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Multidisciplinary Intervention of Early, Lethal Metastatic Prostate Cancer: Report From the 2015 Coffey-Holden Prostate Cancer Academy Meeting

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Abstract

BACKGROUND—The 2015 Coffey-Holden Prostate Cancer Academy Meeting, themed: "Multidisciplinary Intervention of Early, Lethal Metastatic Prostate Cancer," was held in La Jolla, California from June 25 to 28, 2015.

METHODS—The Prostate Cancer Foundation (PCF) sponsors an annual, invitation-only, action-tank-structured meeting on a critical topic concerning lethal prostate cancer. The 2015 meeting was attended by 71 basic, translational, and clinical investigators who discussed the current state of the field, major unmet needs, and ideas for addressing earlier diagnosis and treatment of men with lethal prostate cancer for the purpose of extending lives and making progress toward a cure.

RESULTS—The questions addressed at the meeting included: cellular and molecular mechanisms of tumorigenesis, evaluating, and targeting the microenvironment in the primary tumor, advancing biomarkers for clinical integration, new molecular imaging technologies, clinical

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trials, and clinical trial design in localized high-risk and oligometastatic settings, targeting the primary tumor in advanced disease, and instituting multi-modal care of high risk and oligometastatic patients.

DISCUSSION—This article highlights the current status, greatest unmet needs, and anticipated field changes that were discussed at the meeting toward the goal of optimizing earlier interventions to potentiate cures in high-risk and oligometastatic prostate cancer patients.

Keywords

molecular imaging; diagnosis; biomarkers; therapeutics; oligometastatic

INTRODUCTION

The Coffey-Holden Prostate Cancer Academy (CHPCA) Meeting is an annual action-tank-structured scientific conference focused on a topic of critical importance and attended by a group of approximately 75 investigators. The 2015 CHPCA Meeting was the third iteration of this event as sponsored by the Prostate Cancer Foundation (PCF) [1,2] and is a revamp of the biannual NIH-sponsored Prouts Neck Prostate Cancer Meeting, a source of many significant advances in prostate cancer that was held from 1985 through 2007 [3]. In 2014, PCF renamed this event in honor of Drs. Donald Coffey and Stuart Holden for the tremendous impact they have made on the understanding and treatment of prostate cancer [2].

The theme of the 2015 CHPCA Meeting was “Multidisciplinary Intervention of Early, Lethal Metastatic Prostate Cancer,” and was held in La Jolla, California from June 25 to 28, 2015. The meeting was attended by 71 investigators and included 31 young investigators, as a critical historical objective of the meeting is to engage and support the upcoming generation of researchers. The goal of the meeting was to address the most critical questions, unmet needs, and strategies surrounding early detection and treatment of lethal metastatic prostate cancer. The major topics of discussion included targeting the primary tumor, developing clinical biomarkers, cellular and molecular mechanisms of tumorigenesis, molecular imaging, and the multi-modal care of high-risk and oligometastatic prostate cancer patients.

DEFINING THE POPULATION OF PROSTATE CANCER PATIENTS WITH LETHAL DISEASE

Despite advances in prostate cancer diagnosis and treatment, it remains the second most common cause of cancer-related death in men [4]. The men at greatest risk of progressing to castration resistance prostate cancer (CRPC) and death are those that present with high grade, high volume, locally advanced M0 disease or M1 disease with distant metastases [5–9]. Men presenting with localized prostate cancer (stage M0) should, at a minimum, be further subcategorized into those with high and very high risk disease. Men with very high risk disease (primary Gleason pattern 5, multiple high risk features, or more than four cores of high grade cancer) have significantly inferior outcomes when compared to high risk men, with 63% versus 22% developing metastases and 38% versus 10% dying from their prostate

cancer by 10 years, respectively [10]. Men with aggressive localized prostate cancer can also be further sub-stratified by risk models such as CAPRA-S or Stephenson/Eggener and undergo genomic tests such as Decipher to identify those with the highest chance of disease progression after surgery [11–13].

For men presenting with or who have progressed to metastatic disease, there is an increasing push for stratification into low volume (oligometastatic) and high volume states, which may affect clinical management in the future. While a consensus definition of the oligometastatic state does not exist, most agree on a limited (≤5) number of metastatic sites with no visceral metastases [14]. These men have superior outcomes compared to those with high volume M1 disease. However, it is not clear if this is due to lead time bias or if the oligometastatic state is actually a unique clinical entity with enhanced curability [15–18]. Improved molecular imaging and other diagnostic methods for the earlier identification of these oligometastatic patients could optimize treatment strategies that prolong life and possibly achieve cure in some cases.

ATTITUDES TOWARD THE CARE OF VERY HIGH RISK AND OLIGOMETASTATIC PATIENTS

We employed an informal survey of CHPCA Meeting attendees (primarily from academic centers) and community prostate cancer specialists within the Large Urology Group Practice Association (LUGPA, which represents approximately 3,000 physicians and roughly one third of practicing urologists in the United States) to gauge attitudes toward the treatment of men with very high risk localized and oligometastatic disease. Responses from community and academic prostate cancer specialists were highly paralleled, and reflected a notion that these men may be curable with aggressive use of currently available or experimental therapies. There was a consensus that these men require careful study, should receive treatment counseling in multidisciplinary clinics, and should be encouraged to participate in clinical trials [19]. There was overwhelming support for aggressive local therapy for these men, even in the oligometastatic state, with the majority of those surveyed favoring surgical approaches (radical prostatectomy, RP) combined with adjuvant radiation therapy (RT) rather than RT alone, to allow for more accurate staging, debulking to improve local symptoms, and to allow acquisition of tissue for molecular analysis. The majority also favored treatment to the metastatic sites in oligometastatic disease.

