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COMMENTARY

WHO International Consultation on Prostate Cancer: A summary

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During the past three decades, prostate cancer has assumed an increasingly prominent role in health care policy and delivery in many western countries. Prostate cancer is now the most commonly diagnosed non-skin tumor and the second leading cause of death after lung cancer. The dramatic rise in the incidence of this disease has been directly linked to the dissemination of testing for prostate specific antigen (PSA) and is highest in regions where annual PSA testing has become commonplace.

The introduction of PSA testing has resulted in several significant changes concerning how scientists, clinicians and public health officials deal with prostate cancer. PSA testing has impacted how we identify prostate cancer, the type of cancers we diagnose, and how we stage and manage this disease. This manuscript summarizes the papers presented at the WHO International Consultation on Prostate Cancer concerning the advances in screening, prevention and therapy for prostate cancer and highlights the future challenges that lie ahead.

A) Early detection and screening

In 2009 two publications appeared in the New England Journal of Medicine that advanced our understanding of the impact of PSA testing on the early detection of prostate cancer. On first glance, the conclusions from these studies appeared to be contradictory. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial demonstrated no benefit from PSA testing, whereas the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial suggested that PSA testing reduced prostate cancer mortality by 20% but with the caveat that at least 48 men required treatment to prevent one prostate cancer death.

Closer inspection of the study designs of these two trials reveals that the PLCO trial evaluated the impact of intensive annual PSA screening against modest PSA testing, whereas the ERSPC trial evaluated the impact of PSA screening versus no screening. The ERSPC trial tested whether PSA testing is efficacious, while the PLCO trial explored whether PSA testing is effective from a population perspective. When considering broad public health policies, this distinction helps guide appropriate clinical application. PSA screening must be efficacious if it is to be effective, but it may be not effective from a public health perspective even when it is efficacious for an individual patient.

In the PLCO trial, men were recruited to study centers and randomly assigned to receive either annual PSA tests for six years and digital rectal examinations for four years or usual care. If a study participant was found to have an abnormal PSA test or digital rectal examination, study researchers referred him to his primary care physician or other health care provider for further evaluation, a possible prostate biopsy, and treatment if the biopsy specimen was positive for cancer cells. In the ERSPC trial, potential study participants were identified from population registries and invited to participate in the study. Men who were found to have an abnormal PSA level were offered a transrectal ultrasound and prostate biopsy. Men with positive biopsies were provided definitive treatment.

Both of these studies have been the subject of numerous analyses and editorials identifying many technical problems inherent to both studies. Both trials, however, have identified the major public health issue of over diagnosis of prostate cancer as a result of repeated PSA testing. In the ERSPC study 42 cancers had to be identified and managed in order to prevent

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one prostate cancer death. Many men who would not otherwise have been diagnosed with prostate cancer are undergoing biopsy and treatment. Without more information concerning the impact of PSA testing on health care quality of life and the economic costs associated with widespread PSA screening and treatment, it is currently inappropriate to adopt population based PSA testing as public policy.

One promising method to manage the problem of over-diagnosis of prostate cancer is genetic testing. Available markers currently explain approximately 25% of the heritability of this disease and researchers anticipate that within the next two years, the number of identified markers will increase from 35 to over 100 and will have the potential of explaining almost 50% of the heritable factors associated with prostate cancer. Potential clinical applications of these genetic tests include: a) defining a sub-population of healthy men who have an excessive risk of developing clinically significant prostate cancer, and b) integrating the information provided by genetic factors to assess an individual patient's risk of developing clinically significant disease. Unfortunately, there is no data presently available that can be used to differentiate men with clinically significant disease from those who have clinically insignificant disease.

