UROONCOLOGY

Invited Review

A Urologist's Personal View of Prostate Cancer

Bir Üroloğun Prostat Kanserine İlişkin Kişisel Görüşü

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ABSTRACT

A urologist's personal experience with multiple surgical, hormonal, and radio/immunotherapeutic options for the treatment of advanced prostate cancer and thoughts on the role of old and new therapies.

Keywords: Cancer; prostate; treatment.

ÖZ

Bir üroloğun ileri evre prostat kanseri tedavisine çok sayıda cerrahi, hormonal ve radyo/immünoterapi seçeneklerine ilişkin kişisel deneyimi ile yeni ve eski tedaviler hakkındaki düşünceleri.

Anahtar kelimeler: Prostat; kanser; tedavi.

Prostate- specific antigen (PSA) was first approved in 1986 as a marker to monitor for disease recurrence after radical prostatectomy and subsequently in 1996 as a diagnostic or screening marker. Intrigued by the possibility of PSA as a test for early detection, I became an early adopter. In 1990, at age 50, I began personal annual PSA testing. My first PSA was 2.4 ng/mL. I was quite content as this represented a result well below the accepted norm at that time of 4.0 ng/mL and implied good prostate health. Gann was the first to point out that PSA should be considered a continuous variable with increasing levels predicting increased risk of prostate cancer.[1] However, Vickers and Lilja have recently established the normal median PSA of a 40–50 year-old as 0.68 ng/mL and that approximately 50% of the cancers that will be lethal arise from the cohort of men whose PSA is >1.6 ng/mL at age 45-49 or >2.4 ng/mL at age 51-55, the upper 10 percentile of PSA for each age group.[2] In 1998, monitoring was discontinued for two years. In 2000 the level had risen to 6.5 ng/mL confirmed on several determinations. Transrectal ultrasound guided biopsies revealed Gleason 4+3 adenocarcinoma.

The year was 2000–available treatments for localized prostate cancer were surgery, external beam radiation, or brachytherapy. Minimally invasive laparoscopic and robotic-assisted approaches had not yet been introduced in the USA. As a surgeon, I favored surgery with its removal of billions of cancer cells in a 2–3 hour procedure and the information of pathologic staging that might direct further therapy. For node positive pathology an Eastern Cooperative Oncology Group (ECOG) trial[3] has been published demonstrating a survival benefit for adjuvant androgen deprivation. Recent observational studies also have supported the addition of adjuvant pelvic radiation for an enhanced survival benefit.[4] For node negative disease with unfavorable pathology, adjuvant radiation had been tested in three randomized trials studying patients.[5-7] The Southwest Oncology Group (SWOG) trial demonstrated an overall survival benefit to adjuvant radiation therapy.[5] The German[6] and European Organisation for Research and Treatment of Cancer (EORTC)[7] trials demonstrated a biochemical failure free benefit.[6,7]

My prostate pathology was favorable reporting pT2, margin negative, N0, but Gleason 4+4 with a tertiary pattern of 5. Postoperative PSA's were undetectable at less than 0.1 ng/mL. Recovery of urinary continence and sexual function was satisfactory. However, I believe it is accurate and

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appropriate to advise patients that it is highly unlikely that sexual function will recover to match preoperative baseline, and that even urinary function; in the best of circumstances, may have occasional lapses. At one year my PSA remained less than 0.1 mL. Several months later it climbed to 0.2 and then to 0.35 ng/mL. I could see nothing but a continued upward trend and that I would take action sooner or later. The question was, should it be sooner? At the time there were data from salvage radiation series that men whose PSA's were less than 1 ng/mL had better outcomes than those whose PSA's were greater than 1 ng/mL. The large multi-institutional cohort reported by Stephenson showing a clear correlation of postsalvage radiation PSA recurrence-free survival to pre-salvage PSA level had not yet been reported at that time.[8] Some series advocated androgen deprivation together with salvage radiation for patients with high-risk features.[9] A Phase III trial comparing salvage radiation with or without Bicalutamide 150 mg (Casodex) daily for 2 years (RTOG 9601) had been completed and was presented at the 2016 American Society of Clinical Oncology Genitourinary Cancers (ASCO-GU) conference.[10] In this trial, the addition of anti-androgen monotherapy to adjuvant radiation therapy provided biochemical, metastases- free, and overall survival benefit, but this information was unavailable in 2001. I conferred with several "experts". Most advised against immediate therapy and specifically against radiation. This is in keeping with the general urologic practice as reported by an American Urological Association (AUA) survey in 1996 whereby only 13% of urologists stated that they employed salvage radiation therapy. Almost 10 years later in 2004, the CAPSure database assessment noted a slight increase to 20%.[11] Salvage radiation is delivered on the assumption that failure after radical prostatectomy is local in the area of the prostate bed. But is PSA recurrence after radical prostatectomy due to local failure or distant failure, or both? My bone and computed tomography (CT) scans were normal, as is usually the case, and were not helpful in making this determination. I made the decision to receive 6 months of androgen deprivation along with prostate bed radiation. The bone mineral density preserving effects of zoledronic acid had just been reported and I opted to receive zoledronic acid during androgen deprivation.

