The Debate on Prostate Cancer Screening: What Does the Wisdom from the Old Books Whisper?

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Abstract

Prostate cancer is a prevalent problem in male healthcare. The previous decades have witnessed some significant improvements in the knowledge of aetiology and pathology, as well as practice of screening, treatment, and follow-up of the disease. A downstaging at the time of the diagnosis and increase in the survival were vivid with the advancements, albeit the screening of the disease using regular prostate specific antigen measurements was previously debated. In this paper, the authors aimed to inform the reader on the course of the prostate cancer along a century by sailing along the chapters of the old urology textbooks.

INTRODUCTION

Textbooks are the cornerstone of education. In conjunction with civilised society and the initiation of modern printing techniques, they have become a kind of joint monument of humankind, manifesting the era in which the books were written.[1] From the perspective of prostate cancer investigators, the authors would first like to provide the reader with an additional point of view on the effects of the modern approach to treating prostate cancer, by tracing the course of the disease through textbooks from different decades, and then discussing the place of the prostate-specific antigen (PSA)-focused prostate cancer screening on ageing males' healthcare.

As one will clearly realise from the referred narratives, prostate cancer was a major concern in the healthcare of an ageing male, which is quite akin to today's world, while even archaeological evidence suggests that the disease has always been a valid problem that might have been the culprit of mortality.[2,3]

COURSE OF PROSTATE CANCER DIAGNOSIS, TREATMENT, AND PROGNOSIS OVER DECADES

History has witnessed some merges in the practice of handling an individual with a prostate cancer diagnosis. The variance is not only evident for the treatment modalities; the paradigms of the diagnostic approach have also evolved over time.[4,5]

Harry C. Rolnick's two-volume textbook, *The Practice of Urology*, had its roots in Rolnick and Daniel N. Eisendrath's collaborative reference

book *Urology*, which was initially published in 1928.[6] The company made further publications of the book in 1930, 1934, and 1938.[7-9] When *The Practice of Urology* was published in 1949, it praised Huggins' research on the effect of hormones on the prostate and significant amount of phosphatase enzymes in the gland.[10] They classified malignancy into three distinguished types, namely the inflammatory, disseminating, and scirrhous types, which are entirely irrelevant to the current classification. The clinical presentation was defined as having dramatic symptoms, while the diagnosis was recounted to be based on surgical removal of the organ after a suspicious prostate examination per rectum. Serum acid phosphatase measurements, which further evolved into PSA measurements, were proposed to have both diagnostic and prognostic value. Yet the author conceded that the diagnosis was often too late to undertake surgery, which was the only curative method during the era.[10]

Meredith F. Campbell had created a legacy in urology with his comprehensive work titled *Urology*, first published in 1954.[11] After his death in 1969, the tradition continued with the name *Campbell's Urology* until the 9th edition. The bible of urology was kept alive in the name of *Campbell-Walsh Urology* in the 9th–11th editions, while the contemporary edition honours the names of Campbell, Walsh, and Wein.

The 2nd edition of *Urology* by Campbell has a well-sourced chapter for 'Carcinoma of the prostate', authored by William W. Scott, and William N. Toole.[12] The authors cited prostate cancer as the third-leading cause of cancer mortality, with an uncertain aetiology, and a diagnosis solely based on a rectal examination. Biopsy amenities were also restricted; thus, a surgical biopsy was prevalent. They further reported that their journey with operable prostate cancers started with 5.1% in 1949, and the rates rose to 19.0% in 1958 by careful and widely performed prostate examinations and biopsies. They concluded that a 5% rate of operability within the USA was a reasonable figure. Hypophysectomy and adrenalectomy, which seem ridiculous today, were discussed in the text, along with periprostatic radioactive gold injections and endocrine therapy. As a corollary to the diagnosis of the disease in its late phase and insufficient treatment stances, the authors summarised the chapter by citing prostate cancer as a common disease with an unknown aetiology, and often a lethal result.[8]