TREATMENT OF THE PRIMARY TUMOR IN THE SETTING OF METASTATIC PROSTATE CANCER

Data from preclinical and autopsy studies suggest a dynamic interplay between distinct metastatic sites and the primary tumor [20,21]. There is ongoing debate on whether disease progression can be significantly slowed and/or cured in men with oligometastases, by targeting both the primary tumor and metastases. This concept has rarely been explored in prostate cancer [14]. The rationale supporting a therapeutic impact of cytoreductive surgery includes decreased symptomatic local progression, removal of a source of persistent

systemic tumor cell seeding, a possible shift in the patient's metabolic milieu that negatively impacts cancer progression, and elimination of an immunologic sink.

A clinical benefit from cytoreductive therapy has been suggested in retrospective, population-based studies of men treated with varying modalities for metastatic prostate cancer [22–24]. Prospective clinical trials are currently underway to evaluate the risks and outcomes of treating primary prostate tumors in the setting of metastatic disease. A phase III randomized trial being conducted at MD Anderson is comparing best systemic therapy (BST) with BST plus RP. The endpoint is CRPC progression and the goal is to identify the biologic prostate cancer subsets that most benefit from definitive treatment of the primary tumor. Six centers across the U.K. are participating in the TRoMbone trial, which is comparing the outcomes of patients who receive treatment as usual versus treatment plus RP. The randomized phase II HOR-RAD trial in the Netherlands is comparing ADT versus ADT plus external RT of the prostate in bone metastatic prostate cancer patients. The primary outcome is overall survival (OS) and secondary outcome is biochemical progression and quality of life. The STAMPEDE trial in the U.K. uses a multi-arm, multistage design to explore the effect of combinations of approved agents in non-castrate clinical states, including metastatic disease [9]. Newly diagnosed M1 patients are randomized to receive RT, in addition to standard of care (androgen deprivation therapy, ADT) or standard of care only. In addition to providing evidence to support or refute benefit of cytoreductive therapy, all of these trials provide new opportunities to collect tissues for biological and genomic analyses, which will provide valuable insight into pathways and indicators of metastatic tumor behavior.

TREATMENT OF METASTASES IN OLIGOMETASTATIC PROSTATE CANCER

Macroscopic metastases may represent "communal sanctuaries" for metastatic cells from multiple sites and act as supportive niches where cancer cells evolve and increase their competence to seed new metastatic sites. These may also serve as locations in which cancers can increase immune-tolerance. Metastasis-directed therapy might thus alter the evolution and trajectory of systemic disease. Dr. R. Jeffrey Karnes (Mayo Clinic) recently published an institutional experience of post-prostatectomy men undergoing salvage lymph node dissection for clinical recurrences [25]. This and other studies suggest a fraction of men may achieve disease control (albeit with limited follow up time) that warrant study in prospective randomized trials. Interestingly, preliminary data presented by Dr. Karnes suggests an enrichment of myeloid derived suppressor cells in prostate cancer-containing lymph nodes with up-regulation of PD-1 ligand, suggesting that removal of these nodes may enhance anti-tumor immune responses.

TARGETED RADIATION OF METASTATIC SITES

Stereotactic body radiation therapy (SBRT) is a strategy for precise targeting of metastatic sites, with minimal, acceptable reported toxicity, excellent local control rates and in limited published experiences, survival benefits similar to surgical series [16,26]. Currently, SBRT is being studied in the oligometastatic setting in multiple malignancies, coupled with radiation sensitizers (i.e., NCT01728779) and in prostate cancer with oncologic and biologic

endpoints, with emphasis on immune-biology (i.e., NCT01558427, NCT02192788, NCT01777802, NCT01859221). Beyond its locally ablative properties, radiation may promote a systemic immune response to distant metastases, indicating therapeutic synergy may be achieved in combination with immune modulators [27]. Multiple trials are being initiated in oligometastatic men to study and potentially capitalize on this principle. PCF has recently supported an effort led by Dr. Phuoc Tran (Johns Hopkins University) to examine SBRT combined with ADXS-PSA, a vaccine consisting of a live attenuated *Listeria monocytogenes* strain expressing a Listeriolysin O-PSA fusion protein (Advaxis), in men with oligometastatic prostate cancer.