How can "early" salvage radiation plus androgen deprivation be supported? The evidence for local failure after radical prostatectomy has been documented with prostate bed biopsy studies showing cancer in up to 40% of PSA failure cases.[12,13] The 10-year clinical local failure rate in the SPG4 trial and the control arm of SWOG 8794 approached 20%, a rate higher than the distant failure rate.[14,15] However, studies using magnetic resonance imaging have shown a much higher incidence of bone metastatic disease than would be found by the traditional bone scan,[16] and disseminated tumor cells are present in the bone marrow in men with PSA failure with unexpected frequency.[17] These findings also support the distant failure component of PSA recurrence. Observational studies from Stanford demonstrated the benefit of using androgen deprivation and whole pelvic radiation versus prostate bed radiation alone.[9] Fortunately a number of trials are in process that will resolve uncertainties concerning combination adjuvant/salvage therapy combined with androgen deprivation as well as the benefit of extended field radiation. RTOG trial 0534 (ClinicalTrials.gov identifier NCT00567580) is a three-arm trial testing prostate bed radiation only versus prostate bed radiation plus androgen deprivation versus whole pelvic radiation plus prostate bed radiation plus androgen deprivation. The UKNCI Canada RADICALS trial (ClinicalTrials.gov identifier NCT00541047) is testing adjuvant versus salvage radiation each with no, short-, or long-term androgen deprivation.

I received radiation in a traditional four-field box technique up to a dose of 64 Gy. Urinary and rectal symptoms of irritation I experienced resolved with time. Androgen deprivation was quite tolerable, but the dramatic suppression of libido and function brought me to the powerful recognition, beyond any text description, of the power of the steroid molecules to imprint and drive behavior. I was delighted to discontinue androgen deprivation after 6 months of therapy at which time my PSA had fallen to less than 0.02 ng/mL. This level was maintained over the next 3 years. Serum testosterone recovered and I truly felt that the clock had been reset and that my quality of life had been restored to the pre-hypogonadal state. Equipoise had been re-established and life was good. That is not to say that life had been previously bad. I only use this well-understood colloquialism to express my renewed state of well-being. However, 36 months after initiation of androgen deprivation and 33 months after completion of salvage radiation, the PSA began another series of rises. It is worth reflecting on the emotional impact of the first rise after radical prostatectomy and this second and subsequent rises. The first PSA rise after surgery brought home the fact that surgery had failed to remove all cancer and that "cure" (yes, I was in this thought mode) had not been achieved. There was significant anxiety and disappointment that actually exceeded the negative visceral response at diagnosis. I was entering the universe of the ticking PSA clock. The second PSA failure confirmed that I was in the story for the long haul.

Faced once again with a rising PSA, I made the decision to begin combined "triple" androgen blockade, a combination of luteinizing hormone-releasing hormone (LHRH) agonists, anti-androgen, and 5-alpha reductase inhibitor. While the PSA fell, it did so somewhat sluggishly and after reaching a PSA nadir of 0.2 ng/mL began rising at 9 months post-initiation of therapy. Anti-androgens were withdrawn without response. There is ample data that a PSA nadir is a prognostic factor with regard to subsequent outcome[18] and further data suggests that PSA lower than 0.2 ng/mL, and at the ultrasensitive undetectable level of less than 0.01 ng/mL, is desirable. I had entered the castration resistant disease state. The term "castration resistant", I believe, will need further refinement. Ample evidence now exists that the androgen receptor (AR) continues to drive prostate cellular proliferation and prevents pharmaceuticals from blocking AR activity which provides effective treatment and survival prolongation. The term "castration recurrent" may better describe this disease state.

