SOLVING THE PROSTATE CANCER PUZZLE

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When a man presents with a prostate cancer diagnosis, I often feel like I am starting an intricate jigsaw puzzle with only one piece to build upon. The diagnosis can be a "corner" puzzle piece, but that is not enough to even guess what the finished puzzle picture will reveal.

We start with the diagnosis. How accurate is it? How complete is it? How old is it? In my estimation, one elevated PSA alone is not enough to go on. A one-time elevation can be a fluke, caused by outside forces (ejaculation within 48 hours prior to testing; bicycling and other trauma to the perineal area; acute or chronic prostatitis; etc.). What we would like to see is a PSA history to indicate the trajectory of the score. Also important is a review of the family history of prostate and other related cancers (breast, ovarian, pancreatic cancers), and information on the patient's profession and lifestyle.

In addition to the PSA, I have always ordered a PAP (Prostatic Acid Phosphatase) lab test, especially since some prostate cancers produce little if any PSA. Meanwhile, even with higher PSA readings, a PAP enzyme can alert the physician to early spread of cancer beyond the gland. In the past and even prior to PSA testing, urologists came to realize that an elevated PAP resulted in nearly 100% cancer relapse following prostatectomy deeming patients to be non-candidates for radical prostatectomy. One can easily understand why urologists quickly abandoned the PAP once PSA became available. Regardless, I strongly recommend PAP testing in my patients and treat these patients differently.

To me, the PAP is as important as the PSA (even more important if elevated), and provides another piece of the puzzle. I have published no fewer than five articles on the continued importance of PAP in the PSA era. Thereafter, Johns Hopkins, Walter Reed and RTOG corroborated my findings. Despite this, the PAP is rarely ordered.

A confounding fact is that not all prostate cancers produce PSA. Some of the angriest ones cannot be identified by PSA at all, especially Gleason 9-10 and intraductal cancers.

Other serum markers, such as CGA, NSE on CGA are also important since their elevation typically suggests a more aggressive cancer and will require a significantly different treatment design.

The PSA elevation *red flag* usually triggers the need for a biopsy. Again, this is an area of controversy. It is vital to understand that the typical prostate biopsy consists of 8 to 12 tiny core samples from the gland. This random sample biopsy can totally miss an area of aggressive neuroendocrine variant growth, giving the patient a dangerous "false negative" finding. This random sample approach may find cancer but it is not able to reveal the extent of disease in the areas not sampled. The larger the gland, the higher the probability that cancer can be missed. We don't know how many men today are living pseudo-happy lives believing that they do not have prostate cancer, based on a single random sample biopsy, when in fact their cancer is growing every day (some very rapidly!).

My preferred method for biopsy is using 3D Color Flow Power Doppler Ultrasound for guidance; I have published a 98% predictive accuracy using this method. This advanced technology allows the physician to see, in real-time, areas of abnormal blood flow (indicating tumor growth) within the prostate gland.

Hypoechoic (dark) and hypervascular (cancers are associated with many, many vessels) areas become targets for a *guided* biopsy, assuring a highly accurate analysis. I also use the transperineal approach which has many advantages over rectal biopsies, including the ability to reach every part of the gland including the largest prostate glands. I use a sterile technique and have had a 0% risk of infection, which is in stark contrast to obtaining prostate tissue using the transrectal route.

Where 3D CRPD TRUS is not available, I strongly recommend performing ultrasound biopsy fused with multiparametric MRI (mpMRI) using a 3 Tesla magnet.

In the puzzle analogy, we now add a few of the edge pieces to diagnosis corner piece. What to do now?

The decision of how to treat the prostate cancer should not be made in haste. The choice will impact the man's life from this day forward. There are many, many solutions – some good, some not appropriate due to the man's situation. I always recommend that the patient seriously look at his options; take the time to get second (and third) opinion, if necessary.

I must insert a caveat here – buyer beware. Because prostate cancer is so common, the diagnosis is ripe for exploitation. There has been a 20-year tug-of-war between the surgeons and the radiation oncologists, to capture market share. In some ways this has been good. It has inspired innovation in both arenas. Marketing of these treatment choices is nearly as robust as the used car industry! The downside is that the innocent and frightened patient is now faced with making a critical decision that he may be ill equipped for by selecting from novel treatments lacking long term data as it relates to cure and side-effects.