EARLY ADMINISTRATION OF SYSTEMIC CHEMOTHERAPY

Three recent clinical trials tested whether early administration of docetaxel chemotherapy improves survival in men with metastatic, hormone-sensitive prostate cancer. The CHAARTED and STAMPEDE clinical trials both identified improved median OS for men with higher burdens of metastatic disease [28,29]. While the smaller GETUG-AFU 15 trial did not show similar improvements [30], the accumulation of clinical trial data indicates that a subset of men benefit from early aggressive therapy. Thus far, subgroup analyses of men without radiographic metastases have not shown similar survival benefits [28,29] and the question remains as to how early in the disease process can docetaxel chemotherapy confer a survival benefit. The ongoing CALGB 90203 study seeks to answer this question by randomizing men with high-risk localized prostate cancer to receive neoadjuvant ADT plus docetaxel followed by RP versus immediate RP alone. The primary endpoint of CALGB 90203 is the rate of 3-year biochemical progression-free survival. As we await reporting of this trial, the lack of clear benefit in CHAARTED and STAMPEDE for men with limited or no metastatic disease at the time of presentation suggests an underlying biologic difference driving tumor behavior. Chemo-resistance in men with a lower disease burden may be due to disseminated tumor cells (DTCs) existing in a dormant state and/or the bone microenvironment providing paracrine cell survival/supportive signals. Curative interventions for these men will require targeting of chemo-resistant tumor deposits. An upcoming clinical trial developed by Dr. Kenneth Pienta at Johns Hopkins University seeks to eliminate the role of the bone microenvironment in supporting dormant tumor cell survival by using an anti-CXCR4 therapy to “evict” dormant DTCs from the bone metastatic niche followed by systemic administration of docetaxel chemotherapy. The functional and mechanistic consequences of this novel therapeutic approach will be evaluated in extensive correlative studies.

Both short- and long-term toxicities are a significant concern with earlier use of docetaxel, especially if eligibility for primary therapy with surgery or radiation could be impacted. Novel drug delivery methods are of high interest, including nanoparticle delivered treatments, antibody drug conjugates and cellular platforms loaded with beads carrying therapies. These delivery methods hold promise to deliver higher payloads of chemotherapy in a targeted fashion with less toxicity than traditional systemic delivery. Drs. Oren Levy and Jeffrey Karp of Brigham and Women’s Hospital have developed a mesenchymal stromal cell delivery platform with strong pre-clinical evidence of efficacy and an improved toxicity profile [31]. Advanced manufacturing and testing of this platform for clinical use is

underway. Studies will be needed to address how cellular delivery platforms may interact with other treatments, especially immune based therapies that may be inhibited by the presence of mesenchymal stromal cells.

ADVANCED TARGETING OF THE ANDROGEN AXIS

Numerous studies have evaluated neoadjuvant or adjuvant ADT. While a clear benefit for ADT exists when combined with RT as primary treatment, similar improvements have not been found in the peri-surgical setting. This may relate to the inability of traditional ADT to sufficiently suppress tissue androgens such as testosterone, androstenedione or DHEA [32,33]. More aggressive targeting of the androgen axis in the neoadjuvant setting, with the addition of abiraterone acetate (AA) and enzalutamide to ADT, was found to induce significant declines in PSA in the majority of patients. Pathologic complete responses (pCRs) were observed in approximately 10% of patients in these trials suggesting a minority of patients may benefit from this neoadjuvant approach [33]. However, a significant number of patients with residual disease in the prostate also had nodal involvement. Within residual tumors, genomic analysis of separate foci conducted by Dr. Steven Balk (Beth Israel Deaconess Medical Center) identified diverse mutation profiles including PTEN loss, PIK3C mutations and BRCA1/2 alterations. Greater molecular profiling may enable patient stratification and has been embedded in two neoadjuvant/adjuvant clinical trials led by Dr. Mary Ellen Taplin (Dana Farber Cancer Institute). The first randomizes patients to receive neoadjuvant ADT and enzalutamide with or without AA, followed by RP. The second randomizes patients to receive neoadjuvant ADT and AA with or without ARN-509 followed by RP. These patients are then further randomized to 12 months of adjuvant therapy with the neoadjuvant regimen or observation.

IMMUNE TARGETING OF PRIMARY AND METASTATIC DISEASE

Major advances in immunomodulatory therapies have occurred in the last decade. The generally favorable toxicity profiles and particularly the lack of overlapping toxicities with other systemic therapies, further broadens the utility of immunotherapies in multi-modal treatment strategies. Immune therapies have been hypothesized to have greatest efficacy in patients with a lower disease burden. The loss of MHC class I molecules that occurs in metastatic disease further supports earlier use of these agents. Treatment of prostate cancer biopsies in an *ex vivo* culture model with epigenetic modifying agents significantly increased expression of multiple cancer-testis antigen family neoantigens and indicates that epigenetic therapy may improve immune recognition of tumor cells. A trial with a similar rationale combining pembrolizumab with cryotherapy for enhancement of neoantigen presentation is being tested in oligometastatic patients (NCT02489357). An ongoing trial at Memorial Sloan Kettering Cancer Center is testing a multi-modality intervention that combines ipilimumab with Degarelix in men with newly diagnosed prostate cancer followed by RP (NCT02020070). The underlying rationale for this trial is that ADT will induce an apoptotic response in tumor cells and promote the release of novel tumor antigens, while simultaneous checkpoint inhibition would prime cancer-specific T cells to promote durable anti-tumor responses. Subsequent RP may provide both local control and enhance persistent

anti-tumor immune responses. These and other studies will test the role of immunotherapies as adjunctive therapies in early treatment of lethal prostate cancer.

