Towards a better Diagnosis of Prostate Cancer: A Review of Prostate Cancer Screening Tests

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ABSTRACT

Being one of the commonest cancers amongst males, better diagnostic or screening techniques can prevent lot of mortality and morbidity. Prostate cancer is one of the few cancers with better outcome if diagnosed early. Although current screening tests tends to produce more false positives, still they remain mainstay for the better management of prostate cancer. Lot of dilemma surrounds the specificity of Prostate Specific Antigen (PSA) as an effective tool for screening tool for prostate cancer. Number of other tools like TRUS, MRI, Biopsy, Stockholm 3 Model and Prostate Cancer Antigen 3 are now available for screening and diagnosis of the condition. It is a time to take an integrated approach for reducing the false results. Present article represents various modalities along with their pros and cons available for the diagnosis and screening of prostate cancer.

INTRODUCTION

The cancers are posing challenges for every country in terms of mortality, morbidity, economic loss and social dissociation. It has been observed that the "lead time" or the duration between the time when a cancer is diagnosed by a conventional test and the time when a cancer is detected by a screening test, plays a major role in prognosis. It is basically an advantage offered by the screening test. One of the commonest cancers observed amongst males is the prostate cancer.[1] It is the leading cause of mortality amongst males.[2] With ever increasing screening modalities it has also become a most commonly diagnosed cancer also in certain countries.[3] Just like with most cancers, screening test play a significant role in reducing mortality.[4,5] Screening for Prostate cancer has a rich history, right from the mid-1980s. The Prostate Specific Antigen (PSA) has been the main stay for prostate cancer screening since long. Enough evidences have been gathered to show that the elevated levels of PSA can be linked to cancer. However, prostate cancer screening with the PSA has been one of the most controversial issues when it comes to screening for cancers.[4-6] This is due to the fact that the elevated levels of PSA can also be caused by a wide range of other potential disorders as we would see in detail later. This makes PSA screening test to have a low specificity in diagnosing prostate cancer. This is implicated in over diagnosing and over treatment leading to increased physical, mental and economic burden on the patient. This is why even though PSA screening has played a significant role in the diagnosis of prostate cancer many still believe that better methods need to be employed in order to address the fall backs of this screening test. In the same vein, studies have shown that despite hundreds of diagnosis being made

only a few patients die from prostate cancer.[7] About 98.9% of 5 year survival rate was recorded in patients who were diagnosed of prostate cancer between 2005 and 2011 in the US. Current article aims at evaluating some conventional screening tests of prostate cancer, as well as more recent ones that are claimed to have a better sensitivity.

MATERIAL AND METHODS

More than 100 resources were sought for the review of the subject, which included published articles from indexed journals, articles from renowned medical information sites, published reports of research agencies and guidelines published by various recognised associations. Following screening of, 27 sources were finalized for the abstracting the information. The care was taken to include recent as well as older sources with relevance to current scenario. The same have been referenced where ever applicable.

RESULTS

Although many diagnostic modalities are available for the prostate cancer, not all of them are suitable as screening tests.

Characteristics of the ideal screening test
An ideal screening test must have certain properties for it to be a successful. Below is a list of such characteristics.[4,8]
- The test must be sensitive enough to detect the diseased even while asymptomatic.
- The application of test must lead to relative risk reduction.
- The application of the test should ultimately result in gain in life expectancy of the patient.
- The screening test should be affordable or cost effective to most patients and the service provider.
- The cost per life saved because of application of the screening test should be acceptable.
- There should be gain in quality-adjusted life years after successful application of the screening test and treatment.

The above characteristics would be the lens through which

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the current article reviews the various screening tests that shall be discussed below. The objectives of a good screening program can be summarised in two points, the first is its ability to detect the disease at an early enough stage when treatment is possible and the second is the identification of risk factors and employing its use in disease prevention.[8] There are other factors that also play a role and must be employed to maximize the benefits of a screening tests and the potential for clinching an appropriate diagnosis. There are different studies that have been carried out to determine some of them. For example, the age range for patients to be screened, their race and family history all play a role in the aetiopathogenesis of prostate cancer and thus should be considered in prostate cancer screening as we would see below.

