ACTIVE SURVEILLANCE: A DARK SIDE?

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Just as I was becoming increasingly interested about the trend toward more and more newly diagnosed men opting for "active surveillance," an article popped up on the internet entitled "Prostate Cancer: Docs Drive Treatment Choice," and it came across MedPage Today on August 25, 2014.

The article begins, "Physicians who diagnosed low-risk prostate cancer had more influence over the decision to enter active surveillance than did the disease characteristics, a review of 12,000 cases showed."

The article further reports, "analysis of factors that influenced treatment decision showed that the diagnosing physician had more than twice the impact on the choice of upfront therapy as compared with disease characteristics, as reported online in JAMA Internal Medicine."

"Active Surveillance" has taken the place of so-called "Watchful Waiting" in most circles today, bringing a more proactive approach to following the diagnosis of what is thought to be early stage or low risk prostate cancers (although in some baffling cases – patients with intermediate risk cancers are also being encouraged to pursue a course of Active Surveillance). Active surveillance means that the patient and his doctor initiate a systematic plan for follow-up appointments to assess the patient's "progress," or lack of progress, as the case may often be. This may mean having a repeat PSA test every 60, 90 or 180 days, as well as other lab tests. Active Surveillance may also require repeat or even bi-annual biopsies, PCA-3 urine tests, grey scale ultrasounds, multi-parametric MRIs and high resolution color-Doppler transrectal ultrasounds. On first blush, this may sound quite reasonable. The main objective is to spare the patient from side effects secondary to primary definitive therapy, especially incontinence and erectile dysfunction. The hope is that a high percentage of men won't require treatment while a smaller percentage of patients will eventually need to be treated.

On the one hand it is surely a step in the right direction, abandoning the merely "waiting" mode - what exactly are you waiting for anyway? Patients who pursue Active Surveillance are waiting to see if their prostate cancer is going to progress, and if it does, how fast and by how much. But on the other hand, it can ensnare the unknowing but trusting patient in a spiral of tests and more tests but with the important potential loss of opportunity for curative treatment. I have witnessed patients who didn't like their Urologists and then turned back to their GPs or Internists, or sought advice from Oncologists who then followed the patient frequently performing DREs and PSAs, and hopefully who may also have sent patients for baseline advanced imaging to better assess actual tumor burden. Following only PSAs alone (with or without percent-free PSAs) can be dangerous. Many patients who opt for active surveillance also take numerous supplements. When their PSAs decline, they often attribute this to their altered diet and lifestyle, while in reality the cancer may have mutated to a more aggressive status. This is a phenomenon unique to cancers. They are by definition growing faster than normal cells, increasing the likelihood of mutations, many of which are typically higher in grade and even resistant to hormone therapy. Even some physicians don't understand that the more aggressive the cancer becomes, the less PSA is secreted.

When I follow patients with Active Surveillance, my goal is to slow the upward PSA climb, decrease the PSA velocity and ultimately the PSA doubling times - although I become increasingly concerned when the PSA declines (unless this is the result of Avodart or Proscar or other novel agents.) My program includes advocating lifestyle changes with exercise, stress reduction, dietary alterations, and taking supplements which have been identified to slow prostate cancer progress. I have found Avodart and Proscar to be associated with unwanted side-effects, including but not limited to breast enlargement and tenderness, as well as a higher rate of erectile dysfunction than anticipated. For example I often recommend vitamin D-3, pomegranate and soy products, along with other supplements, as reported in Harvard Health publications, Harvard's Men's HealthWatch, as well as the American Cancer Society, "What's New in Prostate Cancer Research and Treatment."

Decision Making 101

Let's examine the scenario to understand what is happening. Whether a man first learns of an abnormal finding (either elevated PSA or abnormal DRE) through a Primary Care physician or an Urologist, the definitive biopsy is typically performed by the Urologist. The vast majority of American men are in the hands of an Urologist when they learn, as a result of a first biopsy, that they have prostate cancer.
The Urologist is right there at this moment of crisis. This Great Physician figure is the first person to know of the diagnosis and naturally the patient asks him, “What should I do?” He may go so far as to ask, “If I were your father or brother, what would you recommend?”