IDENTIFYING MOLECULAR FEATURES OF HIGH-RISK PROSTATE CANCER

Gleason pattern 3 is usually considered indolent while the presence of Gleason patterns 4 and 5 indicate a high risk for development of metastatic disease. Laser capture microdissection and exome sequencing of adjacent Gleason 3 and 4 patterns revealed many shared mutations and suggest clonal origin [34]. However, micro-heterogeneity was also observed, as many genetic alterations were unique in adjacent sites of Gleason 3 and 4 patterns, most involving loss of tumor-suppressors [34,35]. Gene expression analysis revealed that some of the Gleason 3 pattern tumors resembled Gleason score 8 or higher tumors, demonstrating that there are molecularly distinct Gleason 3 patterns: indolent and Gleason 3 associated with Gleason 4 [34]. These molecular features could potentially be used to identify Gleason 3 patterns that are most likely to emerge as high-risk disease [34]. Additionally, prostate tumors can consist of heterogeneous clones with different tumor initiating and propagating properties [36].

Identifying actionable drivers of aggressive disease and defining relevant mouse models is critical. A recently described approach used computational methods to identify disease drivers that are conserved between mice and humans [37]. Transcriptome analysis was performed on several mouse models representing distinct stages of the disease and human Gleason score 6–10 tumor samples to identify transcriptional factors and their targets that associate with prostate cancer progression [37]. FOXM1 and CENPF were identified as a synergistic transcription factor pair with potential as biomarkers to predict biochemical recurrence and outcome [37]. In an alternative approach to identify shared actionable oncogenic drivers, copy-number alterations in four genetically engineered mouse models reflecting distinct stages of the disease were assessed and associated with human prostate cancer data. A high frequency of copy number gains in Met, HGF, Jun, and Yap were identified [38]. Further in vivo functional assays validated Met as a potential driver of prostate cancer [38]. Integrating mouse and human genetic profiling will provide insights to relevant mouse models of human disease and may also reveal new drivers of the disease and indicate novel therapeutic strategies.

EVALUATING AND MODELING THE TUMOR MICROENVIRONMENT

An improved understanding of how prostate cancer cells are influenced by the various primary, dormant, and metastatic tumor microenvironments is critical for advancing the treatment of early lethal metastatic prostate cancer. Factors including tumor stromal cells, the immune system, extracellular matrices, and soluble molecules such as oxygen and host growth factors, can significantly alter the milieu and affect tumor characteristics and therapeutic responses. Several key research areas need addressing: improving modeling of the crosstalk between cancer cells and the microenvironment, targeting the microenvironment, and understanding the impact of current therapies on the microenvironment.

Three models were analyzed that describe the complex interplay between the microenvironment and cancer cells and shed light on the establishment of metastases. The “seed and soil” concept was first introduced by Paget in 1889 to describe how seeding of metastatic cancer cells is dependent on the host organ microenvironment (soil). This model was based on the observation that distribution of metastases are non-random and are dependent on the primary tumor and secondary site. A second approach using a Markov chain Monte Carlo mathematical model classifies metastatic tumors as “spreaders” or “sponges” [39]. This approach, based on data from large autopsy studies, can classify tumors as (a) self-seeding of the primary tumor, (b) reseeding of the primary tumor from a metastatic site, or (c) reseeding of metastatic tumors. Furthermore, this model can predict future pathways and timescales of systemic disease. Finally, the cancer diaspora model was examined which is based on a social science model of scattering away from an established homeland, that is the primary site. The diaspora paradigm models the qualities of the primary tumor microenvironment and targeted sites of new metastases, the fitness of cancer cell migrants as individual cells or populations, and the rate of bidirectional migration of cancer and stromal cells between cancer sites [40]. This model may yield insights into therapeutic strategies such as ecologic traps wherein cancer cells are directed toward a place where they can be more effectively targeted.

Studying the tumor microenvironment in vitro has been a challenge as traditional cell culture models fail to recapitulate the complex and constantly evolving and changing environment. Novel tools allow for compartmentalization, increased sensitivity, and discrimination of how subtle changes in structure can impact biological function. Microfluidic systems have been designed to study the impact of various environmental components such as chemoattractants and matrix components on prostate cancer or stromal cell properties. Integration of microfluidic co-culture platforms with multi-photon imaging based techniques allow determination of phenotypic cell behavior and enzyme activities [41]. Further, compartmentalization of these systems allows for studies that elucidate tumor heterogeneity. Organoid cultures derived from human prostate tumor tissues are another promising system for studying tumor-stromal cell interactions.

POTENTIAL TARGETS AND THE EFFECTS OF CURRENT THERAPEUTICS ON THE TUMOR MICROENVIRONMENT

The microenvironment niches in different organ sites that prostate cancer cells can occupy may uniquely impact responses to current therapies and represent potential targets for novel agents. For instance, reactive tumor stroma can predict biochemical recurrence and prostate cancer specific death [42,43], and may induce castrate resistance, even in the presence of next generation AR antagonists such as enzalutamide [44]. Hypoxia can reduce the efficacy of RT and has been associated with early biochemical failure after RT in prostate cancer [45]. Further, hypoxia combined with genomic instability can serve as a biomarker for both aggressive disease and the hypoxia driver phenotype which is associated with locally aggressive disease, metastases, and RT resistance [46]. Improving targeting via hypoxic radiosensitizers, hypoxic cell cytotoxins, and reduction in oxygen consumption is underway.