On the other side of the Atlantic, John Blandy announced his book, *Urology*, which was published by Blackwell Scientific Publications in the UK in 1976. Blandy co-authored the 'Carcinoma of the prostate' chapter with Kenneth E.D. Shuttleworth.[13] They came around with the previous authors on the late presentation of the disease that is characterised by either the symptoms of urinary outflow obstruction or metastases. They described rectally positioned hand-guided transperineal or transrectal true-cut prostate biopsy techniques, as well as radical retropubic prostatectomy. Interestingly, they illustrated a bladder wall tubularisation procedure to overcome post-prostatectomy incontinence, and they proposed a pelvic exenteration procedure in the treatment of prostate cancer in the name of super radical prostatectomy.

Even the awareness of the disease seems to affect the course of the disease onward two decades between Rolnick's *Urology* to Blandy's *Urology*.[14] The Blandy text debates the situation of early-diagnosed prostate cancer, which is thought to be a matter of active surveillance or radical treatment, as well as some cases that may not necessitate any intervention during their natural lifespan, which is considered for watchful waiting in contemporary practice.[13]

DISCOVERY, ANNOUNCEMENT, USAGE, AND CONTROVERSIES OF THE PROSTATE-SPECIFIC ANTIGEN

Arguably, the most prevalent discovery affecting the clinical approach to an either a patient or a healthy senior who admitted for regular screening, is a type of protein that is most widely known as PSA. This protein was heralded by independent researchers in slightly different steps of the discovery. At least nine prominent scientists were involved in the distinguishing, description, and purification of the molecule during a 20-year period between 1960 and 1980.[14] However, even the labour of the molecule has some controversies.[15]

Despite its non-specific nature, PSA was swiftly engaged in the urologists' armamentarium and become a valuable tool in the diagnosis, risk-

grouping, observational management, as well as the post-treatment follow-up of a patient who has or is a candidate for having prostate cancer. Furthermore, PSA measurements were initiated to being obtained from asymptomatic seniors, and the practice found itself a place as a population screening tool. The screening was either offered or discouraged from time to time by public health institutions or urological associations due to the available evidence.[16]

The contemporary clinical guideline of the European Association of Urology (EAU) endorses offering a risk-adaptive screening approach focused on the risk groups and life expectancies, while the American Urological Association (AUA) also underlines the importance of a screening strategy, weighing the risks and benefits as well as using a shared decision-making approach. Both associations are compatible with each other's conception on avoiding PSA screening in subgroups who may get more harm than benefit from the treatment, and will probably get no benefit from an active treatment modality in his natural lifespan.[17,18]

The National Comprehensive Cancer Network (NCCN) is also in favour of practicing an early diagnosis strategy for well-informed individuals who are in risk groups and/or would benefit from the early diagnosis.[19] On the other hand, the United States Preventive Services Task Force (USPSTF) made an official statement against routine PSA screening in 2008 and 2012, which was revised to make a decision considering possible benefits, and building an informed decision-making strategy for small groups in 2017. The final decision of the USPSTF in 2018 still underlines the potential of a small benefit, which is not always prevalent, and which may bring harm together.[20]

CONTEMPORARY EVIDENCE AND DEBATE ON THE PROSTATE CANCER SCREENING USING PROSTATE-SPECIFIC ANTIGEN IN ASYMPTOMATIC SENIORS

There is a high level of evidence on the benefits, or the possible harm, of PSA-based prostate cancer screening. For the attention of the reader: the discussion and the debate are on the role of PSA-based prostate cancer screening on a population level, though it should not be confessed with the role of PSA measurements in symptomatic individuals.