For everyone except the Urologist, this is a potentially problematic, inherently unfair, situation. A diagnosis of cancer can make your heart skip a beat, and turn a normally intelligent man into a frightened man-child. Because early prostate cancers rarely cause any symptoms, many men are taken by surprise when they first hear the diagnosis. Other than anxiety about the biopsy, most patients actually feel perfectly healthy at the time of the biopsy. In perpetual denial, they most likely were not expecting the diagnosis. Now what to do?

Too often, unless the patient has had some reason to suspect that his biopsy would be found positive or he has known another man who was diagnosed or he is unusually well informed about prostate cancer, while still in shock at being diagnosed, he will present a blank slate upon which the doctor can write.

Years ago, the Urologist’s pat answer would be surgery to remove the diseased gland, unless the patient was very elderly or had other serious health issues. Surgery – that is what the urologist learned in medical residency training; that is what he does best.

In the last two decades many new treatment modalities have usurped surgery’s position as the most “popular” method of treating prostate cancer, although many naive gentlemen still make the surgery decision before fully examining their options or understanding the consequences. During the past two decades, among came a variety of radiation modalities such as seed with or without IMRT radiation, Proton beam therapy, Cyberknife, and other treatment methods including heating and freezing, and non-curative hormone treatment – even late-night-TV promises of “cures” from mysterious pills. In this new marketplace and in the face of increased competition, the once very busy Urologist/Surgeon began to lose “market share.” His piece of the prostate cancer pie has dwindled. Additionally, as mentioned above, Oncologists and even Internists have gotten involved in caring for “low risk” prostate cancer patients. (The public doesn’t like to think of medicine in business terms, but the truth is if the practice is not run like a business, it cannot survive.)

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According to the NCCN (National Comprehensive Cancer Network) guidelines, all patients should be counseled about all treatment modalities, outcome monitoring after treatment and encouraged to seek a second opinion. We don’t really know how often this actually happens. It might be interesting to be a “fly on the wall” in the Urologist’s office to learn how those conversations go immediately after the positive pathology report is shared. We do know, however, that more and more newly diagnosed low-risk patients are opting for “observation,” aka Active Surveillance, which is a perfectly reasonable choice in many cases. Unfortunately, we are now also hearing of men having higher volume and often bi-lobar Gleason 6 cancers typically exceeding Active Surveillance criteria, and especially Gleason 3+4=7 malignancies being offered Active Surveillance as a viable treatment option too!

It is ill advised to merely follow a Gleason 3+4=7 prostate cancer as they typically behave aggressively. Recognize that even with treatment in the finest surgical centers of the world, following radical prostatectomy for Gleason 7 cancers, only 50% of men enjoy disease-free survival at 10 years and similar results with standard radiation. These results would surely be expected to be lower in community settings where the physician typically performs far fewer procedures and has no interest or obligation to publish his data.

Back to Mr. Jones. His Urologist, Internist or Oncologist instantly has another suggestion for the newly diagnosed patient. “If you are opposed to surgery, let’s start a program of Active Surveillance and just watch to see where this cancer goes.” Sounds good to Mr. Jones and he now embarks on this newly paved road.

Does anyone see a problem with this? From the patient’s perspective he has dodged the surgery bullet for now. From the physician’s perspective, he has secured Mr. Jones in his practice until such time as the cancer starts to prove aggressive. What is the downside for the urologist? The unwitting patient may not even have been told that he may very well be opting out of his first, best chance for a cure by not electing for definitive treatment (radiation or surgery) at this early stage before the disease advances at which time he may require far more aggressive treatment. If the patient has merely postponed investigating his options, he could find himself dealing with serious consequences later on at which time treatment may be associated with far more unwanted side-effects. His disease may even become incurable. He also doesn’t know (and doesn’t know that he doesn’t know) whether the “random sample” biopsy was accurate, and that he may actually have higher volume disease.