Given the reliance of prostate cancer on AR signaling, understanding the effect of hormonal therapies on the tumor microenvironment is critical. Castration reduces prostate androgen levels by approximately 75% [47], which can be substantially further reduced by the addition of agents such as AA [33]. However, other steroid pathway precursors and intrinsic tumor microenvironmental factors can compensate for exogenous reduction of androgen levels [48]. Upregulation of other nuclear receptors (i.e., estrogen receptor, glucocorticoid receptor) may contribute to resistance to AR blockade [49,50]. The microenvironment also modulates the effect of chemotherapy [51] and may prohibit elimination of disseminated malignancies [52]. Genotoxic cancer treatments can activate conserved damage response programs in stromal cells which can then promote epithelial to mesenchymal transformation, resistance to apoptosis, increased angiogenesis, and enhanced proliferation and reseeding [53]. Continued characterization of microenvironmental factors that can be targeted independently or to improve the effects of other therapies are critical for advancing treatment of oligometastatic disease or preventing metastases.

ADVANCING BIOMARKERS FOR CLINICAL INTEGRATION

Clinical integration of cancer biomarkers is critical for forwarding personalized medicine, yet few bio-markers with clinical utility have advanced to widespread use and several are currently in use without sufficient evidence of clinical utility. Biomarkers relevant to the treatment of advanced prostate cancer broadly fall into two groups: (1) prognostic bio-markers, which give an indication of the likely course of disease after a therapy; and (2) predictive bio-markers, which provide an estimate of the likelihood of beneficial response before a therapy is applied. Numerous potential prostate cancer biomarkers have been discovered in tumor tissue, blood and urine. However, the bottleneck in moving these discoveries into the clinic has been at the stage of biomarker validation [54]. Across all solid tumors, fewer than 10 biomarkers have undergone validation in level I evidence (LOE1) studies using a prospective randomized clinical trial design or a prospective-retrospective trial [55]. To address this, a Biomarker Validation Coordinating Center for prostate cancer was recently established with funding from the U.S. Department of Defense Congressionally Directed Medical Research Programs. This multi-institutional effort is validating tissue-based biomarkers for ongoing clinical trials, with the aim of developing LOE1 studies to support their use. With efforts such as this and the recent FDA proposal to enforce regulatory oversight of laboratory developed tests [56], there will be increasing incentive for assay validation.

GENOMIC PROFILING ASSAYS FOR PROGNOSTICATION IN PROSTATE CANCER

Advances in next generation sequencing have led to an explosion in the genomic data available for prostate cancer and have enabled identification of numerous potential actionable driving mutations and copy number alterations. However, most of these data are either from localized primary or late mCRPC tumors. Less information is available on patients with early lethal prostate cancer who rapidly recur or progress after local or second line therapy or patients who present with metastatic disease at diagnosis. Integrated genomic

and transcriptomic molecular profiling assays compatible with formalin-fixed paraffin embedded (FFPE) tumor tissues have been developed and are readily scalable to examine biopsy specimens from early lethal cases [57,58]. Our rapidly improving ability to perform genomic analysis on CTCs or cell free DNA have generated enormous promise for liquid biopsies as biomarkers in prostate cancer, though the utility of these assays are yet unknown. Issues with utilizing CTCs to study genomics of early lethal disease include the very low number attainable in the low disease burden state and inconsistencies in defining markers. CTCs are traditionally considered $CD45^{-}CK^{+}$ but small $CD45^{-}AR^{+}CK^{-}$ CTCs and other phenotypes have been observed. Assessing TMPRSS2-ERG translocation or PTEN-loss via FISH may be helpful in validating some of these samples. Cell free DNA isolated from plasma is another promising avenue for characterizing disease progression and therapeutic resistance. Analysis of serial CTC and cell free DNA samples as compared to tissue samples has revealed complex and dynamic site-to-site and temporal heterogeneity, with potentially distinct mechanisms of resistance at different sites [59]. Pre-analytic and analytic validation studies are sorely needed in this space.

Comparing diagnostic samples with post-treatment samples is important for parsing out targetable truncal driver mutations from alterations that drive therapy resistance. Mutations in p53 have emerged as highly enriched in metastatic prostate cancer [60] but are present at a low frequency and are frequently subclonal in primary prostate cancer. Small cell carcinomas have frequent loss of p53, Rb and PTEN [61]. Examining whether these alterations confer an aggressive phenotype even in tumors that lack small cell carcinoma morphology may be informative. Studies in non-responding patients have identified rare driver mutations present in CRPC but not matched primary tumor samples in genes including β-catenin and PIK3C [21,57]. Such “n of 1” findings are hypothesis-generating and may aid in identifying novel mechanisms of lethal disease. However, designing studies to test the prognostic/predictive relevance of these variants in a statistically meaningful way is challenging. Ultimately, targeting the truncal alterations may hold the most promise.

EXPRESSION-BASED ASSAYS FOR PROGNOSTICATION IN PROSTATE CANCER

Several RNA-based gene expression assays have been developed for use as genomic predictors of outcome in prostate cancer. Importantly, these prognostic tests must demonstrate clinical utility by improving on current multivariable clinical-pathologic nomograms, such as the Eggener and CAPRA-S risk models in the post-surgical setting. Most relevant are tests designed to identify patients in the biopsy or post-surgical setting who are at high risk for disease progression and may benefit from adjuvant or earlier therapies.

