Urology Case Reports 7 (2016) 64–66

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Elevated Prostate Health Index (*phi*) and Biopsy Reclassification During Active Surveillance of Prostate Cancer

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ARTICLE INFO

Article history:
Received 11 April 2016
Accepted 18 April 2016

Keywords:
Prostate cancer
Biomarkers
Active surveillance
Prostate biopsy

ABSTRACT

The Prostate Health Index (*phi*) has been FDA approved for decision-making regarding prostate biopsy. *Phi* has additionally been shown to positively correlate with tumor volume, extraprostatic disease and higher Gleason grade tumors. Here we describe a case in which an elevated *phi* encouraged biopsy of a gentleman undergoing active surveillance leading to reclassification of his disease as high risk prostate cancer.

Introduction

Active surveillance (AS) is one approach to reduce the overtreatment of indolent prostate cancer and is increasingly recognized as a primary management strategy for low-risk disease, particularly among older men. While adoption of AS has risen significantly,[1] there remains a lack of consensus regarding monitoring strategies (i.e. the frequency of biopsy, imaging and tumor marker ascertainment). The development of biomarkers for clinically significant prostate cancer can help guide patients and providers, particularly those who elect to defer routine surveillance biopsy.

At our institution, %free PSA has been routinely assessed in men on active surveillance. Since 2015 some providers have opted to utilize the Prostate Health Index (*phi*), which is calculated from total PSA, free PSA, and [-2]proPSA (Beckman Coulter, Inc.), during monitoring. Here we present the case of a gentleman on AS where *phi* was used to recommend biopsy, which resulted in disease reclassification.

Case presentation

The patient presented in 2005 at age 73 due to an abnormal rectal examination (clinical stage T2a) and serum PSA of 3.6 ng/mL. Twelve-core transrectal biopsy showed Gleason score $3+3=6$ prostate cancer involving 20% of one core, and a prostate volume of 66 cc (PSA density = 0.05). As such, the patient was diagnosed with NCCN low-risk prostate cancer. After appropriate counseling with his provider, the patient elected to undergo monitoring on AS.

Confirmatory biopsy 1 year from diagnosis revealed Gleason score 6 disease in 10% of one core, consistent with his diagnosis of low-risk disease. Subsequent biopsies in 2007 and 2008 demonstrated no evidence of cancer and his rectal exam was unchanged. Although not consistent with our institutional AS protocol, at this time the patient elected to defer annual biopsy in favor of serial PSA and clinical examination.

Follow-up serum biomarker and prostate biopsy data are listed in Table 1. In 2010, serum PSA was 2.7 ng/mL with 42.1% free PSA. Subsequent PSA levels remained less than 4.0 ng/mL until a value of 5.6 ng/mL was detected in 2014 – 10 years after diagnosis (Fig. 1). Follow-up testing in 2015 revealed a serum PSA of 10.4 ng/mL with 41.1% free PSA; an initial *phi* was obtained and found to equal 96.0. Serum markers were confirmed on a subsequent measure, and at the insistence of his provider, the patient agreed to undergo repeat biopsy, which revealed extensive cancer in 10 of 12 cores. The

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http://dx.doi.org/10.1016/j.eucr.2016.04.012

Table 1
Biomarker measures during follow-up

	2/2005	2/2006	2/2007	3/2008	9/2010	8/2011	9/2012	8/2013	8/2014	9/2015	10/2015
PSA total (ng/mL)	3.6	2.4	2.6	2.3	2.7	3.2	3.5	3.4	5.6	10.4	11.1
% free PSA					42.1	36.6[a]	38.1[a]			41.1	39.7
phi						32.9[a]	36.9[a]			96	99.6
Biopsy	X	X	X	X							X
Volume	65.5	68.5	65	61.5							74
PSAD	0.05	0.04	0.04	0.04							0.15

[a] Indicates retrospective assessment of stored laboratory specimen.

maximum Gleason score was 4 + 5 = 9, and 7 cores contained high-grade (i.e. Gleason score 8–10) disease. Bone and CT scans showed no areas of uptake or lymphadenopathy concerning for metastasis. The patient was offered localized treatment options and opted to undergo radiation therapy.