Screening and Diagnostic Tests for Prostate Cancer
Medical History and Physical Exam

A thorough medical history and physical examination by a skilled person itself has a great sensitivity of identifying the condition involving enlarged prostate, which can be confirmed by subsequent tests. In earlier stage, it may not be sufficient enough to diagnose the condition, but it does lead to the right protocol to be followed for the diagnosis of prostate cancer. History taking such as the age[9], race and family history[10] of the patient or the presence of lower urinary tract symptoms[11] could point the physician in the direction of a prostate disease that necessitates further screening test. Of course the first screening test is the Digital Rectal Examination (DRE).[12] Here the physician inserts his gloved and lubricated finger into the patient's rectum to feel for any enlargement or mass in the prostate. This is a major pointer to prostate disease although not entirely specific for different reasons. First an enlargement in the frontal part of the prostate may not be felt on DRE and also an enlarged prostate is not in itself sufficient to diagnose a malignancy.[13]

Prostate Specific Antigen (PSA) Blood Tests

In the year 1986 the prostate specific antigen test became the hallmark of prostate screening tests and it has revolutionized prostate cancer screening for the past 32 years. Its utility has, however, been marred by controversies following series of researches that question its sensitivity strongly. As mentioned earlier "sensitivity" is the backbone of any ideal screening test. The PSA is secreted from the epithelial cells that line the prostate gland. It is usually found in minute quantities in the serum of a healthy man which is elevated in malignant disease of the prostate as well as other prostate conditions like infection (prostatitis) and benign prostatic hypertrophy. The normal PSA serum levels in a healthy man have been placed in the range of 0-4ng/mL.[14] This is such that anyone with a PSA level of greater than 4ng/mL was considered to be at risk of prostate cancer and would require further investigation like a prostate biopsy.

Trans Rectal Ultrasound (TRUS)

The Trans Rectal Ultrasound is one of the screening and diagnostic tests used for prostate cancer. TRUS, alone has never been considered as a screening test. It is almost always used in conjunction with the PSA test or following a DRE. It has the benefits of being quick and being minimally invasive. But it is also not diagnostic. It can, however, be a guide with both screening and therapeutic functions. The procedure involves the insertion of a lubricated probe the size of a finger into the rectum of the patient which transmits echoes to a computer screen helping the physician to visualize the prostate. It can be used to delineate the size of the prostate gland as well as estimating the PSA density. It can also be used to guide prostate biopsy needles during a prostate biopsy.

Prostate Biopsy

As such, biopsy is not a screening test as it would fall short on the point of "acceptability" and "affordability". This is referred to as the gold standard in prostate cancer diagnosis. However, it is never used as the first test applied after a clinical examination. It is an invasive procedure and makes use of histological techniques carried out on a biopsied prostate tissue to make the diagnosis of prostate cancer. Because it is invasive it is only used in patients who have a high chance of having prostate cancer from the aforementioned screening test. This includes patients with enlarged prostate on DRE, elevated PSA levels and PSA density from TRUS. It is usually done through the aid of a biopsy needle passed through the rectum to obtain prostate tissues which are then sent to the histology lab to be viewed under a microscope. This further buttresses the need to have better screening tools in place as it will significantly reduce the need for prostate biopsies in patients who may not need it.[13,15]

Recent Screening Techniques

There are some new screening tests for prostate cancer which are being considered strongly for screening and been looked into because they help to alleviate most of the problems and setbacks of the aforementioned prostate cancer screening tests.

Prostate Cancer Antigen 3

The prostate cancer antigen 3 (PCA3) is a gene that is overly expressed when there is presence of a prostate malignancy. This makes it an ideal tumor marker for prostate cancer. A lot of patients with abnormal PSA and prostate volume tend to still have normal biopsies.[16] For these patients the PCA3 would be of great help as it is independent of prostate volume and it has a higher specificity for prostate cancer when compared to the PSA.

