retrospective comparative effectiveness study of the 2 procedures [34]. Using data from the SEER-Medicare database from 2003 to 2007, the analysis included outcomes from 6899 open retropubic radical prostatectomy (RRP) and 1938 minimally invasive procedures in men aged 65 years and older. Main outcome measures included postoperative 30-day complications, the incidence of anastomotic stricture occurring 31 to 365 days postoperatively, incontinence and erectile dysfunction more than 18 months postoperatively, and postoperative use of additional cancer therapies, a surrogate for cancer control [34].

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Over the course of the study, the use of minimally invasive radical prostatectomy increased almost 5-fold from 9.2% in 2003 to 43.2% in 2006-2007, with a corresponding decrease in the use of open RRP over the same period (Figure 7). Investigators found advantages and drawbacks to both surgical options (Table 2). Minimally invasive surgery was associated with a shorter hospital stay, lower transfusion rates, and fewer anastomotic strictures than open RPP ($P < .001$ for all comparisons). Long-term findings, however, showed significantly more incontinence ($P < .001$) and erectile dysfunction ($P < .001$) with minimally invasive surgery than with open RRP [34].

The most important outcomes for patients tend to be urinary control, sexual function, and PSA. According to several large studies, up to 98% of patients can achieve continence (ie, no pad use at 12 months) following both RALP and open prostatectomy [35,36]. Therefore, claims of superior continence rates following RALP are unfounded; excellent results are possible following either procedure.

Potency outcomes following RALP and open prostatectomy also appear to be comparable. In theory, the improved visualization associated with RALP should improve the ability to preserve neurovascular tissue compared with open prostatectomy, but to date a clinically meaningful improvement has not been demonstrated. Since 1999, several trials of open prostatectomy have shown postprocedure potency rates of 68% to 90% within 6 to 18 months [37,38].

Figure 6. Biochemical failure-free survival following HIFU in UK (A) and German (B) studies [30,31]. Part A reprinted with permission from Macmillan Publishers Ltd: [30], copyright © 2010. Part B reprinted from [31], copyright 2010, with permission from Elsevier.
More recent trials have shown potency rates of 68% to 84% within 6 to 24 months following RALP [39,40].

Cancer control rates, as measured by surgical margin status and short-term biochemical recurrence, also appear to be similar following RALP and open prostatectomy. Positive surgical margins in pT3 patients have been observed in up to 48% of patients undergoing open prostatectomy and 50% of patients undergoing RALP [41,42]. In cost-effectiveness studies, several investigators have shown a cost advantage to open prostatectomy [43,44]. The costs associated with RALP are up to $3600 higher per case than those of open prostatectomy, especially in centers that perform fewer than 500 RALP procedures per year [43,44].

Most patients diagnosed with localized prostate cancer are candidates for either RALP or open radical prostatectomy. Both approaches are technically demanding, and postsurgical functional and cancer-control outcomes are dependent on the skill level and experience of the surgeon. To date, studies have shown that RALP lowers transfusion rates, lowers use of pain medications, and shortens convalescence, but without an advantage in continence or potency. Moreover, RALP is more costly than open prostatectomy, without a demonstrated advantage in cancer control or quality of life [43,44]. Overall, when deciding between options for prostatectomy, data to date suggest that it is more important for patients to select an excellent surgeon rather than a particular procedure.

### The Emerging Role of Options for Targeted Therapy

E. David Crawford, MD

Several indicators suggest that localized prostate cancer is widely overtreated, perhaps as a result of over-diagnosis. In the Scandinavian trial of prostatectomy versus watchful waiting among men with clinically localized prostate cancer, only a small proportion of individuals benefited from treatment. Many men died despite curative treatment, and most of the men who entered the trial ultimately died from another cause, suggesting that they could have avoided prostate cancer therapy and its potential treatment-related morbidities [21].

Recent findings from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial confirm the limited benefits of annual PSA testing and DRE on mortality from prostate cancer [48]. In the trial, 76,693 men at 10 US study centers were randomly assigned to receive either annual screening (n = 38,343) or usual care (n = 38,350). In the screening group, men were offered annual PSA testing for 6 years and DRE for 4 years. Patients and their physicians were notified of the results, and were free to determine the best course of follow-up evaluation and treatment. Men in the usual care sometimes received screening, according to the discretion of individual providers [45].