In 2008 with a testosterone level within the castrate range, and with a PSA on the rise after trial of bicalutamide withdrawal, I was searching for other options. There was no Level 1 evidence to support any pharmaceutical therapy at that time and unfortunately that remains true to this day. I was advised with regard to transdermal estradiol patch which I began and have continued to the present.[19] Estradiol slowed my PSA doubling time but of equal importance improve my sense of well-being. A few observations about estrogen therapy are pertinent. Recall that the Veterans Association Urologic Research Group studies demonstrated that oral diethylstilbesterol (DES) was associated with a cancer survival superior to orchiectomy. The cardiovascular morbidity associated with oral estrogen, however, overwhelmed the cancer specific benefits resulting in an inferior overall survival outcome. David Byar, the lead statistician for the veteran studies concluded that DES, in addition to lowering testosterone, exerted a direct cytotoxic effect on the prostate cancer cell.[20] Estradiol delivery via a transdermal patch bypasses the first pass through the liver which is responsible for the metabolic changes predisposing to cardiovascular mortality and thereby dramatically reduces this concern. Estrogen is barely mentioned in the guidelines of the major oncology societies. It is essentially overlooked and very much underappreciated. Traditional ADT deprives the male of both testosterone and estrogen thereby compounding adverse events. In addition to its cytoxic toxic effects, estrogen reduces/eliminates hot flashes, preserves bone health, and is now recognized to support sexual function.[21-23] The Patch trial (ClinicalTrials.gov NCT00303784), a large randomized controlled trial (RCT) being conducted in the United Kingdom, is currently randomizing men to traditional LHRH analogues (control arm) or transdermal estrogen patches with the primary endpoint of overall survival and a number of secondary endpoints which include PSA response, quality of life and bone health. Hopefully the Patch trial will substantiate the benefits of estrogen therapy and bring it back into the mainstream of prostate cancer therapy.

In 2012, my PSA had gradually risen to10 ng/mL and a technetium bone scan which I was receiving annually revealed a solitary metastatic site in the third lumbar vertebrae. I was asymptomatic. In view of the evidence of progression on imaging, now with M1b castration resistant prostate cancer (CRPC), I was eligible for a Phase 2 clinical trial combining 2 "hormonal" agents each of which had individually proved effective in extending survival in Phase 3 RCT's for patients with M+ CRPC.[24,25]

Abiraterone acetate is characterized as an androgen synthesis blocker as it interferes with the C-17 hydroxylase, C20, 21 lyase enzymes on the pathways converting precursor steroid molecules to androgens. Enzalutamide is characterized as an androgen receptor blocker as it displaces androgens from binding to the AR by preferentially occupying the receptor niche. With different mechanisms of action to interfere with androgen receptor activity, there was the potential for inducing as complete an androgen blockade environment – as with all trials LHRH agonist therapy continued – as was currently possible. Furthermore there appeared to be no indication for overlapping toxicity other than that associated with further depletion of testosterone activity. The trial protocol required pre-entry bone biopsy which was accomplished under CT guidance without difficulty. The vertebral biopsy analysis seemed ideal for this drug combination. The specimen stained strongly positive for the androgen receptor. There was no evidence of neuroendocrine de- differentiation, no androgen receptor splice variant (AR-V7) detectable and steroid receptor co-activator (SRC), a proliferation driver, was negative. All factors lined up for an excellent response. Nevertheless during the six months on trial my PSA doubled from a level of 10 to 20 ng/mL. There was no good explanation. Was prednisone given with abitaterone, perhaps, a culprit via a "glucocorticoid hijacking mechanism"?

It was time for a new start. Our department at Eastern Virginia Medical School had been involved with the earliest sipuleucel-T trials.[26,27] The final analysis of the Phase 3 IMPACT trial led to FDA approval in 2010.[28]

