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Platinum Priority – Editorial

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Is Androgen Deprivation Therapy “Another Deficient Therapy” for Gleason Score 9-10 Prostate Cancer?

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Approximately, 160 000 new cases of prostate cancer (PCa) are diagnosed per year in the United States (US), the majority of which are cured. However, approximately 30 000 men die each year in the US of metastatic castrate-resistant PCa of which upwards of half began as localized or locally advanced disease. Thus, improvements in primary definitive management of these men can have a significant effect on mortality.

In this month's issue of *European Urology*, Yang et al report [1] on the association between androgen deprivation therapy (ADT) and overall survival (OS) in Gleason score (GS) 8 versus GS 9-10 PCa using the National Cancer Database. Their findings suggest that GS 9-10 disease is less sensitive to ADT, and its use in combination with radiation therapy (RT) is not associated with improved OS. These results add to mounting evidence suggesting Gleason pattern 5 disease is resistant to conventional ADT (cADT). Dr. Anthony D'Amico first astutely observed that phase III trials assessing long-term cADT in combination with radiation for localized high-risk and locally advanced PCa failed to show an OS benefit when higher proportions of men with GS 9-10 PCa were enrolled and suggested inherent resistance of Gleason pattern 5 to cADT in combination with radiation [2]. Huynh et al. [3] subsequently noted worse all-cause and prostate cancer-specific survival (PCSS) in men with GS 5 + 3 or 3 + 5 versus 4 + 4 disease treated using RT and cADT.

The realization that GS 8-10 disease represents an overly heterogeneous population led to the development of a “very high-risk” (VHR) group which includes primary pattern Gleason 5. It is now well established that failure of either surgery or RT occurs more frequently in VHR disease [4]. Furthermore, the Pathologic Grading System of the International Society of Urological Pathology has separated GS 8 (Grade Group [GG] 4) and GS 9-10 (GG 5) disease as distinct entities, a change that has been validated [5].

Are there additional treatment data that agree with Yang et al? In a retrospective, multicenter cohort of GS 9-10 disease, Kishan et al. [6] found significant improvements in PCSS and distant metastasis with combined external beam radiotherapy (EBRT)-brachytherapy compared with EBRT alone or radical prostatectomy but, importantly, no differences in outcomes when stratifying by use of cADT. In fact, men treated with combined EBRT-brachytherapy were treated with only an average of 12 mo of cADT versus 21.9 mo for the EBRT patients and still had better outcomes. Similarly, Sandler et al. [7] reported an improvement in distant metastasis among men harboring GS 10 disease treated with EBRT-brachytherapy plus cADT compared with EBRT plus cADT. These data suggest that Gleason pattern 5 disease may be less radiosensitized than lower-grade disease and that physical dose escalation may be able to overcome this insensitivity to cADT.

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The biological explanation for the potential insensitivity of Gleason pattern 5 disease to cADT, however, remains unknown. From a histomorphological standpoint, there is no clear evidence to support why Gleason pattern 5 disease should be resistant to cADT; however, the dedifferentiated phenotype completely lacking morphological features reminiscent of benign prostate glands in pattern 5 could indicate a general loss of dependence on signaling pathways relevant to the prostate lineage such as the androgen receptor (AR). In fact, there does appear to be a group of high-grade lesions with reduced AR dependence and signaling output, characterized by low prostate-specific antigen values, lower PCSS, and associated with neuroendocrine features [8]. Genetically, there is strong evidence to suggest GG 5 tumors have a higher level of genomic instability with an increased rate of copy-number alterations and alterations in key signaling pathways (*TP53*, *PTEN*, and *RB1*) that have been associated with resistance to ADT [9]. In particular, alterations in *TP53* are strongly enriched in pattern 5 lesions and have been shown to be associated with rapid progression to castration resistance [10]. Related to these genomic alterations, it may also be that Gleason pattern 5 disease more rapidly achieves castrate resistance or that the presence of GS 9–10 disease at diagnosis is a surrogate for more rapidly progressive disease which is also more likely to have disseminated microscopically. Investigation of time to castrate resistance, time to distant metastasis, stratifying men with GS 8 into 4 + 4 versus 3 + 5/5 + 3 and correlation with advanced imaging modalities like prostate-specific membrane antigen-based positron emission tomography will be critical to understanding the nature of this important clinical problem. Equally contributory would be studies that further profile the genomic landscape of Gleason pattern 5 disease, understanding that obtaining sufficient patients for these endeavors likely require a large, multi-institutional effort.

The accumulating evidence of cADT resistance in GS 9–10 disease now begs the question: what are the best strategies to treat these men? Answering this question in a randomized fashion will be challenging, given the rarity of the disease. The relatively low rates of biochemical progression-free survival following treatment of these men highlight the need for further testing of radiation dose escalation, supracastration, and chemohormonal approaches to treat Gleason pattern 5 primary tumor as well as target possible metastatic clones. The work by Yang

et al generates many additional novel questions for men with GS 9–10 disease. There is clearly a need to explore better therapeutic options and, importantly, genetically profile Gleason pattern 5 disease to allow for precision medicine approaches in the hopes of improving cancer-specific outcomes.

Conflict of interest: PTT co-owns the patent “Compounds and Methods of Use in Ablative Radiotherapy” (patent#: 9114158). PTT receives institutional research support from Medivation Inc-Astellas Pharma and RefleXion Medical and has consulted for RefleXion Medical.

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