Prolaris is 46-gene expression panel initially reported to predict death from prostate cancer in a conservatively managed cohort and biochemical recurrence in a RP cohort using biopsies or RP tissue [62–65]. Oncotype DX GPS is a 17-gene expression panel that is largely validated for prediction of adverse pathology at RP using needle biopsy [66]. The Decipher assay is a 22-gene panel that predicts for metastatic progression and survival after

RP [11,13,67,68] and has been recently demonstrated to identify men who may benefit from adjuvant versus salvage RT following RP [69]. An important caveat of these tests is that they generally show only incremental improvement on established clinical-pathologic risk prediction models. While small shifts in the c-index may still be useful for clinical decision making, head-to-head studies of these assays, cost-benefit analyses and formal clinical utility studies are needed prior to adoption into routine clinical practice.

TISSUE-BASED PROTEIN AND MORPHOMETRIC BIOMARKERS IN PROSTATE CANCER

Gleason grading remains the most powerful prognostic biomarker in prostate cancer and is based entirely on tumor growth pattern. However, digital slide scanning and automated image analysis platforms have revolutionized our ability to characterize tumor morphology and quantify tissue-based bio-markers. Thus, quantification of tumor morphology and nuclear structure may add substantially to what can be done with the human eye. Image analysis algorithms using mathematical constructs such as fractal dimension (providing a statistical index of shape complexity) and lacunarity hold promise to add to and perhaps surpass traditional prostate cancer grading. Multiplex immunohistochemistry or immunofluorescence assays are tissue sparing and have become a useful method to deconvolve the constituents of the tumor microenvironment, and may add important information to genomic and transcriptomic datasets. Finally, quantification of highly validated immunohistochemistry assays allows interrogation and quantification of cellular signaling events within specific cellular compartments, and may elucidate functional and dynamic biomarkers to guide application of targeted therapeutics in advanced patients.

ANDROGEN RECEPTOR SPLICE VARIANTS AS PREDICTIVE BIOMARKERS IN PROSTATE CANCER

Recently, AR splice variants (AR-Vs) lacking the ligand binding domain have generated much interest as potential ligand-independent mediators of resistance to AR-targeted therapies. AR-Vs may be expressed due to alternative splicing events or in some cases, to DNA rearrangements of the AR gene locus [70]. In vitro, AR-Vs appear to play a functional role in AR signaling [71,72] and expression of variants is sufficient to restore the broad AR cistrome upon ADT [73]. In a recent clinical trial, expression of AR-V7 in CTCs correlated with resistance to enzalutamide and AA [74], making it arguably the first attractive candidate for a predictive biomarker for response to AR-targeted therapies in prostate cancer. Tumors expressing AR-V7 often remain sensitive to taxane-based therapeutics [75] and preclinical data suggest they may respond, at least indirectly, to BET bromo-domain targeted therapies [73]. Expression of AR-Vs is detectable in hormone therapy-naïve primary tumors and even peri-tumoral tissue and is associated with an unclear prognostic significance [72,76]. Thus, the clinical settings in which AR-Vs act as predictive biomarkers remain to be clarified.

BONE MARROW DISSEMINATED TUMOR CELLS AS INDICATORS OF RESIDUAL DISEASE

Disseminated tumor cells (DTCs) found in the bone marrow are often considered dormant and have been associated with biochemical recurrence in patients with no evidence of disease following RP, indicating they may be sites of early metastases. However, the clinical significance and numbers of DTCs remain unclear due to heterogeneity in markers and phenotypes. Descriptions of a $CD45^{-}EpCAM^{+}$ population of bone marrow cells with an erythroid-like instead of prostate gene expression profile has illuminated a need for validation of prostate origin and careful interpretation of results. CK^{+} cells with epithelial-mesenchymal transition-like expression of nuclear Twist, TGF-β, Slug, and Zeb1 have been observed in bone metastases by Dr. Colm Morrissey's group (University of Washington). DTCs with $CK^{-/low}$, AR^{-}, neuroendocrine, and/or cancer stem cell phenotypes may also occur. The clinical significance of DTCs may also be affected by plasticity of tumor dormancy and the signaling pathways, such as p38, that modulate the transition between dormant and proliferating cells [77,78]. Further studies are needed to clarify the utility of DTCs as early indicators of residual, potentially lethal disease in patients who have been treated with curative intent.

