TRUST BUT VERIFY: THE VALUE OF PSA

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PSA usage has its advocates and its critics. The USPTF took the position of totally negating the use of PSA. On the other hand there is substantial data indicating that with its use the mortality rate has decreased substantially. This has become an almost religious argument. We consider a case herein where we examine a patient who has a first degree family history of aggressive prostate cancer and who has been watching PSA increases over time. The material is presented in a typical clinical presentation manner and includes information from state of the art techniques. The presentation also exemplifies the attempt to use a Bayesian technique of taking into account facts know at certain points of time to guide in the selection of the following set of actions. The overall conclusion is that using such an approach may result in an ever widening outcome consensus rather than a clarifying one. Namely with new techniques we may get conflicting data where the PSA, albeit the initiating factor, plays a possible confusing role.

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Dr. McGarty is currently the Managing Partner of The Telmarc Group. He has been on the faculty of MIT from 1969 through 2012 with various lacunae in industry. The opinions in this paper are his alone and may be subject to change and alteration at any time. There is no intent to provide medical or professional advice and the patient data contained herein has been released by the patient with the names withheld. mcgarty@alum.mit.edu Dr. McGarty wants to thank Dr. James McKiernan at Columbia Medical Center for his insight advice. The opinions contained herein are those solely of Dr. McGarty and do not reflect the views of any others. The patient data is accurate as best as possible and its release has been done with full understanding and agreement of the patient. Details have been redacted that would lead to any patient specific disclosure.

Contents

1 INTRODUCTION

PSA usage has its advocates and its critics. The USPTF took the position of totally negating the use of PSA. On the other hand there is substantial data indicating that with its use the mortality rate has decreased substantially. This has become an almost religious argument. We consider a case herein where we examine a patient who has a first degree family history of aggressive prostate cancer and who has been watching PSA increases over time.

The material is presented in a typical clinical presentation manner and includes information from state of the art techniques. The presentation also exemplifies the attempt to use a Bayesian technique of taking into account facts know at certain points of time to guide in the selection of the following set of actions. The overall conclusion is that using such an approach may result in an ever widening outcome consensus rather than a clarifying one. Namely with new techniques we may get conflicting data where the PSA, albeit the initiating factor, plays a possible confusing role.

2 THE CLINICAL PRESENTATION

A 72 year old man has been followed with PSA tests, DRE and two prior prostate biopsies. The family history is a father who dies of PCa. The father, at age 74, had a PSA of 4 and then at 76 the PSA rose to 40, with an inoperable PCa and the father underwent a set of ADT procedures but dies at age 78. The current patient had seen his PSA velocity increase at 67 and underwent a biopsy with a diagnosis of HG PIN, in several regions.

The details on all PSA and %free data are shown in Figures 1 and 2. They demonstrate over more than 20 years an increasing level of PSA. Figure 2 demonstrates a consistent high level of %Free even to the present. However the PSA velocity as shown does at time the initial biopsy was driven by a significant PSA velocity where the PSA went from 1.5 to 2.2 in one year. The PSA in the previous PSA had been 0.6 to 1.4 over the past fourteen years. The sudden increase and the family history indicated a concern which initiated the biopsy[1]. The first biopsy results are:

A. Prostate, right apex, biopsy: Benign prostatic glands and stroma.
B. Prostate, left apex, biopsy: Prostatic intraepithelial neoplasia, high grade, focal. Glandular hyperplasia of prostate.
C. Prostate, left peripheral zone, biopsy: Prostatic intraepithelial neoplasia, high grade, focal, Glandular
hyperplasia of prostate.
D. Prostate, right peripheral zone, biopsy: Benign prostatic glands and stroma.
E. Prostate, transition zone, biopsy: Prostatic intraepithelial neoplasia, high grade, focal. Glandular
hyperplasia of prostate.