Magnetic Resonance Imaging (MRI)

This is usually done when screening test is suggestive of a cancer. It is used to delineate the prostate and it can also reduce the need for needless biopsies. However, the TRUS is preferred over MRI as it has more benefits and the cost of the MRI scan makes it not first line for most physicians. When employed, however, it can help in leading to a more accurate diagnosis of prostate cancer.[17,18]

Shear-Wave Elastography (SWE)

The shear-wave elastography is a new screening test for prostate cancer which different studies are showing may

L2

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help provide the leap needed towards a better diagnosis of prostate cancer. The study done by a team from Dundee University showed that this ultrasound method which is non-invasive, is far more accurate and reliable in the diagnosis of prostate cancer. This scan method according to the study can detect cancers that even the MRI could not. This in itself shows the potential of the SWE. Nevertheless, the test still needs to be subject to more extensive trials using a larger sample size to be able to accurately compare it to the aforementioned screening tests. Nevertheless, it no doubt provides a pathway towards better screening tests for men's most popular cancer.[19]

DISCUSSION

It is noteworthy that benign prostatic hyperplasia also produces similar lower urinary tract symptoms as prostate cancer. To add on this, benign prostatic hyperplasia can give similar findings on digital rectal examination. This in itself is a drawback to the use of history and examination as a potential screening tool; especially when viewed from the lens of the characteristics of an ideal screening tool. There is also paucity of research to show appropriately the sensitivity of DRE in prostate cancer screening as most studies look at it in combination with the prostate specific antigen (PSA) test which we will look at next.[20] The acceptability of the DRE also poses a major hurdle to its use as a screening test.

It was said that the males between ages 55 to 65 years would benefit from PSA blood test as a part of screening, but this was not without its many draw backs. First, the poor sensitivity of the PSA screening test owing to the fact that about 70% of false positive results are due to either infection or BPH. This led to over diagnosis and most times unneeded treatment of patients with undesirable complications and anxiety.[21] Some studies have found sensitivity, specificity and positive predictive values as 21%, 51% and 30% respectively.[22] This has been a major drawback to the use of PSA as a screening tool and even though some studies have tried to question its role on account of this, it is still generally regarded as a helpful preliminary tool. With improved understanding of the aetiopathogenesis of prostate cancer, the rate of over diagnosis has been reduced compared to the 80s, when the screening test was first introduced. Nevertheless, PSA screening tests is still surrounded by doubts and suggestions of improving it with other strategies like PSA density, free PSA and the velocity of PSA. However, these recommendations have not been properly reviewed by a randomized controlled study and hence little data is available as to the usefulness.[13,23]

For patients with prostate cancer, TRUS can help in cancer staging which would also affect modality of treatment of these patients.[13,23,24] One of the meta analysis has shown the sensitivity, specificity and positive predictive values as 51%, 59% and 41%, which are better than PSA levels.[25] The low acceptability by the patient due to discomfort and bleeding is also a major drawback in using it as a screening test.

The reason of mentioning biopsy in the middle of screening tests is to emphasise that a screening test must be followed by a diagnostic test. It would greatly reduce the burden on patients and health system without missing the cases of prostate cancers in the community.

Stockholm 3 Model

A new screening model for patients of prostate cancer was developed following a research carried out on about 60,000 men in Sweden. This Stockholm 3 (S3M) test aims at reducing needless biopsies which usually results from the use of PSA screening test alone. S3M makes use of analysis of over a hundred genetic markers, about 5 protein markers and clinical data in screening patients. Gronberg et al, have described details of the S3M scoring but it uses different clinical history like age, family history of prostate cancer in a first degree relatives and any previously done biopsy. In the blood biomarkers, there are the free and total PSA with their ratio, hK2 and MIC1. Prostate examination and the prostate volume are also considered. Usually a positive test requires referral to urologist. Different studies have shown the advantages of the S3M model which makes it to carry a better predictive value for prostate cancer. One is that it finds aggressive cancers in men whose PSA levels are low, it reduces the need of unneeded biopsies and its answers are simple enough to interpret.[26]

Unlike the PSA, the sample needed for PCA3 is urine and not the blood. The prostate is initially massaged by DRE and then the initial part of the urine is taking to measure the PCA3 levels. It suffices to say that the PCA3 has better positive and negative predictive values making it to reduce the need for unwarranted repeat prostate biopsies.[27]

CONCLUSION

The different screening modalities described above go to show the importance of prostate cancer screening. It should be said that work still needs to be done to better improve the sensitivity of these screening tests as this will help to greatly reduce having to carry out needless biopsies with its own many complications. Nevertheless, it cannot be overstated that we currently have improved modalities for screening prostate cancer that has greatly improved when compared to the genesis of prostate cancer screening. So there is no doubt a better future going forward for prostate cancer screening.

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Section: Pathology

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L4

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