Outside of the legitimate treatment protocols, there are charlatans out on the web and elsewhere offering all kinds of herbal and magical "cures." Even some degreed and certified physicians are sending their prostate cancer patients out of the country for non-FDA approved treatments consisting of who knows what! Examples are NanoKnife, PhotoDynamic Therapy (PDT), MRI LITT, Radio Frequency Ablation (RFA) and Focal Laser Ablation etc.

Meanwhile, others are using approaches which are investigational yet **"convenient"** (shorter amount of time on treatment) with no good long term data, e.g. Cyberknife, SRS, Hypofractionated Proton and Photon regimens, Cryosurgery, and HIFU.

Innovation be praised! As a result of this competitive environment we now have tools to diagnose the patient to the nth degree, learning more about his particular cancer than ever before. Exquisite imaging innovations, such as 3D color flow power Doppler TRUS, multi-parametric MRIs using PI-RADS analysis, have given the physician new ways of "seeing" the gland and the tumors within it. Information is key; the more the better.

With this barrage of testing and imaging, we are able to start building a profile of the patient and his cancer. The next step is to determine the most appropriate treatment, taking into consideration the patient's geographical location, other health issues, insurance, etc. Regardless of the patient's choice, we encourage considerable research on his part as your first choice of treatment will be your best chance or eradicating prostate cancer forevermore. Never go into a treatment choice with the mindset of "well, if this fails I can always do x, y or z." Find the best practitioner you can, even if you need to travel. Ask questions. If you don't understand the answer, ask again. Request the names of

several patients that you can speak with about their experience with a particular doctor. Research the doctor on the internet. Visit a support group. In most cases (with the exception of very aggressive malignancies), it is not imperative to make a decision right away. Take your time to find the doctor and office that you feel confident in and comfortable with.

A very important part of the patient's research will involve evaluating the technology in place at each doctor's office. Nearly every community and hospital across the U.S. now has access to robotic surgical options (especially the DaVinci robot). These sound high-tech, and they are, but they are no more effective than a regular scalpel performing a standard "open retropubic" prostatectomy in the hands of an experienced surgeon. Behind the advertising hype is a huge monetary investment in the robot that must be returned. We advise patients to investigate track records and ask for published success rates. Beware that quoted success statistics are worthless unless they have been reviewed by a third party or published in a respected medical journal. The same goes for the growing number of Proton Treatment centers. Lots of money invested in Protons has inspired big marketing budgets, yet equivalent survival outcomes when compared to earlier forms of radiation, e.g. 3D CRT, while even more reported GI problems have been documented with Protons when compared to even regular IMRT.

Insurance companies are now wising up and denying payment for Protons in patients having prostate cancer. I expect many Proton centers to close over the next 5-10 years.

My career has been based upon offering men a proven, published, curative option to the surgical one. It was my belief in medical school that technology would one day make radiation therapy a viable option for defeating prostate

cancer with the best cure data and the least amount of side effects. Today there are thousands of men (my patients and those of other leading radiation oncologists) that have proven me correct.

My years of experience, my choice of the most talented staff, and my energies at pushing the technology envelope have allowed me to assemble a technology armamentarium unmatched anywhere. In addition to highly advanced external radiation, my partner and I developed a "multi-modal" two-step protocol including brachytherapy (seed implant) as the most effective method of irradiating the bulk of the cancer within the gland Long ago, I identified the superiority of brachytherapy alone compared to Radical Prostatectomy with better local control rates and never having to say the word "incontinence," while maximally preserving sexual function. The problem is that the prostate gland has no real capsule (try googling this) and most cancers are already microscopically outside of the gland before most treatments begin, e.g. Radical Prostatectomy (especially when using the DaVinci Robot, Brachytherapy alone, Cryosurgery, HIFU, Cyberknife, SRS, Protons, PDT, NanoKnife, etc.

Today, many proponents of treating only the prostate from edge to edge either don't know or do know but wish to use the word "capsule" to lure patients into their particular treatment. I note that so many urologists get away with using the term "capsule" to inform convince a patient that his cancer is "contained," so that he is a candidate for Radical Prostatectomy.

We continue to refine both the application of external radiation and the design of implanted radioactive sources (brachytherapy). Our Center remains the only "brachytherapy research institute" in the country. Patients routinely travel to

Sarasota from all over the world to receive our tested and proven multimodal therapy.

Returning to the jigsaw analogy, after gathering information from the lab tests, imaging studies, patient interviews, medical records and other sources, we can complete the outer edges of the puzzle. An individualized treatment plan tailored to the patient's specific finding, rounds out the puzzle.