The IMPACT trial had randomized men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer to a cellular based immunotherapy treatment arm versus a control arm and demonstrated a statistically significant survival benefit for the patient receiving immunotherapy. FDA approval was a breakthrough decision which brought the first immunotherapy for any cancer to the clinic. Since then there has been an explosion of interest in immunotherapy with a number of dramatic successes in its use in the treatment for other malignancies. Immunotherapy can be characterized with attributes that are admirably suited for addressing the same characteristics associated with tumor cell survival as flexible, durable, targeted, and adaptable, there was no hesitation on my part to move forward with Sipuleucel-T (Provenge) immunotherapy. There was also developing evidence that radiotherapy might potentiate immunotherapy. Some of the beneficial effects of radiotherapy might be attributed to the abscopal effect. Cellular death caused by radiation, specifically high dose radiation producing double- strand breaks and mitotic death, releases a host of antigens which provide a broad repertoire of targets for immunotherapeutic activity.[29] Concurrently the observation that local control of metastatic sites could be accomplished by stereotactic radiation was leading to trials of radiation for men with oligometastatic (defined as 1-3, or perhaps up to 5 metastatic sites) disease.[30,31] The double benefit of local control and the priming by antigen spreading or antigen cascade for subsequent immunotherapy was very attractive. In 2013 when my PSA had risen to 20 ng/mL, I received stereotactic radiation (9 Gy/day x 3) to the isolated L3 vertebrae followed by Provenge therapy. My PSA gradually fell. A follow up sodium fluoride positron emission tomography (PET) /CT scan revealed an additional L1 metastases which was also treated with stereotactic radiation. PSA

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levels gradually declined over 30 months less than 1 ng/mL. Obviously I am very much appreciative of this good fortune and it has influenced my thinking and management of patients with good performance status and oligometastatic disease.

The future is bright with a wealth of developing treatment possibilities on the horizon. Radium 223 (xofigo)[32] will be an option for control of osseous metastases with a survival benefit. Immunotherapies with checkpoint inhibitors are promising. Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated remarkable responses in patients with breast cancer (BRCA) 1/2 and ataxia-telangiectasia mutated (ATM) genetic defects.[33] Perhaps the most remarkable trials are those studying cyclical delivery of super physiological doses of testosterone.[34] This concept is counterintuitive. However, a very provocative editorial appearing several years ago was entitled "The two faces of Janus. Steroid molecules are responsible for both cellular death and cellular proliferation".[35] The challenge will be directing these pathways for appropriate response. However, if high dose testosterone does enter into the clinic, it perhaps will be the only treatment for an advanced cancer that both controls disease while simultaneously allowing the patient to feel stronger and better! An ultimate win/win! And some "old-timers" in the pharmaceutical lexicon as ASA, NSAIDS, statins, metformin, vitamin D are finding a new role in the treatment of prostate cancer.

Against the background, I will make some personal observations pertinent to the care and disposition of men diagnosed with prostate cancer.

Emotions

The emotional impact of a cancer diagnosis is quite profound regardless of how well educated or well informed the patient. I will describe my mindset with a cardiovascular event which I experienced 2 years before the diagnosis of prostate cancer – a mindset that I have discussed and confirmed as similar to the experience of others in the same situation. Certainly the coronary occlusion, which fortunately was promptly treated with two stents with good results was sobering. Total occlusion of the left anterior descending coronary artery, as was my case, has been dubbed the "widow maker" for good reason. Nevertheless, there was optimism. Plans for better diet, more exercise, and healthier lifestyle would allow me to partner with my heart with anticipation of a productive future. The emotional impact of the cancer diagnosis was quite different - a visceral reaction, almost a sense of betrayal and fear - a desire to rid myself of the alien invader by whatever means was my primary thought and plan of action. This, despite the fact that I knew very well that the greatest risk for future morbidity and mortality rested with cardiac disease - I have had six additional stents placed as a reminder of this - and that any prostate cancer morbidity and mortality were certainly many years into the future. With the encouraging recent advances in knowledge about treatments for advanced prostate cancer, morbidity and mortality will decline even farther. As powerful as my initial emotional reaction to the cancer diagnosis was, the news, as I've mentioned, of PSA failure one year after radical prostatectomy was perhaps more profound. A positive spin that I can place on to the roller coaster ride of PSA recurrences that were to follow is that the human psyche turns resilient and tolerates each iteration of "treatment failure" with a greater degree of equanimity. I will paraphrase here an observation made by Wendy Harpham, a physician and medical writer, who was faced with one of many recurrences of a hematologic malignancy. She observed that cancer did not make her life uncertain but exposed her to the uncertainties of life. When she put aside her fears, apprehensions, and concerns about tomorrow and appreciated what she now had, in a way never before possible.

