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Review Article

Prevention and management of prostate cancer: A review.

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Abstract:

The purpose of this review article is to critically assess the prevention and management strategies of prostate cancer. There is also a marked decrease in the mortality rates of prostate cancer in developed countries, the reason is largely unknown, but it is being suggested that it could be due to the early identification of prostate cancer through prostate specific antigen screening and early aggressive therapy. The resistance spills over to the complementary medications such as the androgen inhibiting drugs, abiraterone, and enzalutamide, resulting in the form of cross-resistance. It is an obligation by care providers to counsel the people living with aging male prostate cancer on the importance of consuming healthy foods that will raise the odds of suppressing cancer development. The basis for settling on a restorative lifestyle prevention measure is because it is not associated with any risks compared to other alternatives. Regardless of the positive experience in using Prostate Health Index (PHI), the search for new biomarkers for the aggressiveness assessment of prostate tumors is still needed.

Keywords: Prostate Cancer, Biomarkers, Tumors, Prevention, Management, Prostate Health Index.

Introduction:

Literature search showed that prostate cancer contributes significantly to the overall burden of cancer globally by 1.6 million new cases. Among all cancers that affect men prostate cancer is commonest of all primarily in developed countries. In developed countries, the odds of developing prostate cancer at age of 79 years is one in six.[1] There is also a 40 -fold difference in age-adjusted incidence rates between African American men living in the United States (U.S.), who have the highest incidence rates, and Asian men who live in their native countries as the lowest.[2] The statistics themselves further attributes this to changes associated with lifestyle choices. Published literature indicates that when men, who are at low risk, when migrate to region having high-risk, the incidence and mortality rates increases substantially.[2] Fortunately, after initiation of Prostate Surface Antigen (PSA) screening in the early 1990s, detection of prostate cancer at early stage become possible; on the other hand, due to excellent sensitivity and specificity of PAS the proportionate rise in new cases found looks justifiable.[2] This simply reflect rapid shift at which the pathology is diagnosed early in contrast to past when PSA was not used as a biomarker.[2] This allows the patient to be diagnosed particularly early before the disease progresses to advanced stages, and most of the known new cases are found as localized pathologies.[2] The widespread availability of PSA has been shown to drive up global incidence rates, even in-areas of the world where PSA testing has not seemed to

take hold, for instance, Japan and other adjacent Asian countries.[3]

The mortality associated with prostate cancer is substantial. It is the fifth most common cause of cancer deaths globally, with an annual mortality rate of 366 000 deaths attributed to it alone.[2] Compared to the incidence rates mentioned above, the global variation in mortality rates is lesser at approximately 10-fold difference across countries globally.[2] The highest mortalities attributed to prostate cancer are among patients residing in the Caribbean and the Central and Southern African regions.[2] However, the lowest prostate cancer mortality rates are seen in patients in predominantly Asian countries. There is also a marked decrease in the mortality rates of prostate cancer in developed countries, the reason is largely unknown, but it is being suggested that it could be due to the early identification of prostate cancer early through PSA screening and early aggressive therapy. African countries that have limited support in terms of early diagnosis and treatment tend to display increased or high levels of prostate cancer mortality.[2]

Treatment Modalities:

Variety of treatments are available for the treatment of Prostate cancer. These regimens more effective provided cancer has not metastasized. Otherwise, palliative care is indicated. For any case of prostate cancer, the patient's age and Total Gleason Score of 6 indicate that the malignancy has the potential of spreading to the surrounding tissues, but the progression would be slow. The treatment modalities can be categorized either as pharmacological and non-pharmacological therapies.

