Editorial

Assessment of real-world application of advanced prostate cancer management in Japan

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Prostate cancer remains the second most frequent cancer amongst men worldwide (1) but incidence of prostate cancer tends to be lower in Asia than it is in the Western population (2). However, increase in prostate cancer incidence has been observed more recently (3), and steady economic burden from the disease is more pronounced (4), hence making diagnosis and treatment for advanced and metastatic prostate cancer an increasing priority. The Advanced Prostate Cancer Consensus Conference (APCCC) convened in 2019 and addressed important clinical questions in both the diagnosis and treatment of prostate cancer (5). While the APCCC panel consisted of a diverse group of oncology specialists and scientists from around the world, not every country has access to the same resources, equivalent health care systems, and health coverage varies widely across different countries and even amongst different regions within a nation. The efforts of the Japanese Urological Association 2021 (JUA2021) 109th Annual Meeting to solidify some of the principles and consensus opinion has brought forth the review by Fujita *et al.* (6), which discusses key clinical questions that would serve as a clinical guide for practical management of locally advanced and metastatic hormone-sensitive and castrate-resistant prostate cancer (CRPC) in Japan.

The JUA2021 consisted of 10 voting members which comprised predominantly of Japanese urologists and the topics or clinical questions of relevance that were discussed included the role of the prostate-specific membrane antigen-positron emission tomography (PSMA-PET) scan in the diagnosis and treatment of prostate cancer, controversies surrounding oligometastatic disease, androgen-signaling agent use in non-metastatic CRPC (nmCRPC), relevance of treatment in a patient who remains to have a primary tumor despite diagnosis of metastasis, challenges regarding choice of therapy, in both systemic and local management of *de novo* metastatic castration-sensitive prostate cancer (CSPC), challenges of treatment in those presenting with metastatic CRPC, and relevance of tumor genomic testing and the appropriateness of testing. Japanese prostate cancer experts voted on these key issues and findings revealed several differences compared to the consensus opinion derived from the APCCC 2019. The findings revealed close to 50% of Japanese voting members chose conventional imaging such as computed tomography (CT) and bone scan instead of PSMA-PET in its application for detecting metastasis. In terms of choice of therapy, about 31.3% of Japanese urologists preferred ADT alone in the management of low-volume metastatic CSPC compared to only 7% of the APCCC panelists who chose it. The choice of androgen-signaling agents for treatment of M0 CRPC centered on darolutamide and enzalutamide by Japanese urologists and finally, about 56% of Japanese urologists have not recommended routine *BRCA1/2* testing only for those in the metastatic CRPC (mCRPC) setting compared to 46%

of voters at the APCCC.

The results of this review are not surprising. While PSMA-PET scan has become widely available and a mainstay of diagnostic testing in certain parts of the world like Australia or Germany, there are countries lacking access or third-party payers/insurers have not been routinely recognizing these imaging modalities as standard-of-care practice. For instance in the United States (US), despite the US Food and Drug Administration (FDA) approval of certain PSMA tracers like 68Gallium Ga-PSMA-11 from the University of California San Francisco (UCSF) and University of California at Los Angeles (UCLA) on December 2020, 18F-DCFPyL Pylarify approval on May 27, 2021, there are still a swarm of denials by different insurers (7), which makes routine utilization of PSMA-PET scan challenging across different indications. This is despite the National Comprehensive Cancer Network (NCCN) updates on guidelines for prostate cancer imaging, where they suggested foregoing conventional imaging stating it is not a prerequisite prior to obtaining a PSMA-PET which can be an equally effective frontline imaging (8). While the increasing use of PSMA-PET has revolutionized the field by increasing detection of metastatic disease in both primary and recurrent settings alike, there still exists the conundrum of lack of prospective trial data to guide clinical practice and confirm survival improvements as it relates to earlier discovery of subclinical disease seen on PET imaging with concomitant negative correlative conventional imaging (9). The choice of PSMA-PET imaging in various settings also varies. For instance, in patients after prostatectomy, 51% of respondents at JUA2021 chose CT and bone scan and 33% chose PSMA-PET/CT/magnetic resonance imaging (MRI) imaging while 64% chose PSMA-PET/CT/MRI for identifying oligorecurrent metachronous disease after radiotherapy, which is somewhat more concordant with that of the APCCC with 75% choosing PSMA-PET scans for the same population of patients.