Granted, at this time we don’t have a crystal ball or the ability to know exactly whether Mr. Jones’ cancer will prove to be aggressive (a “tiger”) or whether it will turn out to be indolent, non-life threatening (a “pussycat”). Fortunately,
by scrutinizing each biopsy specimen and using advanced imaging, especially multi-parametric MRI or high resolution color-flow Doppler ultrasound (as touted by specialists in 2007 – PCRI Insights) and special pathologic bio-marker testing, we may finally be able to realize how aggressive or non-aggressively this cancer will behave. There has, however, been limited progress on the pathologic front using biomarkers in contrast to multi-parametric MRI and color-flow power Doppler ultrasound where inroads are steadily being made. The bottom line is that statistics indicate that between 25% and 40% of these "low risk" patients will require treatment within five years.

For the Urologist (and even for the Internist and Oncologist) there is no downside, but rather an extended relationship with the patient. In the meantime and partially in the shadows, many physicians, especially Urologists now maintain ownership or partial ownership in the MRI centers and other diagnostic and treatment centers to which they refer, despite this being prohibited by the Stark Anti-Trust law (a subject for another discussion, at another time or you might Google: "America: Beware the Uro-Rad"). Interestingly, doctors including Oncologists and even Internists are also getting involved in this rapidly growing "industry" created by this growing subset of Active Surveillance patients. Where will this Active Surveillance trickle down end – with even other medical professionals wanting a piece of this growing industry?

I have personally reviewed cases where repeated multi-parametric MRIs were interpreted by the original radiologist showing only "minor change," only to have them reviewed by an independent, unbiased and especially skilled radiologist who identified significant progression of this subset! I've seen the same with color-flow power Doppler ultrasound. It makes one wonder if this situation is evidence of an ill-advised extended relationship with the actively surveilling original physician and/or the Radiologist who knows that the relationship with that patient ends once the cancer progresses. Each time the patient is referred for a test at one of these physician-owned centers, the doctors will receive compensation (both the referring doctor and Radiologist). Maybe Mr. Jones' cancer will remain in the pussyfoot realm – not life threatening – for a good long time. We can only hope so, but there is a good chance – 25% to 40% -- that it will become a tiger.

Every case is different, of course. I follow numerous patients with Active Surveillance although I am a very strong proponent of adhering to strict guidelines for select low-risk patients which are nearly identical to guidelines at Johns Hopkins Medical Center. These include Gleason score ≤ 6, maximum of three biopsy cores containing cancer and no core containing 50% cancer or greater unless advanced imaging reveals greater disease burden. Recent long-term studies performed at Johns Hopkins Medical Center have shown that 12-core biopsy results are in many cases unreliable. Also, I should point out, with men who are resistant to the idea of Active Surveillance, I wouldn't deny a patient definitive treatment either if he is very frightened from his cancer diagnosis (the "big C") and wants to be treated. If not treated, this may provoke significant anxiety, possibly resulting in other diseases (for example stress induced high blood pressure, insomnia, etc.) and this is coupled with all the uncertainty associated with the biopsies in the first place. I believe that it would be a travesty for Medicare and private carriers to deny payment for these individuals, as some of the strongest proponents of Active Surveillance have proposed. Read on …

Considering the Gleason Score
One particularly confounding situation is posed by the patient whose pathology reveals a Gleason 7. This is where the predictive ability of the Gleason scale becomes really dicey. As you may know Gleason scores are expressed as the sum of two figures. When a Pathologist looks under the microscope at a prostate specimen, he determines which type cancer cells are most common on a scale of 1 to 5, with 5 being the most aggressive. This is the first number of the Gleason Score. The second most common type of cancer cells identified determines the second number. A Gleason 7 can therefore be a 3+4 or a 4+3. The order of those numerals may be clinically important. To most physicians the position of the four in the equation presents a line of demarcation. If the 4 appears in the first position (i.e. 4+3=7) it is generally agreed upon by most physicians that this Gleason 7 is more "risky" than if it appears in the second position (i.e. 3+4=7), although neither, in my opinion, should ever be followed with Active Surveillance. I believe virtually all patients with Gleason 7 scores (3+4 or 4+3) should be treated definitively with intent to cure, unless, of course, the patient suffers significant other comorbid illnesses so that his expected survival is ≤ 10 years. This is especially the case in otherwise healthy elderly men who have aggressive cancers yet are often denied definitive treatment based solely on their advanced age and commonly receive hormonal therapy alone, which is often associated with greater morbidity than had they been treated definitively.