Bartsch et al.[20] pioneered the field of prostate screening studies with their valuable work in Tyrol, Austria. Their study compared the mortality rates and oncological stages between Tyrol, a federal state with a newly-implemented PSA screening programme, with the rest of the country in which there was no kind of screening offered during the study period. Their non-randomised study started in 1993, and the results were announced in 2001. They reported a nationwide reduction in mortality as well as a downstaging of the disease. Moreover, the reduction and the stage migration in Tyrol was reported to be better respective to the rest of Austria during this study period. Further updates of this study are also published, and it is reported that an ongoing reduction of mortality was relevant in this studies' population even after 10 years of follow-up.[21,22]

The initial randomised evidence is made available by Labrie et al.[23] with their 11-year long study. The Quebec study randomised more than 46,000 males to either screening (over 30,000 males) or non-screening (the remaining population). Overall, they reported more than a 60% reduction in prostate cancer-specific mortality, which was quite spectacular, and criticised in the subsequent papers.[24]

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial can be clearly considered as a milestone, considering its extensive targets, in both prostate cancer research and the field of medical oncology. This study randomised more than 75,000 males in screening and non-screening arms with very close number of individuals in both groups. With a high compliance to the screening which is a little over 80% and 10 years of follow-up, the researchers reported similar prostate cancer mortality rates in both groups.[25] Unfortunately, despite its well-planned initiation, the data of the PLCO study is reported to be missing some essential requirements to draw a reliable decision of the screening.[26]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) study can be considered as the most undistorted data

with the highest level of evidence we have in contemporary literature.[27] Participant groups also published the district data from participant countries of the ERSPC, which is quite valuable in evaluating the patterns of screening and the clinical results in different European countries.[28-30]

Furthermore, 13 and 16 years of follow-up data from the ERSPC was also published.[31,32] This study successfully enrolled and followed up more than 180,000 males from seven countries, and the ERSPC data showed a substantial reduction in prostate cancer specific mortality at 9, 12, and 16 years of follow-up. The benefit is far more remarkable in some participant countries, namely Sweden, for instance.[30]

The USA data also approved the findings of the ERSPC. Howrey et al.[33] made a retrospective analysis of data from 1,067 counties and reported that 61 deaths were prevented between 1998 and 2006 for every 100,000 males receiving a PSA test in 1997. The same PSA test number resulted in 1,597 males undergoing prostate cancer treatment during the same period. Thus, they concluded that the PSA-based prostate cancer screening resulted in a notable increase in prostate cancer diagnosis and treatment. However, the overall reduction mortality was modest at best, and they pointed out the risk of overtreatment and overdiagnosis in exchange for the modest reduction in mortality.

FROM HISTORY TO TODAY: WHERE ARE WE NOW?

Since the late 1980s, PSA has been used in the diagnosis of prostate diseases, either benign or malign. This test was approved by the U.S. Food and Drug Administration (FDA) in 1994 and is widely adopted by urologists in their daily practice. Since then, extensive usage of PSA levels in evaluation of healthy senior males started to affect the course of the disease. As mentioned above, the disease has long been a leading cause of mortality with low chance of surgical cure.

About three decades after the approval of PSA for use in the routine clinical practice by FDA, the last edition of the urologic bible, *Campbell Walsh Wein Urology*, comprehensively discusses the aetiology and pathology of prostate cancer with a special emphasis on providing a management strategy to patients without leading to any harm.[34] It is now argued that more diagnoses are made or are made earlier than needed, causing damage for the sake of treating the cancer or leading to the stress of individuals because of continual screenings. All this confirms that what has been done in the clinical evaluation of prostate cancer has commutated a lethal monster to a domestic beastie.

Of course, all of the achievements cannot be attributed solely to PSA screening. During this period, oncological care, surgical care and approaches, preventive measures in the healthcare systems and, overall, technology and life quality have all improved. However, the authors still think that this screening is the leading factor during the presented timeline that changed the practice of care for patients with prostate cancer. In the light of their journey through the urological texts, the authors again propose that the prostate screening collaborating with PSA measurements should continue, while the research on the management of the disease and application of the screening to different populations should also continue to serve the best practice we can provide to patients.

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