B) Assessing the tumor

The past decade has witnessed an explosion in the number of tools that can be used to assess prostate cancer. Traditional analysis of histology remains the gold standard for diagnosing prostate cancer and assessing the aggressiveness of this disease. The Gleason scoring system has been adopted world wide, but the system is not static. Consensus conferences conducted within the last few years have continued to modify how the Gleason system is applied. Gleason patterns 1 and 2 are rarely used by contemporary pathologists. Pathologists have also modified the definition of Gleason pattern 3. Increasingly men who harbor cribriform glandular patterns are classified as having Gleason pattern 4 disease. Glandular differentiation has become a key factor for many pathologists. Glandular differentiation is preserved in specimens classified as Gleason pattern 3+3 disease. When glandular differentiation is only partially preserved the specimen is usually classified as Gleason pattern 3+4 or 4+3. When glandular differentiation is absent the specimen is classified as having Gleason patterns 4 and 5.

Other factors that continue to demonstrate important prognostic significance include the number of positive cores at biopsy and the extent of tumor in each core. Perineural invasion is often reported, but it is unclear whether this factor provides independent prognostic information. Important changes in staging include the classification of microscopic bladder neck invasion and the intraprostatic seminal vesicle invasion as T3a disease. The diameter of the largest node is also clinically relevant. Sub-classifications of T2 disease provide no valuable information.

Prostate specific antigen remains the most important and widely used biomarker to assess the presence and potential extent of prostate cancer. Unfortunately PSA, like all biomarkers, has significant problems with false negative and false positive values. No single biomarker is capable of distinguishing clinically significant disease from normal pathology or indolent disease. In the future panels of biomarkers will be combined and entered into prediction models. During the past few years several nomograms and risk calculators have been developed.

Researchers have explored the performance of PSA using multiple approaches including PSA kinetics. The inherent analytical and biological variability of total PSA levels affects the interpretation of any single result. Men who will eventually develop prostate cancer have increased total PSA levels years or decades before the cancer is diagnosed. PSA velocity marginally improves the specificity of total PSA, but has limited use for screening or prognostication. The combination of PSA molecular forms and other biomarkers promises to improve the detection of prostate cancer. Examples include the blood markers PHI (−2proPSA, %PSA, tPSA), a four kallikrein panel (tPSA, %PSA, intact PSA and hK2), tissue markers (uPA axis, TGF-bets 1, IL-6R, Endoglin, Ki-67) and urine markers (PCA3).

Panels of biomarkers that capture the biological potential of prostate cancer are in the process of being validated. For advanced prostate cancer, circulating tumor cells appear to offer the greatest promise for predicting and monitoring the response to therapy. Unfortunately, at the present time no single biomarker is clinically useful as a predictor of prostate cancer progression.

Imaging techniques have also undergone significant advances during the past decade. Magnetic resonance imaging in particular shows promise in the diagnosis and clinical assessment of tumor grade and local extent. Prostate cancer is more difficult to detect and localize in the central gland as compared with the peripheral zone. MR offers the potential to improve our ability to identify and biopsy these lesions when compared to transrectal ultrasound (TRUS) and biopsy. Multiparametric MR imaging combines T2 weighted imaging, diffusion weighted imaging and dynamic contrast enhanced imaging. The typical prostate cancer lesion has low signal intensity on T2 weighted imaging, a low diffusion coefficient value, a high choline and creatine/citrate

ratio, high contrast agent permeability and rapid washout. Multiparametric imaging is needed because not all prostate cancer lesions exhibit all of these features. Aggressive cancers appear to demonstrate a high diffusion coefficient and a high choline and creatine/citrate ratio.

MR offers the potential to improve prostate biopsies. Lesions that are often missed on TRUS can be imaged on MR. An experienced radiologist can perform an MR directed biopsy within 30 minutes. An endorectal coil is needed for prostate cancer staging if only a 1.5T magnet is available. If a 3T magnet is available, an endorectal coil is only required to identify minimal capsular penetration. MR imaging can be used for conventional nodal staging using standard criteria for size and shape. Novel contrast agents are still considered experimental and require FDA and EMEA approval. MR offers the potential of outperforming bone scintigraphy when evaluating the axial skeleton for bone metastases. Dynamic contrast-enhanced MR imaging may play an important role in detecting tumor recurrence after surgery or radiation.

