
LEGENDS IN UROLOGY

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A Urological Life

The Canadian Journal of Urology had asked me to submit a “urological life story” several years ago, but I have procrastinated based on an uncertainty of what to offer of value to the journals readership. At the 2015 Annual Meeting of the Society of Urologic Oncology in Washington, DC, I was given the opportunity to speak on the topic of “A Urologist’s View of Prostate Cancer”. The presentation was focused on my experiences with the disease and was well received. The Editors suggested I use this presentation as a topic focus. Since my professional interests and personal life interest have merged in the prostate cancer discipline, I agreed that this was an opportunity to share my thoughts and reflect my experiences as a cancer physician and patient.

My personal prostate cancer story began at diagnosis at age 60 in the year 2000. But first, it is appropriate to provide a brief summary of my path to and in urology to this date. No one in my family was involved in the medical profession. My father, who, as part of the newly formed 82nd Airborne Division survived a glider landing into St. Mere Eglise on the dawn of D-day, and survived the Battle of the Bulge, returned home only to be felled by a series of heart attacks. My memory of his illnesses, while hospitalized at a military facility, was treatment with bed rest, an ounce of bourbon BID and two packs of Camels each morning. This was 1954 and emphasizes the enormous strides in the management of cardiovascular disease have been made over the past 75 years. He died at age 44 – certainly prostate cancer would never be an issue for him in his brief lifespan. I, however, would be the beneficiary of the advances in cardiovascular disease management and live to an age of prostate cancer risk.

My first thought of a medical career was at age 20. I just departed a Roman Catholic Seminary and had to find some life direction! I transferred as a Premed Major to the University of Notre Dame, was admitted to Cornell Medical School, completed a 2-year Surgical Residency at Case Western University Hospitals in Cleveland Ohio. The second year of my obligatory medical military obligation took me to Vietnam. There, while struggling as to what direction my surgical career would take, a *New England Journal* appeared in casualty staging flight triage room – a rare happenstance in itself. An advertisement caught my attention. It offered the possibility of Urology Residency Program at a large Mid-Atlantic region medical center. I forwarded a letter of interest with appropriate references and was accepted before I set foot on US soil again and my 12-month overseas duty was completed. Yes, I did get my job through a want ad in a journal. I mention this only to contrast the process with the laborious gauntlet which medical students with current aspirations to urology must face. However, even in today’s much more programmed pathways to goals, the role of serendipity must not be disregarded.

After a stimulating and productive 3-year residency at the Medical College of Virginia under the Chairmanship of Warren Koontz and with his encouragement, I entered a Fellowship in Urologic Oncology at Memorial Sloan Kettering Cancer Center in New York City. I should add that this decision for an extra year of training was looked upon somewhat askance by many graduates at the time – individuals seeking fellowship training were perceived as “slow learners”. Of course, the exposure to the world of surgical and medical oncology in the Fellowship was extraordinary and career defining. I then took a position with a large urology practice which was associated with a recently opened medical school, Eastern Virginia Medical School, in Norfolk, Virginia. The practice was involved in directing the Urology Residency Training Program at Eastern Virginia Medical School (EVMS). The practice furthermore was unique at the time for its size - I was the seventh urologist to join - and its focus on subspecialty divisions which included reconstructive urology (Charles and Patrick Devine), renal vascular surgery (Eugene Poutasse), infertility (Jack Stecker), pediatric urology (Joseph Fiveash and Boyd Winslow), and renal transplantation (William Tynes). My task was to develop a division of urologic oncology.

During the first decade of my practice (1975-1985), the treatments for prostate cancer were quite limited. A few patients were suitable for radiation or surgery (during my fellowship 1973/74, I remarkably did not witness one radical prostatectomy), but the majority presented with advanced disease and orchiectomy was the most suitable procedure. In 1986, the prostate-specific antigen (PSA) test was approved by the FDA for monitoring patients after treatment for prostate cancer. Its potential as a screening tool for early detection was recognized and was FDA approved for this indication in 1992. In 1990, I became an early adapter and, at age 50, had my first PSA evaluation. I was delighted with the results, 2.5 ng/mL, well below the quite arbitrary 4.0 limit which was claimed to predict for good prostate health. In contrast, we now know that the median PSA for a 50-year-old is approximately 0.7 ng/mL and that 50% of cancers destined to become lethal arise from this very cohort of men with PSA greater than 2.0 ng/mL. Annual PSA's were stable for the next 7 years when I experienced the other health liability of the aging male, cardiovascular disease. PSA draws were put on the back burner until the year 2000 when a level of 6 ng/mL, confirmed on several measurements, was found. Prostate biopsy revealed Gleason 4+3 and open radical prostatectomy with pelvic lymphadenectomy found Gleason 8, with tertiary pattern 5, but organ confined, margin negative, node negative pathology.