Offering Active Surveillance for the patient having Gleason 3+4=7 can be dangerous. From years of study and practice, we know that cancer behaves in the manner of its most aggressive component. Gleason score 3+4 and a Gleason score 4+3 should both be considered as potentially dangerous because of the singular appearance of the "4," regardless of the position it holds in the Gleason equation. Upon initial diagnosis and staging of a Gleason 3+4/4+3=7, the patient should be treated definitively with intent to cure as this is the standard of care.
This is logical as he is being treated appropriately to the extent to which the cancer has advanced. Perhaps, the 4+3 has advanced to a greater degree than the 3+4, although he will still be “treated appropriately” to the particular level of advancement. On the other hand, if he is merely “followed,” we must remember that the “4” is aggressive, and really not that much different than following a Gleason 4+4+4+8! (Remember, Gleason 5 is the most aggressive.) The presence of any “4” in the Gleason equation will undoubtedly predict the cancer’s eventual course. Recommending Active Surveillance in this subset (3+4=7) undoubtedly risks placing this patient in a non-curate position when the decision to treat is finally made. At that point the disease may have advanced microscopically or macroscopically to extra-prostatic sites and/or organs beyond the prostate.

And of course, all of this is predicated upon the accuracy of the biopsy in the first place. We have long known that the traditional random sample sextant biopsy and more recently the twelve core biopsy, produced less than stellar results (confirmed by the Johns Hopkins study cited above). Besides the very serious issue of false negative findings, the incidence of under-staged positive results can be startling. Two recent journal articles from 2013* report 30% and 47.8% of these biopsies being upgraded upon a second, more focused type biopsy procedure. So we can assume as many as 1 in 3, and possibly as many as 1 in 2 biopsies are under-staged. Making a treatment decision based on an under-staged biopsy is like trying to watch a movie with one eye closed.

PSA Panic
Along with Active Surveillance comes a phenomenon we call “PSA Panic.” As each succeeding PSA test looms, the patient becomes more and more anxious. Will this biopsy seal the deal and he’ll have to face the music and make a treatment decision? How long will this continue – every 3 months for 3 years? Five years? Five years of active surveillance could equate to 20 separate PSA Panic sessions.

The real problem comes into play when at the end of the “good long time” it may turn out that the first random sample biopsy was inadequate and inaccurate (he was one of those 1 of 3 or 1 of 2, whose Gleason was under-staged because of the poor quality of the biopsy). Suppose Mr. Jones’ Gleason was not really 6 but actually 8. Remember, the higher the Gleason Score, the less PSA the cancer secretes and so this can be easily missed by routine PSA testing. Patients need to be mindful that as prostate cancer mutates to a Gleason 8 – 10, the cancer loses its resemblance to the prostate cell altogether, and therefore secretes little to no PSA. For example, a Gleason 9-10 prostate cancer may simply resemble an aggressive cancer of another origin, such as lung or head and neck¹⁰, and may not even stain pathologically for PSA or PAP as less aggressive prostate cancers do.

Although 5 years of observation and possibly the use of female hormones, supplements, Avodart*/Proscar® and perhaps other novel anti-cancer drugs had kept his PSA rise to a minimum, the cancer may have still escaped the thin porous capsule associated with the prostate and invaded the lymph nodes and bones while he was under active surveillance. By this time, Mr. Jones is now 73 years old and surgery is clearly out of the question, as is localized radiation (that is, curative options). Now even worse, his situation is such that he no longer has disease confined to the gland, and he must navigate options to address the spread of the disease outside of the gland. It will take very aggressive treatment to halt the spread of the disease, perhaps with the assault of strong drugs, such as Xtandi® and Zytiga®, Taxotere®, or possibly palliative (non-curative) "spot radiation" and Xofgo (Ra 223) just to provide him with some quality of life in his last days.