Positron Emission Tomography (PET) combined with computerized tomography also shows promise as a technique to measure the extent of prostate cancer. Many new tracers are available. FDHT targets the androgen receptor and therefore can be used to either guide prostate biopsies to assess the presence of metastatic disease or to assess a patient's response to various chemotherapeutic agents.

Technitium-99 based bone scans have been traditionally used to assess patients who are likely to harbor bone metastases. Recent data suggest that technetium bone scans can also be used as a secondary end point in clinical trials. Patients who develop more than two new lesions on bone scan when compared to their base line scan have clinical evidence of clinical progression.

C) Therapy with curative intent

Men with moderate or high grade prostate cancers (Gleason score ≥ 7) face a substantial risk of disease progression when compared to men with low grade disease. This is especially true for those men who present with clinically palpable disease (stage T2 and T3). Two randomized trials conducted in Scandinavia revealed a survival benefit for men who received either surgery or radiation. The SPCG-4 trial randomized patients between immediate surgical intervention and deferred endocrine treatment. A total of 695 men were enrolled during the period 1989–1999. A review of the study cohort reveals that 76% of the participants had T2 disease and only 11% of the participants had disease detected on the basis of PSA testing. The distribution of Gleason scores was as follows: 48% Gleason 5–6, 23% Gleason 7, and 5% Gleason 8–10.

After a median follow-up of 10.8 years, 39% of the men had died. There was a small absolute difference in overall survival of 7% favoring men undergoing radical prostatectomy, but the difference was not statistically different. After 12 years the overall mortality rate was 33% among men undergoing surgery and 40% among men receiving deferred androgen deprivation therapy. Interestingly the survival advantage only favored those men who were age 65 or less at the time of surgery. Men older than this had similar outcomes in each of the two arms of the study.

The SPCG-7/SFUO-3 trial randomized men to either immediate androgen deprivation alone or androgen deprivation plus radiation therapy. A total of 875 patients were enrolled from 1996 to 2002. As with the SPCG-4 trial, most of the men enrolled had more advanced disease and presented because of clinical findings rather than on the basis of PSA screening. A review of the study cohort shows that 98% of the patients had T2 disease or higher with the majority presenting with T3 disease. Unfortunately, tumors were not graded by Gleason score, but 85% of the patients had WHO grade II disease or higher and 23% had seminal vesicle invasion. A review of PSA values at entry showed that only 24% of patients had a PSA lower than 10.0 ng/ml. These patients had considerably more advanced disease when compared to the typical patient presenting with newly diagnosed localized prostate cancer in the United States during the past decade.

After a median follow-up of 7.6 years, 79 men in the androgen deprivation alone group and 37 men in the radiation plus androgen deprivation group had died of prostate cancer. The ten year overall mortality was 39.4% in the androgen deprivation group and 29.6% in the radiation plus androgen deprivation group. Ten year prostate cancer-specific mortality was 23.9% in the androgen deprivation alone group compared with 11.9% in the radiation therapy plus androgen deprivation group.

The findings in both of these trials are remarkably similar. Men with clinically advanced, localized prostate cancer have a survival advantage after receiving surgery or radiation therapy. Despite their relatively advanced disease, a majority of the men enrolled died from a cause unrelated to prostate cancer within ten years of diagnosis. Among those men who ultimately died from prostate cancer, radiation or surgery lowered this probability by about 50%. Twelve years after surgery and ten years after radiation 12.5% of men undergoing surgery and 11.9% of men receiving radiation died from their disease. For those men in the control arms 17.9% and 23.9% respectively died of prostate cancer after 12 years and 10 years.

Very few of the prostate cancers treated in the Scandinavian trials were diagnosed on the basis of PSA testing and therefore it is difficult to generalize these findings to a contemporary population of men in the United States. At minimum these findings reflect 15 or 20 year outcomes if the lead time introduced by PSA testing is added. Surgery and radiation therapy, however, come at a price. The side effects of surgery and radiation therapy are well known and often include problems with urinary function, bowel function and especially sexual function.