Pharmacological Therapy:

Pharmacological management includes different hormonal therapies; that may be administered as a neoadjuvant or adjuvant drug before primary treatment.[4] This can be achieved by using androgen deprivation. Initial therapy can be initiated with leuprolide, goserelin, and other known luteinizing hormone-releasing hormone (LHRH) agonists. The therapy has to be preceded by anti-androgen therapy when the PSA levels are equal to or greater than 10ng/ml to dampen any clinical response resulting from a testosterone surge associated with this drug.[5] However, when a direct LHRH antagonist is used, for instance, degarelix, there is no associated testosterone surge.[5] Hormonal therapy has been shown to provide increased survival rate when combined with radiation therapy to treat localized prostate cancer.[4]

Chemotherapy is also a treatment option, although studies show that the role of chemotherapy, mainly in the management of localized carcinoma of the prostate, is not promising.[6] Docetaxel has been used as first-line therapy for prostate cancer for the longest time; it was initially used for palliative treatments to its current use as both a neoadjuvant and adjuvant medication.[6] Combinations of chemotherapeutic agents have been used extensively to search for the most effective combinations, but the results have been inconclusive.[5] Further studies also seem to corroborate the narrative of the inefficiencies of chemotherapy in prostate cancer management by suggesting the gradual development of resistance towards chemotherapeutic agents, particularly taxanes.[7] In addition, it indicates that the resistance spills over to the complementary medications such as the androgen inhibiting drugs, abiraterone, and enzalutamide, resulting in the form of cross-resistance.[8]

Non-pharmacological therapy:

Since the symptomatic presentation of prostate cancer starts to develop following the gross enlargement and subsequent spread of the tumor, various treatment modalities of surgery and radiation therapy are employed to offer comparable curative quality to prostate cancer management. Specifically for the presented case of suspected localized prostate cancer, the treatment options include radical prostatectomy (R.P) and radiation therapy (R.T.), which is delivered either as external beam radiation therapy (EBRT) or brachytherapy (BRT). Radical prostatectomy is the complete removal of the prostate gland and its adjacent lymph nodes to achieve a curative outcome. It is beneficial in managing an easily resectable tumor, and it is very dependent on the patient's compliance to undertake the surgery.[9] Furthermore, R.P. has better prognostic outcomes than active surveillance (watchful waiting) or palliative care in localized prostate cancer. Still, it carries a significant risk of developing various complications, for instance, urinary incontinence and erectile dysfunction being the most common.[10]

External Beam Radiation Therapy uses a linear accelerator to generate beams of high-energy X-rays to a tumor within the body. This technique is the most common, and it can be used in combination with other treatment modalities to achieve a cure. Although the benefits of the use of EBRT are slightly considerable, its use has been linked with a moderate increase in the development of secondary cancerous lesions following aggressive therapy.[11] With this knowledge, such risks should be communicated to patients before initiation of treatment.[11] The treatment plan used with EBRT depends on the response of the tumor tissues to radiation therapy. That is, tumors resistant to EBRT therapy should be given a high dose of radiation if it is indicated for them without the risk of developing severe complications.[12] Brachytherapy (B.T) is an internal radiation technique that utilizes either seed-like pellets, wire, or catheters that can be implanted within or around tumors to aid in the destruction of tumor cells through DNA damage.[13] The implants inserted can either be high dose rate temporary implants (HDR-BT) or low dose rate permanent implants (LDR-BT).[14] The use of either type of dosage-dependent therapy confers specific advantages in

the management of prostate cancer. For instance, HDR-BT can treat other cancer types, has low operator dependence, and less irritative and obstructive symptoms. Likewise, LDR-BT patients have more compliant scheduling times, lower cost, and are done in one single procedure with no need for unnecessary reviews.[15] Compared to EBRT, it has more or less similar outcomes with more benefits.