This scenario with Mr. Jones is not far-fetched. We have seen this exact situation in our practice - good, smart men who thought they were doing the right thing by simply observing. After all, their physician had made the decision for them simply by suggesting it (Active Surveillance). I am not suggesting, however, that every Urologist follows this pattern in recommending Active Surveillance, whether correctly or incorrectly (higher volume and often bi-lobar Gleason 6 cancer exceeding typical Active Surveillance criteria or Gleason 7 cancer). I am, however, seeing this as growing pattern, which is a good thing in “low risk” prostate cancer. Most still, however, recommend surgery or radiation, especially the latter if the Urologist has ownership in a radiation facility. (Again, Google “American: Beware the Uro-Rad.”) I am only sharing these scenarios in the hope of educating the newly diagnosed patients about the potential consequences of choosing Active Surveillance too quickly and not seeking a second or even third opinion.

What about “Active Surveillance Following Treatment?”
I have found yet another chapter in the “evolving active surveillance textbook.” This one involves those patients who have undergone some type of definitive treatment and their post treatment PSA fails to successfully nadir. Ideally, after any type of treatment for prostate cancer (traditional surgery, robotic surgery, external radiation, seed implant, cryosurgery, etc.), the PSA should fall to a “nadir” (lowest point) and remain there. It is generally thought that the longer it continues to fall and the lower it falls, the stronger predictor it is of prolonged disease-free survival.¹¹

If the PSA does not fall following treatment, or initially falls but then begins to rise again, this is evidence that disease persists, either within what is left of the gland (the prostate bed) or somewhere outside the gland. This is a demoralizing time for the patient who believed the assurances of his doctor and had every hope that his choice of treatment would defeat the cancer.

This is also a point where the man’s physician (Urologist, Oncologist and even Internist) may advise Active Surveillance. Again this is a dicey time; if there is cancer still present (as suggested by failure to fully reach a genuine nadir) it is best to jump on it quickly, but the physician may favor waiting for a while in the hopes that the PSA will eventually
go down. This saves face for the physician who also failed to solve the man’s prostate cancer problem.

Determining when to observe and when to act and treat is a point of contention, especially since it may take months to several years for a patient’s PSA to rise following initial treatment. We have seen over time that if the PSA fails to reach <0.2 following radiation within 1-2 years, and is not undetectable following radical prostatectomy within 3-6 months’ time, the man is likely to fail.12

The treatment he underwent did not work. Too many Urologists and Radiation Oncologists adopt a wait-and-see mode with “active surveillance following initial definitive treatment,” and do not choose to act until the PSA climbs to 2.0 or higher. They argue that after surgery, tissue remains and may be the cause for the PSA rise (which is extremely unlikely). With radiation, especially with seeds implants, it is even more difficult to make this determination based on a rising PSA since a “benign PSA bounce” often occurs, most commonly within 8-18 months, and possibly even longer, following brachytherapy. This adds more confusion to the situation. Once again, when PSAs rise following radiation or surgery patients are often given PSA lowering drugs, including but not limited to Avodart®, Proscar®, and other novel drugs, each of which carry their own set of side-effects (breast enlargement and tenderness and erectile dysfunction) while the patient’s chance of ever realizing a cure slips away.

In my opinion, following radical prostatectomy, you are wasting critical time that could be used to begin a second-line treatment which can be curative. Ideally, the PSA should never increase above 1.0. It would be even far better (more likely to be curative) if salvage radiation is instituted by the time the PSA reaches 0.4.12 The Prostate Cancer Working Group has stated that after surgery the PSA should not rise above 0.4 before undergoing salvage radiation.13 Unfortunately, this is far more the exception than the rule. In fact, the very best outcomes are reported when the patient is automatically scheduled for post-operative radiation within 3-4 months when post-operative surgical pathologic findings are identified to be adverse (for example, Gleason 8-10 with extra capsular extension, positive surgical margins, seminal vesicle involvement, lymph node positivity). Numerous clinical trials have demonstrated increased survival with early post-operative radiation with no statistical difference in morbidity – urination/bowels/erectile dysfunction15. Such “planned radiation” following surgery is known as adjuvant radiation, rather than salvage radiation. Unfortunately, surveys show that only 7-13% of urologists refer patients for adjuvant radiation with or without hormones.