In 2010 several problems remain. Low risk prostate cancer is poorly stratified and suffers from under or overtreatment. Active surveillance protocols are inadequate. Intermediate risk disease for men with a ten year life expectancy can be treated equally well with either radiation therapy or surgery after careful counseling. Men with high risk disease are often undertreated with monotherapy and have poor outcomes. Surgery is often underutilized for these patients who often require combination therapies for optimal outcomes. Randomized clinical trials are urgently needed to refine active monitoring protocols, to define low risk disease and to evaluate minimally invasive therapies.

D) Natural history of prostate cancer and the role of active surveillance

During the past two decades there has been a dramatic increase in the incidence of prostate cancer in those countries that have adopted screening for prostate specific antigen (PSA). Prostate cancer is now diagnosed at a rate that is 2.5 times higher in the USA where PSA testing is commonplace when compared to the UK where PSA testing is much less frequent. The dramatic differences between prostate cancer incidence rates and mortality rates have led many researchers and clinicians to recognize that prostate cancer is increasingly being over-diagnosed in many countries. While all prostate cancers are likely to progress, many cancers progress at remarkably slow rates and therefore are not destined to become clinically significant.

Several key studies have shaped our understanding of the natural history of disease progression. Between 1989 and 2004, Johansson and colleagues published a series of four articles that documented the outcomes of untreated prostate cancer. Albertsen et al. also reported on the long-term outcomes of a competing risk analysis of men diagnosed with localized disease between 1971 and 1984. Together these studies have shown that men with low grade disease (Gleason score ≤ 6) can frequently survive up to 20 years without evidence of disease progression. Conversely men with high risk disease (Gleason score ≥ 7) often die of this disease within ten years of diagnosis.

Unfortunately these studies do not reflect the impact of widespread PSA testing that has advanced the date of diagnosis by as much as ten years. As a consequence, men diagnosed with low volume, low grade T1c disease are at very low risk of disease progression. For these men intervention with either surgery or radiation frequently carries higher risks than surveillance. Interest in active surveillance of prostate cancer reflects this greater understanding of the relative impact of intervention. These considerations have led clinicians at several academic medical centers to propose criteria that identify men who have a low risk of disease progression. They have relied on concepts originally developed by Epstein that were based on pathological analysis that correlated biopsy findings with those found following radical prostatectomy. The core criteria include: a) men who present with prostate cancer in two cores or less ($< 25\%$ of the total biopsy specimen), b) neither core has more than 50% involvement with disease, and c) tumor histology that contains no Gleason patterns 4 or 5.

These concepts have yet to be validated by clinical trials. To date, support for this approach comes from several case series. Klotz et al. have published the longest follow-up of over 450 men participating in an active surveillance program. After a median follow-up of seven years overall survival is 78.6% and prostate cancer specific survival is 97.2%. Death from competing risks has been 16 times greater than the number of deaths from prostate cancer. Unfortunately, active surveillance carries risks. In the Klotz cohort, over 30% of patients have undergone more aggressive treatment because their disease has been reclassified as higher risk. Of these men, half have evidence of biochemical failure on the basis of a rising PSA. Whether these patients will ultimately die from prostate cancer remains to be determined.

Most likely, the concept of repeated assessments of the tumor over time is here to stay. We know that active surveillance leads to reduced overtreatment, but the risk of missing the window of curability is unknown, as is the optimal parameters for assessing the tumor. Issues related to quality of life must also be evaluated thoroughly.

E) Chemoprevention of prostate cancer

The rising incidence of prostate cancer and the recognition that many cancers are not clinically significant has caused many clinicians to pursue the concept of chemoprevention as a way to prevent overdiagnosis and overtreatment of this disease. The term "chemoprevention" implies that prostate cancer can be prevented. While this is a noble goal, a more

accurate description of current efforts is "risk reduction". Primary chemoprevention refers to the reduction of the risk of prostate cancer development while secondary chemoprevention refers to the reduction of the risk of prostate cancer progression.