After 7 years of follow-up, the rate of prostate cancer detection was 22% higher in the screening group than in the usual care group (116 cases verses 95 cases per 10,000 person-years, respectively; RR, 1.22; 95% confidence interval [CI], 1.16 to 1.29) (Figure 8). Despite the increased detection rate in the screening group, the prostate cancer mortality rate was similar in the screening and usual care groups (2.0% versus 1.7%; RR, 1.13; 95% CI, 0.75 to 1.70). After 10 years, with follow-up complete for 67% of patients, the detection rate remained higher in the screening group (RR, 1.17; 95% CI, 1.11 to 1.22), with a similar lack of effect on mortality between the screening and usual care groups (RR, 1.11; 95% CI, 0.83 to 1.50) [45]. Findings from the PLCO Cancer Screening Trial support the argument that prostate cancer screening leads to overdiagnosis and a potentially negative effect on quality of life, without any benefit on survival.

### ACTIVE SURVEILLANCE

For patients who are diagnosed with localized prostate cancer, options range from watchful waiting on one extreme to definitive treatment on the other. Another option on the spectrum is active surveillance, a strategy designed to avoid overtreatment and limit therapy only to those with evidence of tumor progression. In contrast to watchful waiting, during which patients receive only palliative treatment, patients managed under active surveillance are given curative treatment—radical prostatectomy or radiotherapy—in the case of disease progression.

Klotz and colleagues were among the first to show very high rates of cancer-specific survival in men who were managed with active surveillance. With this approach,
patients were followed by serum PSA monitoring and repeat biopsies, and definitive treatment was initiated in the case of a rapid rise in PSA, upon upstaging of the Gleason score at repeat biopsy, or upon patient wish [27,28]. In general, active surveillance studies demonstrate a very low rate of prostate cancer–specific mortality. In a 2010 analysis, Klotz showed that the 10-year disease-specific survival among men with clinically localized prostate cancer was 97.2%. Men with prostate cancer are significantly more likely to die from other causes; the hazard ratio for non–prostate cancer mortality relative to prostate cancer mortality was 18.6 at 10 years [46].

Despite clinical trial evidence supporting the use of active surveillance in patients with low-risk, clinically localized prostate cancer, this approach is selected by a small minority of patients. According to findings from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry of 11,892 men with localized prostate cancer, only 6.8% elected active surveillance as their primary treatment [47]. Patients and their physicians continue to select other treatment approaches, including radical prostatectomy (49.9%), brachytherapy (11.6%), external-beam radiation (13.3%), cryoablation (4.0%), or primary androgen deprivation therapy (14.4%) [47]. The high prevalence of radical prostatectomy and other intensive treatments continues to fuel the controversy about the overtreatment of clinically localized prostate cancer [48, 49].

**TARGETED FOCAL THERAPY**

Some investigators argue that there is a strong rationale for targeted focal therapy in patients with localized prostate cancer. The vast majority of the currently newly diagnosed prostate cancer appears to be organ-confined. Many of these patients are interested in minimally-invasive options for treating their early stage disease with fewer side effects without decreasing their potential for cure. Accordingly, early trials in targeted cancer were initiated with the hypothesis that a subset of patients with early organ-confined prostate cancer and low Gleason score (6 or less) can be treated with targeted focal therapy, minimizing the rate of complications without compromising primary curative treatment efficacy.

Many prostate cancers are multifocal, so one of the first steps in developing targeted focal therapy was validating the ability to detect and label significant cancers. Successful identification and characterization of tumor features minimizes the risk of incomplete treatment, which can potentially be attributed to missed cancer foci, inadequate treatment of the target tissue, or the selection of inappropriate patients, such as those who demonstrate periurethral and extracapsular extension of the tumor. Unfortunately, this requires advanced imaging techniques, and there are currently no highly sensitive, specific, and widespread radiographic tests for imaging prostate cancer within the gland. Common modalities such as magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and transurethral ultrasound (TRUS) have limitations in imaging prostate cancer. Emerging techniques, such as the use of transrectal optical scanning probes, may improve prostate cancer imaging.

Current biopsy techniques also limit the ability to detail certain prostate cancer features, which in turn limits the ability to deliver more aggressive therapy of the lesion while potentially sparing the noncancerous gland from ablative therapy. Saturation biopsy is a novel approach that enables the identification of the precise location of prostate cancer. Researchers demonstrated the efficacy of saturation biopsy in a study of 86 autopsy specimens and 20 stage T1c radical prostatectomy specimens [50]. Using 3-dimensional (3D) computer models, investigators simulated transperineal biopsies with grid sizes of 5 mm or 10 mm, and 1 or 2 biopsies per grid were obtained with an 18 G, 23-mm long biopsy needle for a total of 12 to 108 biopsies per specimen, depending on prostate size.
In this analysis, cancers with a volume of ≥0.5 mL or Gleason score of 7 or higher were defined as clinically threatening, whereas cancers with smaller volumes or lower Gleason scores were considered clinically nonthreatening. Compared with the 10-mm sampling technique, biopsy sampling with a 5-mm grid detected a greater proportion of clinically threatening cancers among both the autopsy (61% versus 86%) and prostatectomy (95% versus 100%) specimens [50].