THE FUTURE OF MOLECULAR IMAGING

Treatment decisions for early metastatic prostate cancer patients depend on the ability to detect the location and number of metastatic lesions. Radiographic progression has traditionally been defined as the growth and/or development of new lesions on computed tomography (CT) [79] and technetium-99m bone scans [80], which can be limited in their scope (bone metastases only for bone scans) and sensitivity. Several new imaging agents and technologies, namely in positron-emission tomography (PET) and multi-parametric MRI (mpMRI), are emerging that have markedly increased sensitivity and specificity for detection of metastatic prostate cancer lesions in soft tissues and bone. For instance, fluorine-18 sodium fluoride (^{18}F-NaF) PET and whole body mpMRI (WBMRI) were shown to have similar diagnostic accuracy and outperform both ^{99m}Tc-hydroxymethane diphosphonate (^{99m}Tc-HDP) planar bone scans and ^{99m}Tc-HDP single-photon emission computed tomography/CT (SPECT/CT) [81]. As use of these imaging technologies becomes validated and better established, it is expected that clinical states of prostate cancer, particularly oligometastatic disease, will be redefined. In addition, the use of molecular imaging is expanding as a methodology to guide biopsies, monitor treatment responses, assess biological characteristics, and assess spatial and temporal tumor heterogeneity [82,83]. Imaging agents can also be harnessed for theranostics, to combine imaging and targeted delivery of therapeutics with the same compound. However, due to the increased developmental and operational costs of these new imaging technologies, how they will be appropriated into standard clinical use remains critically dependent upon evidence-based decisions based on clinical benefit; whether improved and earlier imaging detection of oligometastatic lesions results in a change in treatment management that ultimately improves patient outcomes [84,85].

In the U.K., the use of WBMRI to detect prostate cancer disease burden has become widespread over the past few years, despite the lack of clinical trials to demonstrate utility. Nevertheless, WBMRI is considered to give information equivalent to a combination of CT, bone scan, spinal MRI & pelvic MRI images. WBMRI DWI has been shown in an early study to detect metastatic bone lesions earlier than bone scans [86]. However, WBMRI needs to be compared in clinical trials with other imaging modalities and with blood-based diagnostic assays such as circulating tumor cells (CTCs) or circulating tumor DNA for a variety of clinical scenarios including: (1) efficacy in early detection of recurrence or metastases, (2) early determination of therapeutic responsiveness, (3) evaluating heterogeneity in therapeutic responses, and (4) phenotyping lesions in combination with other functional imaging modalities to guide biopsy or treatment decisions. Other arising technologies that may lend further improvements if integrated with mpMRI include ultrasmall superparamagnetic particles of iron oxide (USPIO) MRI, which can improve the detection of sub-centimeter sized metastatic lymph nodes [87].

PET imaging has several orders of magnitude greater sensitivity for tumor detection compared to standard conventional imaging such as CT, bone scan, and even MRI, and can also provide highly quantitative images [82]. Established and emerging PET imaging radiotracers for prostate cancer have been previously reviewed [82] and include ^{18}F-FDG to monitor glucose metabolism, ^{18}F-NaF for bone metastases, ^{11}C/^{18}F-Choline or ^{11}C-Acetate to monitor lipid metabolism, ^{18}F-FACBC to monitor amino acid metabolism, and ^{18}F-DHT uptake for imaging AR expression. An emerging new target for PET imaging is gastrin-releasing peptide receptor (GRPR), which is highly expressed by prostate tumors and PIN lesions and can be monitored by radiolabeled (^{64}Cu, ^{18}F, ^{68}Ga, or ^{18}F) GRPR-targeting bombesin analogues. Two of the most promising and emerging PET radiotracers for prostate cancer imaging, ^{18}F-NaF and prostate-specific membrane antigen (PSMA) targeted agents, are discussed further.

Bone remodeling and bone metastases can be assessed by ^{18}F-NaF PET, which is highly sensitive for detection of osteoblastic bone metastases, and therefore of importance for detection of early oligometastatic disease. An ^{18}F-NaF PET quantitative total bone imaging study performed by Drs. Robert Jeraj and Glenn Liu (University of Wisconsin) found substantial heterogeneity of therapeutic responses among metastatic lesions in individual metastatic CRPC (mCRPC) patients, with some lesions responding, some progressing, and new lesions appearing. The change in the number of lesions, maximum lesion PET standardized-uptake value (SUV) response, and the heterogeneity of the SUV response were together the best overall multivariate predictive ^{18}F-NaF PET imaging biomarkers of treatment response. In ongoing PCF-funded studies, the greatest responding and progressing lesions will be biopsied and genomically profiled to interrogate mechanisms of response and identify imaging characteristics that predict biology. In another PCF-funded study, the repeatability of ^{18}F-NaF PET imaging across three institutions with harmonized protocols and instruments was found to be ~95% and was greater than was found for DWI MRI in other studies (R. Jeraj and G. Liu, unpublished data). Thus, with harmonization, ^{18}F-NaF PET may be readily established in clinical practice as a highly repeatable imaging modality for mCRPC. Academic, government and industry stakeholders need to take initiative in creating imaging software and standardization methods for PET instruments.