The two principal targets of prostate cancer chemoprevention have been inflammation and hormonal stimulation of the prostate. Inflammation has been associated with the development of lung cancer in smokers, hepatic cancer in chronic hepatitis and bowel cancer in inflammatory bowel disease. In prostate cancer, inflammation is associated with prostate cancer precursor lesions such as proliferative inflammatory atrophy and is believed to increase genetic instability leading to prostate carcinogenesis. Unfortunately, several studies such as the SELECT trial have failed to show that anti inflammatory agents such as the antioxidants selenium and vitamin E can reduce prostate cancer mortality.

To date, interest in chemoprevention of prostate cancer has centered on the five alpha reductase inhibitors. Two trials, the finasteride chemo prevention trial (PCPT) and the reduction by Dutasteride of prostate cancer events (REDUCE) trial, have both demonstrated that the incidence of prostate cancer can be lowered in men who take these medications. These two trials, however, were fundamentally different. The PCPT trial tested whether prostate cancer incidence could be lowered among men who had normal PSA levels at entry. The REDUCE trial tested whether prostate cancer incidence could be lowered in the subset of men who were previously identified as having elevated PSA levels and therefore were at higher risk of being diagnosed with prostate cancer. The PCPT trial followed men for an average of seven years; the REDUCE trial followed men for an average of four years.

Both trials demonstrated that prostate cancer incidence was lower in men taking 5 alpha reductase inhibitors. The incidence of prostate cancers of all Gleason grades was lowered in both studies, but the primary impact was in the number of low grade cancers. Controversy surrounds both of these trials. The incidence of prostate cancer was four times higher in both arms of the PCPT trial than originally anticipated. Therefore it is unclear whether 5 alpha reductase inhibitors actually prevent prostate cancer or simply decrease the probability that a man will undergo prostate biopsy. Furthermore, these trials have raised a concern that 5 alpha reductase inhibitors may induce high grade lesions. Follow-up in both of these trials have been insufficient to determine whether these agents ultimately lead to lower prostate cancer mortality. Information from the REDEEM study should provide new data concerning the role of 5 alpha reductase inhibitors in men choosing active surveillance as a treatment alternative.

F) Management of advanced disease, new drugs

Treatment of advanced prostate cancer has posed challenges for both clinicians and research scientists. Many drugs have been tested, but few have shown much efficacy in altering the outcome of this disease. Docetaxel, approved in 2004, was the first agent that showed evidence of a survival advantage. Since then researchers have explored many drugs targeting different biological mechanisms. Currently androgen deprivation therapy by either surgical or chemical castration remains the cornerstone for the management of advanced prostate cancer. Unfortunately, the effect of this approach is transient. Many patients developed androgen independent disease that progresses despite low levels of testosterone.

Since data from the TAX 327 and the SWOG 9916 trials were presented in 2004, docetaxel administered every three weeks has become the standard treatment for men with androgen resistant disease. Unfortunately, treatment has improved survival only modestly with an average median survival increase of less than 20 months. Recently cabazitaxel, a novel taxane with a favorable low affinity to multidrug resistant P-glycoprotein, in combination with prednisone has been approved by the United States Federal Drug Administration. A phase III trial demonstrated an overall survival benefit of 2.4 months when compared to mitoxantrone in patients previously treated with docetaxel alone.

The recognition that the withdrawal of antiandrogens can lead to a clinical response has demonstrated the continued importance of the androgen receptor signaling pathway in castrate resistant prostate cancer. Several new drugs have been developed to exploit biological mechanisms of androgen receptor mutation, androgen receptor amplification, ligand-dependent androgen receptor activation or enhanced local production of androgens. MDV3100, a non-steroidal compound, and RD162 are examples of two new agents that target the androgen receptor with higher affinity than bicalutamide. EPI-001 is another new compound that binds to the N-terminal domain of the androgen receptor and targets the trans-activation of the androgen receptor regardless of the presence of androgens. Abiraterone acetate is another interesting compound. This agent inhibits cytochrome P17 which catalyzes two key reactions in androgen biosythesis.