Clinical Trials and Hope

Intertwined with the disappointment of PSA recurrences, is the hope that rests with new effective and approved therapies and the promise of new therapies that are in the process of clinical trial testing and that might be even more effective. The promise of investigative therapies certainly provides hope. However, the time, testing, and travel that clinical trials often demand are daunting and often frustrating. Patients are prepared to participate in and take risks that trials may present in hopes of deriving benefit. They are essential partners in the team moving cancer therapy forward. We must remember that the term "team" implies facilitation of opportunity for all members of the team and, in the case of the clinical trial team, specifically and especially the patient. The time has arrived to fulfill the promise that trials must be more patient-friendly. I have entered many patients into clinical trials, and have personally participated in 2 trials (one after PSA failure following salvage radiation plus androgen deprivation therapy, and one upon developing castration-resistant metastatic disease) and can attest to the difficult regulatory gauntlet they present.

Androgen Deprivation Therapy

The four letter word that best describes the state of androgen deprivation therapy is "LOSS" – loss of energy, interest, vitality, mental and physical activity, muscle mass and strength, cardiovascular health, bone health and most overtly sexual health including erectile dysfunction and diminished libido. I believe the global effect of androgen deprivation is underappreciated and that the debilitating effects of impaired sexual health are often inadequately addressed. They present a challenge to the physician, the patient, and the patient's partner. The long-term strain placed on relationships can be as significant as the strain of the initial prostate cancer diagnosis. A manual recently published, entitled "Androgen Deprivation Therapy – An Essential Guide for Prostate Cancer Patients and Their Loved Ones"[36] – in my opinion, is just that – essential! It deals with problems and possible solutions. As I wrote in my evaluation of this manual, "it was only when I began my personal journey with androgen deprivation therapy that I was able to appreciate the profound impact this treatment has on daily life. Even with my real life experience with androgen deprivation therapy (ADT) accumu-

lated over decades, I know I cannot, within the limits of one or even several office visits, begin to prepare and educate patients for their new reality. I could not even do that for myself! If only a complete user-friendly manual existed. Now it does."

The Lexicon of Cancer

The world of cancer has developed its own vocabulary. And words matter. When used in certain contexts they deliver a specific message. Three of these words are survivor, cure, and war. Soldiers, persevering through battle, just as cancer patients enduring chemotherapy or a surgical procedure, consider themselves as a survivor. One of the major differences, of course, is that in medicine survivorship is a time-limited event usually measured by 3, 5, or 10-year survival curves. Survivorship is not a one-time event as there is always the possibility of subsequent cancer recurrences and further treatment. I am certainly thankful and delighted to be surviving at the present, but I consider my pathway better described by the word participant. I say this because I have, with my physicians, partnered and participated in a number of decisions and then participated in the treatment process whether standard of care or clinical trial based.

Another gold standard word is cure. Certainly every cancer patient looks for a procedure or pharmacologic agent that will rid him of disease and restore life, and hopefully quality of life, as experienced prior to the diagnosis. Cure promises to relegate the cancer experience to the past tense. However, cure is often evanescent. Dormancy may be recognized in the future as an accepted temporary pattern of cancer behavior. I think it is important to note that the Latin root of the word cure is curare which means "to care for". Again, against the background of persistent/recurrent disease, caring for the patient through a series of treatments is more realistic and supportive than the promise of final/complete obliteration of the disease.

Lastly the word war. The war metaphor has entered almost all aspects of our lives. It is commonly used in competitive sports, business, and politics. War became closely associated with cancer when, in 1971, President Nixon, as part of the National Cancer Act, officially declared war on cancer and aimed to defeat cancer in what is now recognized as a very unrealistic timeline. War is energy depleting, resource consuming, and long wars all the more so. Prostate cancer is a disease of long natural history. Patients who enter into a daily battle with the disease forfeit the state of living well with their cancer. Mukherjee, in his biography of cancer, the Emperor of all Maladies, discussed his concern with the cancer war metaphor. He suggested that the war on cancer may have to be won by redefining the meaning of victory. For prostate cancer patients this may involve a state of negotiation whereby they learn to live well and hopefully long with their disease. The emphasis is on thrival as well as survival. This mindset has been described by others as when there are clouds on the horizon one learns to dance in the rain, or those patients do best who learn to dance with their disease. Again, as stated earlier, the appreciation of "today" is affirming and healing.

It has been my privilege to share my story with men receiving the unwelcome news of a prostate cancer diagnosis and also my privilege to witness the courage and strength they demonstrate as they face a future with this disease. I appreciate the opportunity to share my story with you.

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