[1] See McGarty, *The PSA Controversy* (Dec 2010) http://www.telmarc.com/Documents/White%20Papers/79%20PSA%20Controversy.pdf which provides substantial detail on this issue.

The biopsy result of HGPIN in several areas also indicated what many have seen as a clear precursor to PCa, namely HGPIN. Thus closer following was mandated by these two results; HGPIN and PSA velocity[2].

However the % Free PSA was 39% which is quite high for any suspected PCa. Yet driven by the velocity and HGPIN a second biopsy was indicated[3].

Nine months later a second biopsy using ultrasound with 20 cores was performed. This biopsy produced all benign tissue. The patient continued to be monitored by six month interval PSA tests and DRE.

The loss of any HGPIN was surprising but not of significant concern. After all the volume of the prostate was measured at 60 cc and the 20 sample biopsy could at best sample about 2% of the cells. The second biopsy results stated:

A. Prostate, right apex, needle core biopsy: Benign prostatic tissue with very focal and mild acute inflammation
B. Prostate, left apex, needle core biopsy: Benign prostatic tissue.
C. Prostate, right mid, needle core biopsy: Benign prostatic tissue.
D. Prostate, left mid, needle core biopsy: Benign prostatic tissue.
E. Prostate, right base, needle core biopsy: Benign prostatic tissue.
F. Prostate, left base, needle core biopsy: Benign prostatic tissue.
G. Prostate, transition zone, needle core biopsy: Benign prostatic tissue.

The next step was to follow the patient using PSA and % Free. There is always a concern regarding the family history and the apparent velocity level combined with pathologically identified HGPIN.

Almost six years after the initial biopsy the patient presents with a sudden PSA increase. A year earlier the PSA was 2.6, six months later it rose to 2.9 and when the patient presented it was 3.7. % Free was 31% the year earlier, a decline but not significant and no measurement since then. The sudden increase warranted further consideration.

The patient was seen and the DRE was unremarkable. The patient was aware of the sudden increase and expressed concern and reiterated the family history. It was clear that an additional biopsy was necessary.

The current methodology for biopsy would be an MRI guided ultrasound which had been recently made operational. However it was also decided to try a new test, namely the 4K, test, to see what the chance was of a positive biopsy. Although not FDA approved the results from the 4K were promising.

[2] See McGarty, *Prostatic Intraepithelial Neoplasia* (Feb 2011)
http://www.telmarc.com/Documents/White%20Papers/83%20Prostatic%20Intraepithelial%20Neoplasia.pdf
[3] See McGarty *PSA Evaluation Methodologies* (Dec 2010)
http://www.telmarc.com/Documents/White%20Papers/80%20PSA%20Measurement.pdf

The results from the 4K were received as the patient was beginning the MRI and thus the MRI was continued[4].

The 4K results indicated a less than 1% chance of malignancy. The PSA on the 4K was 3.2 and the % Free was 35%. That combined with the other 4K measures gave the lowest possible risk of PCa.

The 4K results stated that there is a 99% chance that the biopsy does not find a high-grade prostate cancer and a 1% chance otherwise. The term high grade means Gleason 7 or higher. Thus this is highly positive for a clear biopsy but since it is not FDA approved it is still considered experimental. The physician and patient discussed the next steps but this was problematic since the patient had already proceeded with the MRI and the results were presented.

The MRI indicated regions in the left and right transition zones and in the apex of the central zone at the boundary of the bladder. The indications were such that the biopsy would be required.

An eighteen core biopsy was performed using the integrated MRI/Ultrasound system. The regions of concern in the gadolinium enhanced MRI were sampled multiple times to ensure the acquisition of adequate tissue. The details of the MRI report are as follows[5]:

Peripheral zone: Normal signal.