Our understanding of the complex molecular pathogenesis of prostate cancer has led researchers to explore several novel drugs that target specific

molecular pathways such as: epidermal growth factor (EGFR) signaling, vascular endothelial growth factor (VEGF) signaling pathways, phosphatidylinositol 3-kinase (PI3K)/Akt mammalian target of rapamycin (mTOR) pathway as well as the insulin-like growth factor pathway. Multiple tyrosine kinase inhibitors with a typical anti-angiogenic profile such as sunitinib and sorafenib have also been evaluated. Unfortunately data concerning long-term outcomes are limited. The anti-VEGF antibody bevacizumab has also been evaluated but the results from a recent phase III trial, CALGB 90401 have been disappointing.

Src and src-family kinases that are involved in multiple signaling pathways central to the development of prostate cancer and the pathogenesis of bone metastases are currently being tested in phase III trials. Other agents under investigation include the mTOR inhibitors everolimus and temsirolimus, various inhibitors of IGF-1R and custirsen (OGX-011), an innovative antisense oligonucleotide directed against the cytoprotective chaperone, clusterin. Tumor-induced epigenetic aberrations believed to be critical for androgen receptor mediated signaling have been targeted with histone deacetylase inhibitors such as vorinsostat and panobinostat (LHB589).

The slow progression and high expression of tumor associated antigens have stimulated the development of several immutherapeutic approaches. The FDA recently approved the first therapeutic vaccine, sipuleucel-T, for asymptomatic or minimally symptomatic metastatic androgen resistant prostate cancer. Sipuleucel-T consists of autologous dendritic cells derived from a patient's own peripheral mononuclear cells. A recent phase III trial reported a survival advantage of four months among men receiving this agent versus those receiving placebo. Other examples of vaccine approaches under evaluation include vector based strategies (Prostvac) or whole tumor cell vaccines (GVAX). Ipilipumab, an anti-CTLA4 monoclonal antibody, represents another immunotherapeutic approach under evaluation.

Several agents targeting bone metastases include denosumab, a fully human monoclonal antibody that specifically binds to the ligand of RANK. This agent was recently reported to be superior to zolendronic acid in delaying or preventing bone fractures. Radium-223 is a new alpha-emitting bone-seeking radiopharmaceutical which shows promise against bone metastases. A number of endothelin A receptor targeted agents such as Atrasentan and ZD4054 are also under evaluation.

Considering the large number of compounds under evaluation the next decade shows promise for the treatment of advanced, androgen resistant prostate cancer. New biomarkers should drive clinical trials that will target specific subgroups of patients with varying biological characteristics.

G) Prostate cancer from the patient's perspective

The past two decades have witnessed a changing role for patients in the diagnosis and management of prostate cancer. Patients are demanding a more active role in decision making and no longer rely exclusively on the treating physician's advice. These changes are part cultural, but are also a consequence of changing technology. Internet search engines enable patients to access enormous amounts of information with minimal effort. The physician is now frequently challenged to keep up with medical literature so he can interpret findings accurately for his patients.

Prostate cancer patients are demanding more information concerning their personal prognosis and whether a specific intervention is likely to prolong their life. Patients are increasingly aware that all treatments carry side effects and are demanding more information concerning the frequency and severity of treatment mishaps. These demands have become quite personal. Patients now seek information on surgeons' individual skills and the frequency of complications. This information is often not available, but the adoption of electronic medical record keeping will greatly facilitate this process in the future.

Patients have become more sophisticated consumers. They recognize the potential trade off between the risks of a disease and the risks of intervention. They are demanding more quantitative information to help them decide what treatments are best for them. They recognize that many treatments may fail and demand information on treatment alternatives and salvage therapies. They recognize that increased longevity may or may not be the primary goal. A high quality of life is more often the preferred outcome.

Historically the role of a physician has been one of a trusted advisor who can help guide a patient by helping them understand how their disease will unfold in the future. Some physicians have become blinded by their own technology and now appear as salesmen touting their wares. The more sophisticated patients will seek the advisor and shun the salesmen. Clinical trials are protected by an ethical code that states that investigators must provide sufficient information to patients to help them make an informed decision. Many patients assume that this also occurs in clinical practice. Patient advocacy groups are working to ensure that physicians perform at this higher standard. If physicians do not, they risk losing the professional respect and privilege that took centuries to build.