So what should be done when the patient’s PSA is rising to a level where the attending physician feels that treatment is warranted? The patient should be treated with some other type of therapy. If he had surgery, he will most likely need radiation therapy as his initial curative treatment, this becomes a far more difficult decision. Studies have demonstrated that the lower the PSA the better, although not 0.4 as is the case with surgery. Instead, following definitive radiation, studies suggest that if a PSA does not nadir to
<0.2 after 2 years, or never nadirs, that if the patient's PSA velocity is steep, and biopsies secure a diagnosis within the gland, patients may be candidates for radioactive seeds using a different isotope than the one used for the initial treatment, (with or without external radiation), cryosurgery or salvage surgery. And he will need more diagnostic exams to try to find out where the active cancer cells are – within the prostate proper or elsewhere. Once again, the lower the PSA is upon initiation of salvage therapy after definitive radiation, the better the outcome will be.16

In our practice today, we have access to a very promising diagnostic procedure for identifying prostate cancer spread into the lymph nodes. Ultra-small super-paramagnetic iron oxide (USPIO) MRI scans performed at few select imaging centers word-wide provide exquisite images showing precisely which lymph nodes have picked up active prostate cancer cells, and which ones are free from them.*

With this information, the most finely focused photon radiation can be delivered to individual lymph nodes using our unique Dynamic Adaptive Radiation Therapy (DART). This advanced treatment modality can synchronize the voxel-size beamlet placement with the patient's internal organ movement, using numerous 4-Dimensional technologies – assuring spot-on targeting while protecting the surrounding tissue and organs. We are now able to treat lymph nodes throughout the pelvis and abdomen and even as far up as the collar bones, (treatment for prostate cancer that has metastasized as far as the collar bones is not typically curative in intent, although it may ameliorate symptoms resulting from hormone resistant prostate cancer and even extend biochemical and disease free survival.) This is next generation treatment at its best, as we are now able to effectively treat patients with positive lymph node disease when a limited number of nodes are involved.

Wrap Up
Back to the issue at hand: Active Surveillance – is it right for you? Should you question your physician if he suggests it? Will it serve your best interest?

If you are skeptical that what I have presented actually happens with many unsuspecting patients, I share this haunting quote from James Mohler, MD, of Roswell Park Cancer Center Institute, Buffalo, NY, which appeared in the MedPage article referenced at the beginning of this essay:

"Primary care physicians and patients should understand that 'Urologists and Radiation Oncologists' believe in their treatment modality and, hence, are biased by their beliefs and sometimes by financial considerations."*  

A prostate cancer educational guide produced by H. Lee Moffitt Cancer Institute, Tampa, Fla., which drew its information from the National Cancer Institute's printed guides, offers these questions for patients who may be thinking about active surveillance to ask their doctor:

- Is it safe for me to put off treatment? Does it mean I will not live as long as if I started treatment right away?
- Can I change my mind later on?
- How often will I have checkups? Which tests will I need? Will I need repeated biopsies? Other costly diagnostics?
- How will we know if the prostate cancer is advancing?
- Between checkups, what problems should I tell you about?

We think that patients should be asking a few more questions like the following:

- How accurate do you think my biopsy is? Could it be that I have more cancer than my Gleason score predicts?
- Do you have ownership in any of the diagnostic centers I will be sent to while participating in Active Surveillance?
- How long do you recommend that I remain in this surveillance mode?
- The patient really needs to ask himself the single most important question: Will I be able to sleep at night knowing that I have a cancer in my prostate with no guarantee that it will not advance to an incurable stage?

*USPIO is not currently FDA approved, therefore requires partial out of pocket payment from the patient.

References:
3. Harvard's Men's Healthwatch, July 2007
7. Active Surveillance Program for Prostate Cancer: An Update of the Johns Hopkins Experience; Journal of Clinical Oncology 2011, June 1; 29(16): 2185-2190

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