We began by installing the first Varian Linear Accelerator in the world, using IMRT. This was in the days of major advances in EBRT – External Beam Radiation Therapy. As our patient flow accelerated, we purchased more sophisticated accelerators and high-end software programs in order to treat more men with greater precision. Concurrent to the wide spread introduction of the DaVinci Robotic radical prostatectomy, our Center created an even more sophisticated radiation delivery system that we named DART – Dynamic Adaptive Radiation Therapy. This delivery system uses multiple 4 dimensional technologies which are all coordinated to achieve the most pinpoint, precise radiation in the world. Today this unique coordination of DART along with the most advanced diagnostics provides our patients with unrivaled therapeutic results. Even the most advanced cases are offered significant relief and quality of life following our treatment.

Today, we often see men who have received treatment elsewhere, only to see their PSA continue to rise, meaning their treatment did not solve the problem. Perhaps he did not have a fully adequate diagnostic evaluation; maybe he bought the sales pitch for a therapy that was not appropriate for him, or was directed by an inexperienced provider, or perhaps simply bad luck.

Many of these pre-treated patients can still be helped, and we are equipped to take on these challenges. Most often we find that these cases

involve prostate cancer spread into the lymph nodes and bone, with the majority being to lymph nodes. Sometimes this could have been discovered before the man's initial treatment, thus eliminating surgery and other treatments as an option (once cancer has spread beyond the prostate's edge, Radical Prostatectomy, Cryoablation, Cyberknife, SRS, HIFU, NanoKnife, PDT, etc. are useless as potentially curative options.)

Our Center has concentrated great effort into finding a way to effectively irradiate lymph nodes outside of the prostate proper which contain active prostate cancer cells, as well as sites of bone spread – and we have achieved great success! By building a suite of sophisticated diagnostic tools, such as USPIO (Ultra-small Super Paramagnetic Iron Oxide), ^{18}F-Sodium Fluoride PET/CT bone scan, ^{11}C-Choline PET/CT, Carbon 11 acetate PET CT, ^{18}F-Fluciclovine PET/CT, Gadlium-68 based PSMA PET CT or mpMRI, we can image the exact nodes or bones containing cancer.

These lymph nodes can now be successfully irradiated by dynamically adjusting the "microbeams" to organ motion in "real time" (specialized radiotherapy created by and available only at the Dattoli Cancer Center). This radiation can halt the advance of prostate cancer through the lymph system, without exposing the critical organs in the path to any damaging radiation. Other methods can also be utilized to attack metastatic bone spread using denosumab and infusional "systemic" bone seeking radiation. Even treatment of lymph nodes above the diaphragm may be extremely effective in eliminating symptoms associated with castrate-resistant prostate cancer, and even offer patients extended biochemical and disease free survival, and even cure (defined as

undetectable PSA, no evidence of cancer, five years or greater following treatment)!

We have been increasingly using genetic/genomic testing to create a "designer cocktail," often immunotherapy, which is given in conjunction with high tech and even infusional irradiation, with or without DART. We are currently excited about the use of "systemic" infusional Lutetium-177 (Lu-177) which targets PSMA (prostate specific membrane antigen) in soft tissue, bone and even blood borne prostate cancer. We will soon be adding this to our armamentarium.

In addition to this panoply of diagnostic and treatment refinements, we are going beyond the disease itself to "treat" our patients holistically with helpful supplements and vitamins. I have long been passionate about the use of quality supplements to potentially thwart malignancies from the beginning, as well as slowing cancer growth, improving bone strength and upregulating the immune system. Following three years of R & D, we recently introduced a proprietary line of these supplements to the public, under the name "D & K Brands." These "prescription grade" and 3rd party validated products are a boon to an industry that is woefully bereft of important regulation. Far too many over-the-counter supplements have been found to contain little of the actual ingredients they claim. Some are actually unsafe concoctions and can result in adverse interactions with prescribed medications. Many even contain impurities, especially prescription drugs, since they are packaged at pharmaceutical plants. Even products which claim to be "pharmaceutical grade" have failed third-party validation. Information about our uniquely created products is available at www.dandksupplements.com. You can rest assured that they are of the highest

quality, safe, pure and manufactured at FDA approved facilities under the strictest GMP standards. All D and K products are rigorously third party validated.

Discovering and assembling all the various "puzzle pieces" of an individual's cancer creates a fairly accurate picture of what is going on, and then allows us to design a treatment plan to defeat each specific manifestation of disease and return the man to wholeness. Solving each puzzle also increases our knowledge of how to treat the next guy.