Management of low-volume metastatic hormone-sensitive prostate cancer is also a field that is rapidly evolving. While androgen deprivation therapy (ADT) has historically been the treatment of choice for any metastatic disease presentation, treatment of low-volume and especially oligometastatic disease is somewhat incumbent upon detection of disease using highly sensitive imaging with PSMA-PET scans. The use of metastasis-directed therapy (MDT) serves to limit ADT exposure on one hand (10), on the other hand, multiple other prospective trials have already shown improvement in survival with upfront systemic intensification of therapy (11). Therefore, ADT alone may appropriately apply to a shrinking subset of patients with metastatic castrate-sensitive prostate cancer. A sobering US statistics shows an underwhelming number of prescribing oncologists utilized first-line novel androgen-signaling agents in only 32% compared to 12% of urology providers from a commercial database usage from 2012 to 2021 (12), which is reminiscent of what is being reflected in the current JUA2021 voting pattern.

Another area of interest is the choice of treatment in M0 CRPC and mCRPC. It appears as though darolutamide was the preferred androgen-signaling agent of choice at both the JUA2021 and APCCC2019 voting conferences, with 29.3% and 16%, respectively. This may not be a surprising finding given potential differences in toxicity and perhaps lesser blood-brain barrier penetration with darolutamide (13). However, bicalutamide remains in prevalent use in Japan, and appears to be heavily utilized in the mCRPC setting. It is interesting to note however, that majority of urologists (70.5%) at JUA2021 preferred subjecting patients to primary definitive prostate therapy with surgery over systemic therapy in nmCRPC patients with an untreated tumor, which is not supported by prospective data, but perhaps explained by the population of respondents who are predominantly urologists surveyed at the JUA2021. Similarly, 71% of respondents at the JUA2021 agreed with primary treatment in metastatic prostate cancer, with 20% choosing surgery regardless of volume of metastatic burden. There was not a consensus to extrapolate surgical results to radiotherapy, perhaps secondary to the lack of radiation oncologists in the panelists at JUA2021. There are other findings which refer to terminology differences, such as the preference for the term "hormone-sensitive" rather than "hormone-naïve" or even "castration-sensitive" which was the least popular. However, one area of dissent is the topic of primary local treatment of *de novo* metastatic hormone-sensitive disease presentation, where majority of the APCCC consensus opinion (80%) preferred pursuit of primary local prostate therapy with or without systemic treatment whereas only 44.2% of the JUA2021 voters opted for local treatment at all, which likely reflects lag of this practice pattern for metastatic prostate cancer. In addition, 31.3% of JUA2021 panelists chose primary ADT monotherapy as management for those patients who present with metachronous cancers, defined as those relapsing after primary local treatment, and still with low-volume metastatic hormone-sensitive prostate cancer, compared to only 7% of the APCCC panelists who chose this treatment,

and ADT monotherapy appears to be the preferred treatment of choice by Japanese urologists for most other indications, which highlight the need to emphasize existing level 1 prospective data rather than personal experiences alone, in making treatment decisions for advanced prostate cancer.

Regarding treatment for high-volume metastatic hormone-sensitive prostate cancer, the choice of systemic therapy appears to be in favor of one androgen-receptor signaling inhibitor (ARSI) with either abiraterone, apalutamide or enzalutamide in about 48.1% of respondents with only 25% choosing either docetaxel or an ARSI with only 5.8% choosing docetaxel only and only 4% chose ADT monotherapy. For treatment of mCRPC, there seems to be a fair number of JUA2021 voters who chose to prescribe bicalutamide routinely (about 19.2%) and about 21.2% in limited resource situation, the latter situation of which is understandable, though somewhat opposite to what was seen in APCCC where close to half (49%) of respondents chose to use bicalutamide only in the setting of limited resources. It is to be noted that consistent and predictable health care resources in a national health care service is provided in Japan, such that offering standard of care medicines are dependent on what is currently available.

Lastly, when queried regarding genomic sequencing and testing, a little over half (56%) of the JUA2021 respondents chose *BRCA1/2* tumor testing only for patients with mCRPC, with 26% choosing this particular genomic testing in the majority of patients with metastatic prostate cancer while a minority few (17%) chose against this testing, which is reasonable since olaparib is the only PARP inhibitor drug currently approved in Japan, and companion diagnostic testing would be a reasonable opt-in only for patients who are considered eligible for this targeted therapy when they have developed mCRPC after prior treatment failure of an androgen-signaling agent and not at the time of they remain treatment-naïve. However, it would be important to note that the prevalence overall of DNA damage repair (DDR) deficiency in men with prostate cancer is variable, ranging from 8.7% to 17% (14-17). In addition, widespread studies of germline variants for Japanese patients with prostate cancer has been sparingly reported (18,19).

In summary, the real-world consensus statement as convened by JUA2021 sheds light on clinical practice patterns in Japan which highly suggests that individual practice patterns for prostate cancer varies from different areas across the globe. Choices of treatment is dependent not just with available data but also regulatory approval for each drug, access to resources, availability of treatment, formulary preferences, perceptions and beliefs of both clinicians and patients, clinical infrastructures, and values placed on endpoints in clinical trials.

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