What followed in the 15 years since surgery to the present date is a story all too familiar to many patients and urologists, namely, primary PSA failure, salvage radiation, subsequent PSA recurrences, androgen deprivation therapy (LHRH agonist, 5-alpha reductase), first and second generation anti-androgens (bicalutamide and enzalutamide) androgen synthesis inhibitors (ketoconazole and abiraterone), transdermal estradiol, subcutaneous mastectomy, immunotherapy (GM-CSF and sipuleucel-T), stereotactic radiation, and clinical trials. I will discuss a number of issues in the context of the above described personal clinical history.

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 and the cancer event occurring within 2 years of each other – 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 of PSA failure one year after radical prostatectomy was perhaps more profound. Like any patient undergoing therapy, I was anticipating a “cure” from surgery. With PSA failure that likelihood diminished and the reality of a recurring problem, the PSA ticking clock, engendered concerns of a compromised professional career, strained relationships, and the prospects of declining health. 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, she found TODAY.

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 two 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 (ADT)

The four letter word that best describes the state of ADT 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”¹ – 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 ADT that I was able to appreciate the profound impact this treatment has on daily life. Even with my real life experience with ADT accumulated 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.”

Estrogens

In 2008 when I entered the M0 castration-resistant disease state, there was no Level I evidence supported therapies in this space. And that still remains the case today. After consultation, I initiated transdermal estradiol which slowed my PSA doubling time and improved my quality-of- life. I continue this therapy through the present, and when possible, advise it for patients. A series of clinical trials testing estrogens versus orchiectomy were conducted in the 1960’s by the Veterans Association Urological Research Group. They demonstrated the cardiovascular morbidity/ mortality associated with oral diethyl stilbesterol (DES). These trials also concluded that, while the overall mortality with DES was inferior to orchiectomy due to excess cardiovascular mortality, the cancer specific mortality favored DES. Based on these results, David Byar, the lead statistician analyzing these trials, concluded that DES acted directly on the cancer cells in addition to inhibiting testosterone secretion. Currently estradiol delivery via a transdermal patch bypasses the first pass through the liver which is responsible for the metabolic changes predisposing to cardiovascular events and thereby dramatically reduces this concern. Estrogen is barely mentioned as treatment in the guidelines of the major oncology societies. It is essentially overlooked and very much underappreciated. In addition to reducing hot flashes and preserving bone health, there is now evidence that it supports sexual function in the male. Traditional ADT deprives the male of both testosterone and estrogen thereby compounding adverse events. Hopefully the Patch trial, a large randomized controlled trial being conducted in the United Kingdom, will bring transdermal estradiol back into the mainstream of prostate cancer therapy. It 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.

Immunotherapy and Oligo Metastatic Disease

In 2010 the FDA, in a breakthrough decision, approved the first immunotherapy for any cancer. The Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial had randomized men with asymptomatic or mildly symptomatic with 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.² 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 as flexible, durable, targeted, and adaptable, attributes that are admirably suited for addressing the same characteristics associated with tumor cell survival. There is evidence and growing interest in attributing some of the benefits of radiation therapy to the abscopal effect. Cellular death caused by radiation specifically high dose radiation producing double strand breaks, releases a host of antigens which provide a broad repertoire of targets for immunotherapeutic activity. Oligo metastases (between 1 and 3 and perhaps up to 5 sites of involvement) present a disease state resting between locally advanced and widely metastatic disease. Stereotactic radiation to the sites and the mitotic cell death it causes not only provides locally control disease, but may provide a priming function for immunotherapy by antigen spreading or antigen cascade as noted above. In 2013 when my PSA had risen to 20, I received stereotactic radiation to an

isolated L3 (9Gy x 3) vertebrae followed by Provenge therapy. My PSA gradually fell. A follow up sodium fluoride PET/CT scan revealed an additional L1 metastases which was also treated with stereotactic radiation. PSA levels gradually declined over 30 months to 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 oligo metastatic disease.

Targeted or Personalized Medicine

The concept of targeted medicine is very attractive but also can be very complicated. The above-mentioned success with stereotactic radiation and immunotherapy was preceded by a disappointing clinical trial outcome when all parameters pointed to likely success. I enrolled in a phase 2 study for men with metastatic castration-resistant prostate cancer that was combining the newly approved androgen receptor blocker, enzalutamide, and the androgen synthesis inhibitor, abiraterone. The combination of two oral agents with tolerable toxicity and different mechanisms of action seemed promising. And furthermore my vertebral bone biopsy analysis pretreatment seemed ideal for this combination. The biopsy revealed adenocarcinoma without evidence of neuroendocrine dedifferentiation. It was AR variant and SRC (a proliferation and invasion kinase) negative and stained strongly positive for the androgen receptor. Nevertheless during the 6 months on trial my PSA doubled from a level of 10 to 20 ng/mL. Was prednisone a culprit in a “glucocorticoid hijacking mechanism”? Again, it’s complicated!

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 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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References

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