Preventive Measures:

The primary preventive measure to contemplate regarding age and genetic-associated risk factors involves modifying lifestyle. Through research, it has been noted that meals rich in fruits and vegetables help prevent cancer.[16] Whole grains, fruits, and vegetables are regarded as the source of a healthy diet since they are rich in fiber, phytochemicals, antioxidants, and various other contents that boost the body's defense mechanism to fight cancerous cells.[16] Besides, such a dietary plan is naturally free of fats besides having low-calorie content. Also, it is an obligation by care providers to counsel the people living with aging male prostate cancer on the importance of consuming healthy foods that will raise the odds of suppressing cancer development. The basis for settling on a restorative lifestyle prevention measure is because it is not associated with any risks compared to other alternatives.[17] According to Turner B et al[18] the screening procedure for prostate cancer in the U.S. has been a subject of debate that has not been solved up to date. The prostate-specific antigen (PSA) testing is not efficient in detecting prostate cancer.[19] This approach frequently produces unreliable outcomes, as held by NCI that roughly 80% of +VE prostate-specific screening outcomes are negative.[18] Hence, a few post-test manifestations that most patients witness incorporate agony, high body temperatures, bleeding, difficult urination, infection, mental disorders associated with false-positive outcomes, and overdiagnosis predicaments. PSA is associated with more disadvantages than surpass benefits.

Therapeutic alternatives for Prostate Cancer:

The most appropriate prostate cancer treatment in most males is watchful waiting that integrates frequent PSA screening. Additional alternatives include the integration of surgery, hormone, and radiation therapy. Radiation therapy utilizes intensive X-rays that destroy the affected cells.[20] Radiation treatment induces minimal side effects, and it is usually supplemented by hormone therapy.

External beam therapy utilizes intensive rays the same way as x-rays to destroy the affected cells, and its effect takes several weeks to be witnessed. Nevertheless, laser therapy is likely to destroy the neurons adjacent to the prostate tissue, resulting in erection dysfunction.

Radical prostatectomy and transurethral prostate resection are among the most well-known prostate cancer surgeries. Transurethral prostate resection relieves the bladder of side effects that result after removing the tumor though it does not get rid of all tumors.[20] Radical prostatectomy integrates removing the prostate gland and adjacent tissues.[18] Hormone therapy functions by reducing testosterone level in the body, helping to shrink the malignant tumor. It is usually supplemented with radiation therapy. Casodex, Lupron, Firmagon, Zoladex, and Trelstar are sample androgen deprivation therapies (ADTs). Some of the short-lived and long-lived side effects of prostate cancer therapy include enlarged breasts, hot flashes, erectile dysfunction, decrease libido, coronary diseases, depression, and diabetes.[18]

Long-Term and Short-Term Implications:

Various lasting and short-lived implications impact prostate cancer treatment. ADT short-term implications incorporate physical impacts like hot flashes, obesity, muscle wasting, and elevated fat levels in the stomach region and breasts that may result in issues in body image. Additional side effects are erection disorders that may impair the ejaculation capacity of victims, fertility, and sexual satisfaction.[21] Lasting implications correlate with resistance to insulin, high odds of osteoporosis development, increased likelihood of mood fluctuations, and cognitive impairment.

Immobilization Techniques:

The immobilization techniques employed in radiation therapy for prostate cancer management follow an almost similar approach when Intensity modulated radiotherapy (IMRT) or Volumetric Arc Therapy (VMAT) is used. The treatment aim is to attempt a radical approach. Therefore, the patient must lie in the supine position. With the aid of immobilization devices, such as the alpha cradle and knee sponges, keep the thighs in a consistent neutral position. The patient is then required to have a full bladder and an empty rectum after using an enema. Retrograde urethrography is used together with C.T. imaging to identify the inferior border of the prostate. The apex is determined relative to the inferior border 1-1.5cm superior to the point where the contrast dye narrows.