Numerous radiolabeled small molecule and antibody-derived agents targeting PSMA are being developed as PET tracers. Low molecular weight ^{18}F-PSMA tracers developed at Johns Hopkins University, which include the first-generation ^{18}F-DCFBC and improved second-generation ^{18}F-DCFPyL, have shown promise for detection of primary prostate tumors as well as bone and lymph node metastases with imaging obtained at one to two hours after radiotracer administration [88,89]. PSMA-based imaging with ^{18}F-DCFBC, unlike ^{18}F-FACBC and choline-based PET tracers, appears to be highly specific for detection of clinically relevant primary prostate cancer and correlates with Gleason score, while importantly excluding nonspecific detection of prostatitis and benign prostatic hyperplasia [90]. ^{18}F-DCFPyL has demonstrated remarkably high tumor to background PET SUV ratios which increase the sensitivity of tumor detection. For instance, ^{18}F-DCFPyL PET detected a large number of lesions overall that were occult or equivocal with conventional CT or bone scan (140 positive and 1 equivocal metastases by ^{18}F-DCFPyL PET versus 30 positive and 15 equivocal metastases by CT and/or bone scan) [89,91]. In Europe, similar results have been demonstrated with ^{68}Ga-PSMA PET which has become widespread in compassionate use clinical settings. A recent study confirmed the improved sensitivity of a PSMA-based PET (^{68}Ga-PSMA-HBED) compared with a choline PET (^{18}F-Fluoromethylcholine) for prostate cancer detection and localization of metastatic prostate cancer in the biochemical recurrence clinical scenario with low PSA [92,93].

Immuno-PET involves utilization of radiolabeled antibodies or engineered antibody fragments against cell-surface proteins. Intact antibodies, minibodies (80 kDa scFv-C(H) 3 dimers), and diabodies (55 kDa scFv dimers) are differentially cleared from the body through different organ routes with different kinetics and thus require different imaging time points and are optimal for imaging different tumor sites [94]. For instance, with ^{124}I-labelling, antibodies are optimally imaged in ~1 week, minibodies in 21 hr, and dia-bodies within a few hours [95]. Other considerations in choosing between these agents include efficiency in uptake and half-life in vivo. Since neither minibodies nor diabodies contain full Fc regions, they are biologically inert, which is desirable in agents used purely for imaging. A phase I trial testing a ^{124}I-anti-PSCA minibody in prostate, bladder, and pancreatic cancer is ongoing at UCLA (NCT02092948). A phase I/IIa trial conducted at Memorial Sloan Kettering Cancer Center tested ^{89}Zr-Df-IAB2M anti-PSMA mini-body (IAB2M) PET imaging in 28 patients with metastatic prostate cancer who also received concurrent bone scans and FDG-PET/CT imaging [96]. IAB2M detected ~82% of bone and ~86% of soft tissue lesions identified in sum by all three imaging modalities, including uniquely detecting ~1/4 of the total lesions identified [96]. The minibody remained imageable in lesions for several days, allowing IAB2M-PET/CT-guided biopsies to be taken several days post-minibody administration to determine concordance with pathology [96]. A phase II study comparing Prostascint with IAB2M in detecting prostate cancer in high risk patients prior to prostatectomy is underway (NCT02349022). Antibody-based PET imaging agents that target immune cells are also being developed to visualize immune responses during immunotherapy.

Discordance and heterogeneity between PET, MRI and CT detection and characterization of metastatic lesions occurs and likely involves tumor biology and the inherent size limitations of these modalities, but the complete nature and clinical relevance underlying these

differences remains to be understood. How PET should be incorporated, combined with other measures of disease burden, and the optimal clinical settings for utilization remain to be determined, particularly because of the high cost of PET compared with standard conventional imaging (bone scan and CT). An emerging multi-modality imaging method includes PET/MRI, which may be better than PET/ CT due to lower radiation exposure and allows for superior registration for real-time motion correction of the two modalities. However, the real value of PET/MRI for prostate cancer remains to be demonstrated but may be realized by combining the anatomic and functional imaging information from both PET and mpMRI in a single simultaneous imaging scan.

CLINICAL TRIAL ENDPOINTS

Despite exciting results from phase III clinical trials such as CHAARTED, extended accrual/reporting times and the reliance on OS as an FDA approvable endpoint dampen enthusiasm for initiating trials in this space. New intermediate clinical trial endpoints could speed the development of promising therapeutic concepts in phase II trials with higher likelihood of success in phase III testing. Given the complexity of multimodal clinical trials combining systemic therapies, surgery and radiation, these decisions are even more critical. The FDA has provided recent guidance for the use of pCRs in high risk, early stage breast cancer as one potential endpoint to support accelerated drug approval. This is a high clinical bar, though pCRs in prostate cancer have been identified in neoadjuvant trials with AA and enzalutamide. Other novel clinical trial endpoints employed in phase II trials, if applied consistently, would provide improved “go/no-go” decision making for these purposes. In high risk/oligometastatic prostate cancer, one potential intermediary endpoint is undetectable PSA in the setting of normalized serum testosterone levels. Further validation of this endpoint with pCRs, progression free survival and OS is ongoing.

CONCLUSION

Overall, the CHPCA Meeting featured in-depth discussions of the most critical issues regarding improving diagnosis and prognosis, optimizing and designing new treatment strategies, and understanding the biological mechanisms of high-risk and oligometastatic prostate cancer. Development of multimodal treatment approaches for the care of these patients was of significant interest. The meeting also included break-out sessions to inspire the establishment of working groups addressing: (1) how to move forward approaches to high-risk localized disease, (2) clinical trial design in low volume/oligometastatic disease, (3) serum and tissue biomarker development, and (4) molecular imaging. The meeting and resulting knowledge exchanges are expected to accelerate studies that will improve outcomes for prostate cancer patients with otherwise lethal disease.

The theme of the 2016 CHPCA Meeting will be: “Beyond Seed and Soil: Understanding and Targeting Metastatic Prostate Cancer.”

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