Mapping refers to the ability to reproducibly localize specific intraprostatic cancer foci by an imaging modality or a combination of imaging modalities. Although this may represent the ideal approach to prostate biopsy, imaging of the prostate is in its early stages both in technological terms and in a clinical validation process. In addition, the costs associated with multiple imaging techniques represent a challenge for routine clinical practice. In the interim, transperineal ultrasound–guided systematic mapping biopsy (TRUS-MB) of the prostate using a superimposed 3D grid in real time achieves a relatively accurate localization of the cancer foci.

Because larger prostate are more vulnerable to postbiopsy complications such as urinary retention and bleeding, it is more desirable to perform mapping or other biopsies on smaller-volume glands. Tandberg and colleagues recently evaluated the treatment times needed to achieve prostate volume reduction with dutasteride prior to 3D mapping biopsy [51]. After a mean treatment time of 19 weeks, the mean prostate volume was reduced from 55.1 cc to 38.3 cc among 39 men with enlarged prostates secondary to benign prostatic hyperplasia (BPH). On the basis of these findings, investigators developed an algorithm to estimate the length of treatment time needed to reduce the prostate gland to the desired size according to initial prostate volume [51].

Onik and colleagues have shown that 3D transperineal mapping biopsy has a potentially significant impact on prostate cancer management [52]. In a study of 180 men who were considering conservative management based on findings of unilateral cancer on TRUS biopsy, 61.1% were shown to have bilateral cancer on 3D mapping biopsy, and 22.7% of patients had their Gleason scores upgraded to 7 or higher. Overall, 70% of patients changed their treatment plan after receiving more accurate staging results of bilateral or high-grade cancer from 3D mapping biopsies [52]. Accurate staging is crucial to achieving good outcomes from focal cryoablation of prostate cancer, or the so-called male lumpectomy. In another study, 120 patients who selected targeted cryoablation based on 3D transperineal mapping biopsy results achieved long-term control rates comparable to those achieved with more radical treatments after up to 12 years of follow-up. Following cryoablation, there were no reports of incontinence, and 85% of patients who were potent prior to treatment maintained potency after the procedure [53].

In summary, recent data clearly illustrate that 3D mapping biopsy plays a pivotal role in the evaluation of men with apparent low-risk disease. This biopsy technique improves the selection of men for watchful waiting or expectant management options, and allows treatment decisions to be made based on true tumor burden, stage, and grade. Advances in marker detection, imaging accuracy, and labeling technology will likely enhance the future application of 3D transperineal mapping biopsy. Until then, additional long-term follow-up is needed before the urology community can understand the value of this approach in a range of patient groups, including older men, who may be more susceptible to biopsy-related complications.

### The Role of Focal Therapy in Treating Localized Prostate Cancer

Frans M.J. Debruyne, MD, PhD

Treatment-related morbidity has improved for men with prostate cancer, but the potential for overtreatment and unnecessary exposure to adverse events leads physicians and patients to seek less radical treatment. Targeted focal therapy, in which only malignant cells within the prostate are ablated, is another option for managing patients with early organ-confined prostate cancer. Improvements in imaging and other technologies have improved the delivery of focal therapy, lowering both the complications and costs of treatment. In addition to HIFU, which has been reviewed extensively by other presenters, techniques for targeted focal therapy include cryotherapy and vascular targeted photodynamic therapy (VTP).

### CRYOTHERAPY

Since its introduction as a minimally invasive procedure in the early 1990s, cryotherapy has been increasingly used in the management of localized prostate cancer with favorable outcomes. Currently, cryosurgery is an appropriate option for certain patients when definitive treatment is indicated for localized prostate cancer.