Discussion

Phi was FDA approved in 2013 to aid in decision-making regarding prostate biopsy and has since become available for clinical use.[2] While *phi* has been associated with Gleason score, non-organ confined disease, and upgrading at radical prostatectomy,[2,3] there are limited data exploring the use of *phi* in an AS population, particularly over long-term follow-up.[4] We herein report the case of a gentleman with disease reclassification while on surveillance which correlated with an elevation in his *phi*.

Several tools have been described to assist in clinical decision-making for individuals such as this gentleman who elected to defer routine surveillance biopsy. These tools include PSA kinetic measures, % free PSA, prostate MRI, and urinary biomarkers.[4,5] Fluctuations in PSA during surveillance have not been shown to reliably predict reclassification,[6] although in some instances rapid PSA doubling can indicate disease progression.[4] Percent free PSA and PSA density have also been used to assess risk during surveillance. This case points out limitations in the use of these metrics, given the patient's free PSA remained extremely favorable at over 35%, and his PSA density was 0.15 at its highest value.

Contrary to the free PSA, the *phi* value of 96.0 best reflected the higher-grade cancer present at the time of assessment. This begs the question as to whether earlier *phi* measures could have prevented this adverse outcome and suggests an area for further study. Certainly, additional research is necessary to better understand cases in which available biomarkers are discordant, as well as to identify those cases in which one marker could prove optimal. Until these and other non-invasive tools are tested and validated in the AS population, this case further supports the necessity of more intensive monitoring techniques such as repeat prostate biopsy.

Conclusion

The utility of *phi* and other non-invasive markers in the AS setting remains unclear, largely secondary to a lack of long-term data. There is hope that combining these markers with other tools such as multiparametric MRI may allow for a less-invasive approach to monitoring men with prostate cancer. Until an alternative approach is validated, however, we must acknowledge the substantial risk associated with deferring prostate biopsy over an extended period.

Conflicts of interest

The authors declare no conflicts of interest.

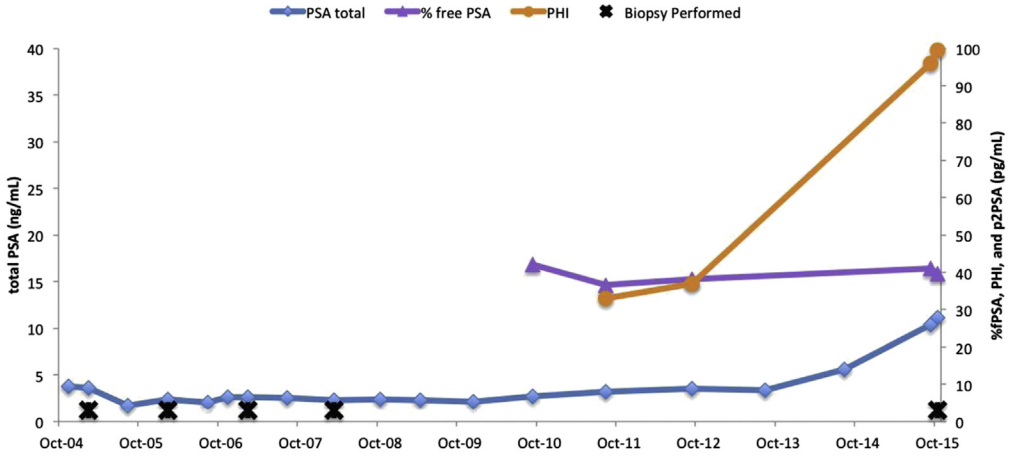

Figure 1. Trends in biomarker measures during follow-up.

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