Central gland: There are 3 lesions in the central gland that are T2 hypointense, diffusion hyperintense, ADC hypointense, and demonstrate early arterial enhancement. Lesions as follows:

1. Right posterior central zone just underneath the bladder measuring 11 x 10 mm
2. Left lateral mid transitional zone measuring 11 x 14 mm.
3. Right anterior transitional zone measuring 6 mm

Capsule: All lesions are contained within the prostate capsule. The right posterior central zone lesion abuts the capsule at the floor of the bladder.

Seminal vesicles: No evidence of invasion.

Lymph nodes: No lymphadenopathy.

The three lesions in the central-transitional zone. Generally PCa is in the peripheral zone and transition zone lesions are consistent with BPH. The main concern is the lesion abutting the bladder.

[4] See McGarty Prostate Cancer Prognosis, (Oct 2015) http://www.telmarc.com/Documents/White%20Papers/128PCaTests.pdf

[5] See Bard et al, pp 83-89. The use of MRI for screening has certain advantages but the ability to be specific is still wanting.

If we compute volume percent on the three lesions we obtain the key elements below:

1. Total prostate volume of 79 cc.
2. Lesion 1: maximum length 14 mm and minimum length 11 mm for volume of 1.02 cc or 1.29% of prostate volume.
3. Lesion 2: maximum length 11 mm and minimum length 10 mm for volume of 0.61 cc or 0.77% of prostate volume.
4. Lesion 3: maximum length 6 mm and minimum length 6 mm for volume of 0.11 cc or 0.14% of prostate volume.

Note that only Lesion 1 has volume slightly greater than 1%.

Also if we examine the PSA to volume ratio we observe that in initial presentation it was 2.1/60 cc or 0.035 and the most recent was 3.2/79 cc or 0.040. Yet as already noted the %free remained well into the 30% range.

An integrated MRI/Ultrasound 18 core biopsy was performed. The biopsy results were all negative[6]. There was no HGPIN, and no inflammation. The prostate size had increased to 80 cc which could have accounted for some of the PSA increase.

The results of the biopsy were all benign. The details are as follows:

A. Prostate, right lateral base, biopsy: Portions of fibromuscular stroma and blood clot, negative for malignancy.
B. Prostate, right lateral mid, biopsy: Portions of fibromuscular stroma and blood clot, negative for malignancy.
C. Prostate, right lateral apex, biopsy: Benign prostate with focal atrophy.
D. Prostate, right base, biopsy: Benign prostate and seminal vesicle.
E. Prostate, right mid, biopsy: Benign prostate.
F. Prostate, right apex, biopsy: Benign prostate.
G. Prostate, left lateral base, biopsy: Benign prostate.
H. Prostate, left lateral mid, biopsy: Benign prostate.
I. Prostate, left lateral apex, biopsy: Benign prostate with focal atrophy.
J. Prostate, left base, biopsy: Benign prostate with focal atrophy.
K. Prostate, left mid, biopsy: Benign prostate.
L. Prostate, left apex, biopsy: Benign prostate.
M. Prostate, right posterior central zone, biopsy: Benign prostate and seminal vesicle.
N. Prostate, right anterior transition zone, biopsy: Benign prostate with focal atrophy.
O. Prostate, left posterior transition zone, biopsy: Benign prostate with very focal lymphocytic inflammation and early healing fibrosis with adjacent fragment of normal glandular epithelium.

[6] See Bard et al pp 115-123. This is a fusion imaging technique using the MRI as a baseline and aligning the ultrasound to ensure targeting of the suspected areas.

The biopsy results are all clear of any malignancy. The soundness of the 4K test was confirmed in this specific case. The MRI did present some problematic regions but the MRI data is not diagnostic.

Figure 1: This shows the details of the PSA by time and the changes and velocity of the PSA. Many mens see similar results but these numbers may be reflective of many processes.