Treatment Delivery and Verification:

The radiation is given in doses that irradiate both the prostate gland and the seminal vesicles if they are involved. The energy rating for the radiation beams of the photons used is in the range of 70-78GY. The treatment is then verified through electronic portal images taken and compared with digitally reconstructed radiographs from the planning C.T. scan, using bony landmarks, the beam edges, and the center.[22] Changes or alterations within the

prostate can be identified using radio-opaque fiducial markers and can show progress with the radiotherapy treatments. They can be used in conjunction with PSA.[22]

Prostate Health Index (PHI):

Currently, it is well-defined that there is a lack of order with perfect performance features essential for detecting and stratifying prostate cancer risk. The Prostate Health Index presents itself as cheap and straightforward for a multivariant methodology to prostate cancer screening and management. The Prostate Health Index enhances prostate cancer prediction at initial and prolonged biopsy phases and may distinguish prostate cancer from chronic prostatitis and enhance insignificant prostate cancer prediction. It can also project disease recurrence after radical prostatectomy.[23]

A study done by Loeb et al.[24] shows that the Prostate Health Index can be applied in an ongoing manner to project high-grade prostate risk on biopsy. Adding Prostate Health Index to presently available tools of predicting prostate cancer risk enhanced the predictive correctness of European Randomized Study of Screening for prostate cancer (PCa) (ERSPC) and the PCa Prevention Trial (PCPT) risk predictors for aggressive disease. The use of PHI in the multivariable risk evaluation results in a significant enhancement in detecting aggressive prostate cancer, possibly reducing harm from unnecessary prostate overdiagnosis and biopsy. Dolejsova et al.[25] carried out research investigating the PHI as a biomarker for the aggressiveness of tumors in prostate biopsy and indication optimization for options of treatment. The study indicated high prostate biopsy inaccuracy in a comparison between definitive Gleason score and biopsy. The researchers tested the ability of the present tumor markers to differentiate between Gleason score six and higher than Gleason 6 tumors. The Prostate Health Index was the best amongst the examined traits. It can give better results in distinguishing Gleason score six tumors and helps in decision-making for appropriate management of prostate cancer patients. In instances of active prostate cancer treatment, the Prostate Health Index also simplifies the process of decision-making for nerve-sparing radical prostatectomy.

Non-FDA Approved Biomarkers:

TMPRSS2-ERG Gene Fusion Test:

Though the particular role of the TMPRSS2-ERG gene fusion test in prostate cancer is not understood clearly, ERG -positive victims exhibit a low level of high Gleason score, poor distinction compared to ERG-negative victims. TMPRSS2-ERG gene fusions might be cancer initiators and expressed at protein and RNA levels in prostate cancer stem cells. ERG over-expression might be an essential biomarker for prostate cancer diagnosis.[26] TMPRSS2-ERG gene fusions within the urinary sediments are associated with a positive predictive score (94%) and a high specificity (93%), with a low sensitivity score (37%). The setbacks of the TMPRSS2-ERG gene fusion test as a biomarker regards tumor heterogeneity since most prostate tumors have multi foci. Besides, there is no clear definition of the prognostic impacts of gene fusion. Some research claim that positive cases of TMPRSS2-ERG gene fusion have a higher aggressiveness of prostate cancer, higher mortality, and metastasis. Other studies have suggested no correlation between this nature of gene fusion and the clinical outcome. Moreover, the gene fusion frequency is low within some populations. Thus, it is challenging to identify a suitable cut-off in the people. Considering these pitfalls, the type of biomarker has been incorporated with PCA3 to develop a urine-based biomarker for PCa. The combination of PCA3 and TMPRSS2-ERG has shown significant sensitivity improvements for the diagnosis of prostate cancer, with a 68% to 76% increase in PCA3 sensitivity. Combined PCA3 and TMPRSS2-ERG scores have improved serum PSA performance for PCa prediction and resulted in high-grade PCa at biopsy.[27]

Oncotype DX Test:

The Oncotype DX is a biopsy test that calculates a GPS (genomic prostate score) based on genes from four pathways related to prostate cancer; androgen signal, stromal response, cellular organization, and proliferation. The primary endpoint of the Oncotype DX test in predicting the risk of adverse pathology at R.P. (radical prostatectomy). This biomarker was designed for application with biopsy tissue, and it has no commercially available test to be used in post-prostatectomy stratification of risk.[28] This test has been confirmed to be a predictor of prostate cancer aggressiveness. It enables stratifying the risk of prostate cancer to guide decision-making for treatment.[29]