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**Table 3. Outcomes Following Cryosurgery for Localized Prostate Cancer [56-60]**

<table>
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</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td>Hemi</td>
<td>Hemi</td>
<td>Hemi</td>
<td>Focal</td>
<td>Focal/partial</td>
</tr>
<tr>
<td><strong>Mean follow-up, mo</strong></td>
<td>15.2</td>
<td>28</td>
<td>70</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>TRUS</td>
<td>TRUS</td>
<td>TRUS/Doppler</td>
<td>Template</td>
<td>TRUS</td>
</tr>
<tr>
<td><strong>Mean PSA, ng/mL</strong></td>
<td>7.2</td>
<td>6</td>
<td>4.95</td>
<td>5.2</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td>≤8</td>
<td>≤7</td>
<td>≤7</td>
<td>≤8</td>
<td>≤8</td>
</tr>
<tr>
<td><strong>Potency, %</strong></td>
<td>70.6</td>
<td>70.8</td>
<td>89</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td><strong>Incontinence, %</strong></td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Disease Control, %</strong></td>
<td>76.7 (biopsy)</td>
<td>88 (&gt;50% nadir reduction)</td>
<td>96 (biopsy); 92 (ASTRO)</td>
<td>97 (biopsy); 83 (ASTRO)</td>
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*TRUS indicates transrectal ultrasound; PSA, prostate-specific antigen; ASTRO, American Society of Therapeutic Radiology and Oncology.*
In 2008, the AUA published a policy statement on best practices for cryosurgery in the treatment of localized prostate cancer [54]. The cornerstone of the AUA report was a trial by Cohen and colleagues of 370 men who were followed for a median of 12.5 years after being treated with cryosurgery as first-line monotherapy between 1991 and 1996 [55]. The 10-year biochemical disease-free survival rates for low-, intermediate-, and high-risk groups were 80.5%, 74.2%, and 45.5%, respectively. The negative biopsy rate at 10 years was 76.9% [55].

Several other studies have also shown favorable disease-control rates in patients who received cryotherapy (Table 3) [56-60]. Treatment-related complications, particularly erectile dysfunction and incontinence, occur with similar frequency after cryosurgery compared with radical prostatectomy. Overall, these findings demonstrate that long-term cryosurgery outcomes are comparable to those achieved with other curative options for localized prostate cancer.

On the basis of these data, the AUA concluded that primary cryosurgery is an appropriate minimally invasive option for men with clinically organ-confined disease of any grade [54]. The procedure, however, may not be appropriate for high-risk patients who may require multi-modal therapy. Moreover, with evidence accumulated to date, the role of primary cryosurgery for treatment of men with clinical T3 disease is currently undetermined. Cryosurgery can also be considered as a treatment option with curative intent in men who have failed radiation therapy. Appropriate candidates for salvage cryotherapy include men with biopsy-proven persistent organ-confined disease, PSA <10 ng/mL, and a negative metastatic evaluation [54].

VASCULAR TARGETED PHOTODYNAMIC THERAPY

VTP is a new approach to focal therapy that involves the in situ activation of cytotoxic agents that attack the tumor vasculature. During VTP, which is also called a focal vascular occluding approach (VOA), patients are given photosensitizing agents that are activated locally with a specific wavelength of light. Focal VOA includes a brachytherapy-like template, through which optical fibers are inserted transperineally in the prostate via ultrasound guidance. The first-in-class photosensitizer TOOKAD (WST09) is a derivative of the photosynthetic pigment bacteriochlorophyll. This agent deeply penetrates the blood vessel network and, when activated, generates reactive oxygen species (ROS) levels. As a result, the entire tumor vasculature is occluded and the tumor is destroyed focally.

VTP is a curative therapy that has the potential to fill the gap for vascular treatment of early-stage and localized cancers. TOOKAD-VTP is currently being evaluated in several multicenter phase II trials, including 2 studies in Europe (PCM 2.01 and PCM 2.03) and 1 trial based in the US (PCM 2.02). Early findings suggest that VTP allows the creation of controlled predictable ablation within the prostate without adversely affecting neurovascular bundles, the rectum, or the urethra [61].

Treatment is well-tolerated and avoids many potential complications associated with focal therapies, including rectal fistula, urinary incontinence, and erectile deterioration. No cardiovascular or hepatic toxicity has been observed. The photosensitizer is rapidly cleared from the liver, thereby avoiding any sunlight exposure complications. VTP is administered as a day-case procedure, allowing patients to be discharged the same day. Should new tumour foci be detected in untreated zones, the procedure can be repeated.

**Summary**

Focal therapy will continue to advance with further clinical studies, additional technical refinements, better imaging, and an improved understanding of the biological behavior of localized prostate cancer. The goal of targeted focal therapy is to treat early stage prostate cancer while preserving quality of life. VTP, the newest focal therapy, offers a new medical option between active surveillance and overtreatment for patients with localized prostate cancer. This represents 60% of patients with newly diagnosed prostate cancer, or approximately 300,000 cases, every year.

**REFERENCES**


49. Carroll PR. Early stage prostate cancer—do
we have a problem with over-detection, over-treatment or both? J Urol. 2005;173:1061-1062.