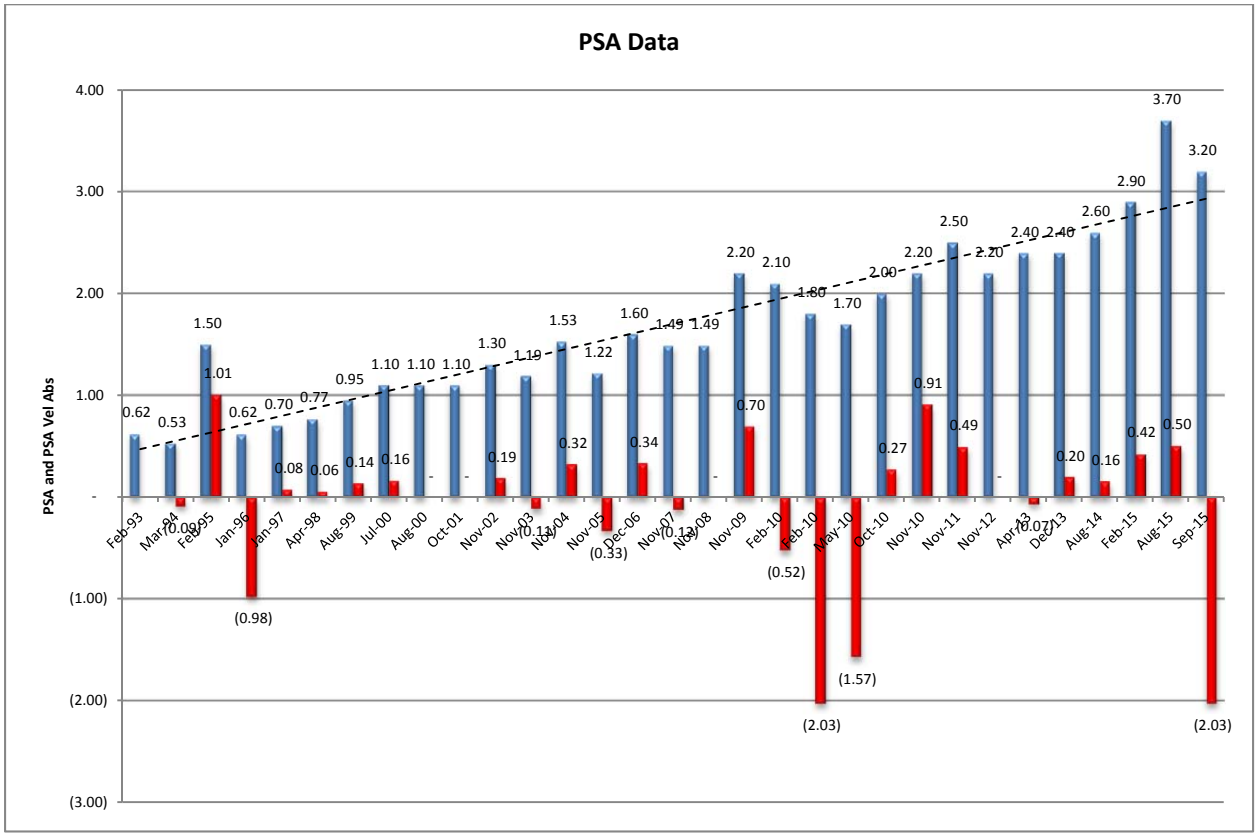


Figure 2: The data below show the % change of the velocity from reading to reading. Although there may appear to be an increasing trend there are many data points depicting a negative drop.