Pro-Mark Test:

The Pro-Mark design is intended to deal with the disparities in biopsy samples, which is a consistency of the anticipated sample constitution variability and pathologist discordance in G.S.—Gleason score.[30] Typically, this is a predictive assay for analyzing the expression of 8-protein biomarkers in formalin-based paraffin-entrenched tissue derived from prostate needle biopsies. The test serves to project the aggressiveness of prostate cancer, especially in patients with a Gleason score (G.S.) of 3+3 or 3+4. It performs a qualitative analysis of the 8-proteins levels (SMAD4, CUL2, FUS, DERL1, PDSS2, YBOX1, phosphorylated, and HSPA9) in the tissues sections of the biopsy using an automatic immunofluorescence technique. The obtained protein levels are utilized in determining the clinically validated risk as an autono-

mous predictor of prostate cancer aggressiveness. The score obtained from the Pro-Mark test can be crucial in distinguishing patients who need active monitoring from the ones who should get therapeutic intervention.[29] A Pro-Mark test is a novel tool that can satisfy a person's risk for prostate cancer and has the potential of aiding in the discussions between the patient and physician about treatment or active surveillance.[31]

Paris Test:

This biomarker determines the expression of a series of 31-cell cycle progression genes, alongside 15 housekeeping genes that predict disease progression. There is a correlation between the genes related to the cell cycle and prostate cancer proliferation. It is a tool for risk stratification, allowing a better monitoring/treatment approach for prostate cancer patients during diagnosis. It implies a common progression risk when lowly-expressed, and the patients might be subjected to active surveillance. On the other hand, when the gene is highly expressed, it implies a higher progression risk of the diseases, and the patients (men) might be treated. The Prolaris test is essentially more prognostic than the presently utilized clinic-pathological variables.[27] The Prolaris assay can assist in making decisions between active treatment and active surveillance in low-risk prostate cancer. It can also imply the need for adjuvant remedies in high-risk persons (patients) with severe pathological characteristics after surgery.[32] The test can be carried out in post-prostatectomy specimens in the form of a prognostic genomic marker. Nonetheless, long-term use in adjuvant treatment needs more clinical trials in the future.

Conclusion:

In conclusion, the use of these interventions in managing localized prostate cancer has been shown extensively to be effective. It has been pointed out that there is supposed to be a robust effort to educate and support patients who suffer from the condition or who are at risk by promoting prostate screening activities and subsidies in prostate cancer treatment to marginalized nations and populations to mitigate the burden that prostate cancer presents.

The literature review has highlighted a gap in the current biomarkers used for prostate cancer diagnosis. Even though the PSA test has been used as a PCa biomarker over a long period, the analysis has shown that it is associated with many limitations and has attracted controversies. Its rules call for an ideal prostate cancer biomarker with the capabilities of distinguishing prostate cancer from benign prostate conditions and distinguishing between indolent and aggressive tumors. Regardless of the positive experience in using PHI, the search for new biomarkers for the aggressiveness assessment of prostate tumors is still needed. The use of the PCA3 test presents a challenge of the lack of an international standard for urinary assay since it relies on the urine obtained immediately after concentrated DRE. Hence, showing a need for a more effective method. Even with their pending approval by the U.S. FDA, the proposed biomarkers seem promising in transforming PCa diagnosis. The combined power of PCA3 and TMPRSS2-ERG has enhanced serum PSA performance for PCa. The Oncotype DX, Pro-Mark, and Prolaris tests will all serve a critical role in PCa treatment decision-making. The newly available prostate cancer biomarkers should select patients for prostate cancer screening, minimize undesirable biopsies, differentiate clinically insignificant diseases from aggressiveness ones, and choose the most appropriate therapy for metastatic patients.

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