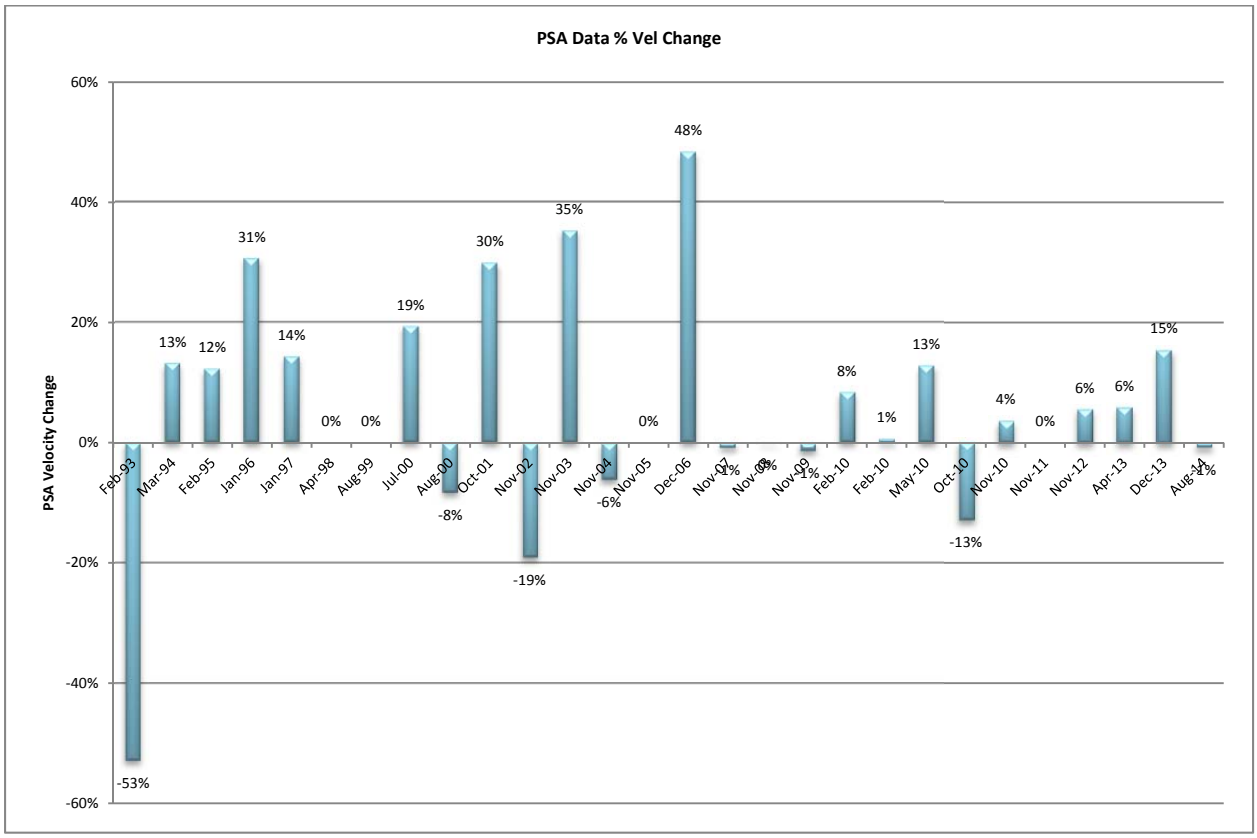
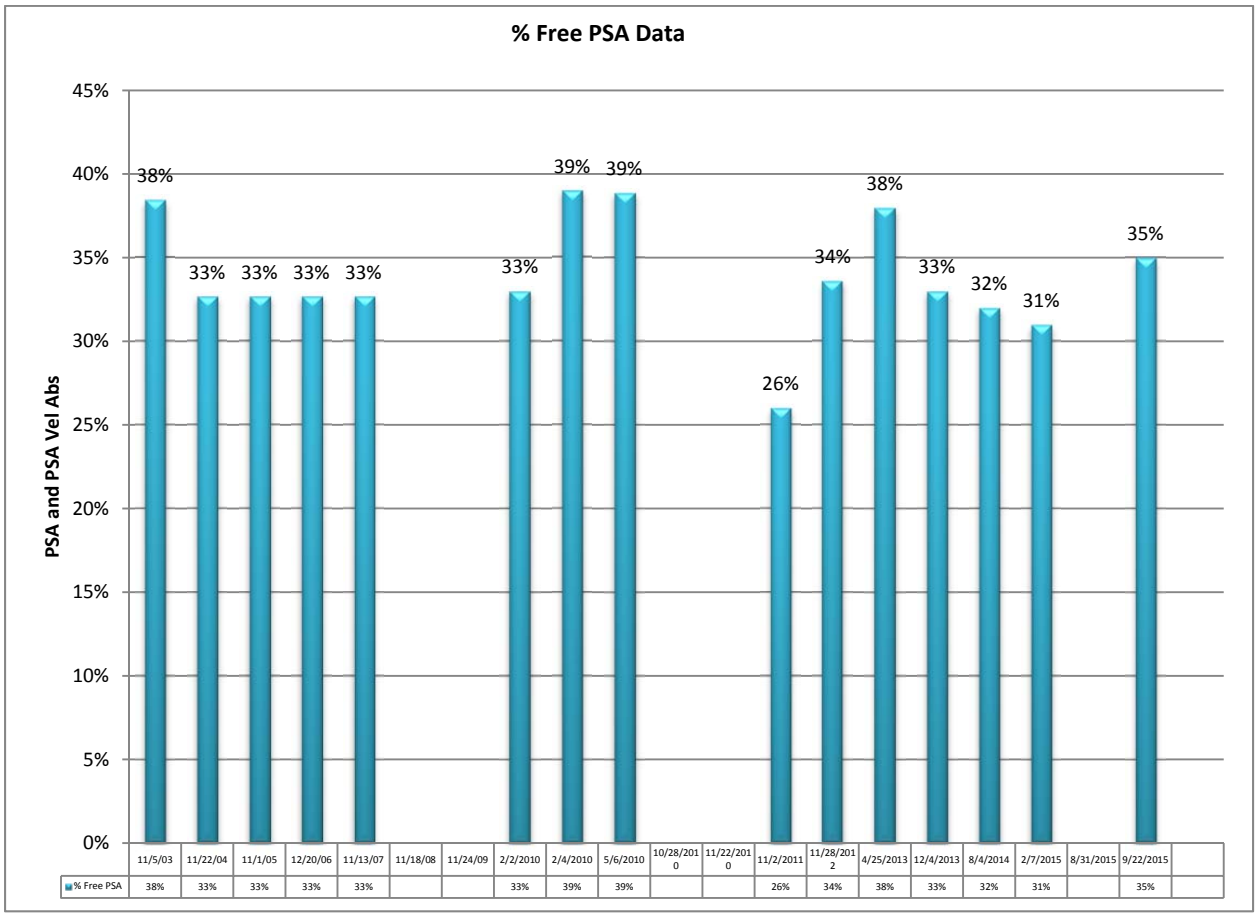


Figure 3: This is a presentation of the %Free of the PSA. Note its variability and the fact in this case it does not go anywhere near the 25% cutoff mark. PSA is volume dependent and %Free is cell type dependent. Thus an enlarging prostate may pari passu have an increasing PSA number but if the cells are benign the %Free generally appears to be high and somewhat constant.



3 BAYESIAN VALIDITY

The analysis that we have performed is predicated on a Bayesian model, namely that prior information will condition the probability of the specific outcome. For example if we have a family history, a prior HGPIN diagnosis, a sudden increase in PSA velocity then we should reasonably anticipated that the biopsy should yield a positive result. That is the essence of Bayes and it is predicated upon significant amounts of clinical data.

The 4K test, however, is predicated upon a sample at a specific time. As we have discussed elsewhere the 4K test uses several elements such as PSA, %free, KLK2, and prior biopsy data. It does not take into account the patient's temporal changes in PSA nor family history. Thus based upon a single point sample, albeit including prior biopsy results, the 4K yields a fairly reliable prognostication of the outcome of a biopsy at a time proximate to the test.

The key question is; what value does prior information have regarding the outcome of a prostate biopsy? We know that PSA alone is problematic. We also know that velocity can be reflective of growth, albeit not of malignancy. We know that %free is a measure of patency of the tissue but is also not totally prognostic.

Thus tests like 4K may be helpful to manage problematic cases described herein. Perhaps the greatest risk is the legal risk to the physician. Relying on a prognostic test that has a margin of error and having a patient who may not be fully informed and accepting of the risk can be a serious concern. The problem of course is that even with an unremarkable biopsy there is still a risk of there being PCa which goes undetected.

The conclusion for any Bayesian test is that all results are probabilistic and short of a prostatectomy for every patient putatively at risk there is no assured process.

4 CONCLUSIONS

PSA has been argued to have little merit in the diagnosis of PCa. However it is currently the standard available. Recently other diagnostic or prognostic tests such as 4K have been introduced but not yet accepted by the FDA.

Let examine this case as the data was received over time:

1. Increasing velocity and family history led to a reasonable suspicion of the potential for PCa.

2. Biopsy confirmation of highly dispersed HGPIN raises the potential for PCa in a short period of time. Now with family history, PSA velocity, and HGPIN, the chance for a subsequent PCa is substantial.

3. A second biopsy devoid of any HGPIN may be a comforting finding but since biopsies sample at best 2% of the prostate this does not materially reduce the chance of subsequent findings and thus ongoing diligence is recommended. Namely continue PSA monitoring.

4. The sudden increase in PSA in one year is not a problematic presentation. Given the family history, the actual PSA velocity and previous HGPIN a biopsy is recommended.

5. The 4K test is an adjunct but may have substantial merit. The low value, <1%, seems to indicate that watchful waiting may be the best next step. However this is not yet FDA approved.

6. The concomitant MRI and its findings however reset the concern. Three lesions, albeit small, 1% and less each on volume, do not appear to be a concern in themselves but given the other factors they do present a necessity for a biopsy of those regions and others.

7. The negative biopsy substantiates the 4K test but it also demonstrates the complexities of dealing with PSA measurements.

We know that men in their 70s have a high risk of even low grade PCa. Thus given the previous conditions in this case one would not have been surprised of even a low grade PCa. This would especially have been the case give a prior HGPIN six years ago.

Thus the question should be; how does one manage this type of case going forward? The three biopsies were all justified in a Bayesian sense give the clinical data available. However what should be the best course going forward? Perhaps a monitoring of PSA with %Free and an annual 4K. There are no clinical trial data that confirm the best path forward and thus it must be done on a case by case basis and with consultation between patient and physician.

In a recent paper by Welch et al they describe three cancer paradigms:

1. Halstedian: … *attributed to William Stewart Halsted, which holds that cancer arises at a single location, grows there, and eventually migrates to local lymph nodes and then to more*

distant organs. If the Halstedian paradigm is correct, effective screening should allow cancers destined to metastasize to be identified at an earlier stage and reduce the incidence of cancers that first present as metastatic disease. This is the classic clonal theory which states that cancer starts and stays in a location until enough mutations occur that drive it outward. Prostate cancer in general follows this course, but not for all.

2. Fisherian: *The lack of change in the incidence of metastatic disease is consistent with the hypothesis that breast cancer is a systemic disease by the time it's detectable — a paradigm typically attributed to Bernard Fisher*. This means that the cancer systemically occurs and is present in multiple locations ab initio. This is the paradigm envisioned for breast cancer. This however does not align with DCIS in the breast which is akin to a lower grade Gleason cancer.

3. Hellmanian: *Samuel Hellman proposed a third paradigm: that for each type of cancer there are multiple paths to metastasis. Aggressive, poorly differentiated cancers tend toward the Fisher paradigm; localized, well differentiated cancers tend toward that of Halsted.* In reality cancers often follow a mixed path.

In the case discussed above the question is: in subsequent follow up, what mindset should be dominant?

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