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Commentary

Are we progressing in prostate cancer management?

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With more than 1.2 million cases worldwide reported in 2018, prostate cancer is one of the most frequently diagnosed malignancies in males [1]. Ductal adenocarcinoma (DAC), a rarer subtype, has been reported in its purest form in 0.2%–1.3% of localised prostate cancers, with 0.8%–12.7% co-existing with acinar adenocarcinoma, the most common histological type of prostate cancer [2]. Thus, under-recognised forms of prostate cancer can still affect thousands of patients and should not be overlooked.

Morphological variants of this common cancer, including DAC and intraductal carcinoma of the prostate (IDC-P), are associated with poor overall survival and progression-free survival outcomes. Tumours often present with a greater Gleason grade, tumour stage, degree of extraprostatic extension, and lymph node involvement [3,4]. The paucity of data on response to different treatment modalities in DAC is explained by the variant's aggressive nature and low incidence, where recruiting sufficient sample sizes is difficult in order to form accurate conclusions.

It is therefore timely that this issue of *Asian Journal of Urology* includes a report by Liu et al. [5] on the oncological outcomes of patients with DAC of the prostate treated with either radical prostatectomy or radiotherapy. They concluded that radical prostatectomy was associated with better survival outcomes in DAC, when compared to radiotherapy. Interestingly, they also found that those in the middle tertile of age and with lower tertile of prostate-specific antigen (PSA) may yield the most clinical benefit from radical prostatectomy.

In an ever-expanding evidence base highlighting major clinical challenges of accurately identifying patients with high-risk prostate cancer, Liu and colleagues were able to directly compare oncological outcomes from a large cohort treated with radical prostatectomy or radiotherapy. This study offers valuable insight into a wide variety of real-world treatment outcomes from the Surveillance, Epidemiology and End Results (SEER; https://seer.cancer.gov) database, aiding urologists in clinical practise. It still remains to be seen if morphological variants may act as prognostic indicators for the efficacy of treatment intensification across different treatment modalities, such as radical prostatectomy, radiotherapy, androgen deprivation therapies and taxane-based chemotherapy. Yet the caveat to locoregional treatment intensification in these variants is that patients often present with distant metastases on relapse after radical prostatectomy [6].

Even if considered to be rare, it is important to recognize, report and increase awareness of distinct tumour pathologies to improve patient stratification and inform future treatment decisions. One important reason for underreporting is the difficulty in morphologically distinguishing between other rare distinct variants such as IDC-P, high-grade prostatic intraepithelial neoplasia (HGPIN), cribriform adenocarcinoma, and ductal adenocarcinoma, where there has been inter-observer variability reported even among experienced uropathologists [7]. Prior to 2017, this was further compounded by the initial non-

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requirement of pathologists to report on this subpathology, as well the evolving definitions and diagnostic criteria of these subpathologies [8].

Despite the growing understanding of these rarer forms of common cancers, there are still some limitations that provide opportunities for further studies. Many genomic analyses and biological studies are from relatively small cohorts, explaining the discrepancies in their findings. Some theories underlying their aggressive nature postulate that genomic instability, PTEN loss, and defects in DNA damage repair pathways are to blame [9,10]. Therefore, the emergence of whole-genome sequencing can aid in studying growth of these pathologies, potential mechanisms for poor patient outcomes and therapeutic response. Similarly, prospective prostate cancer registries and studies can aid in monitoring clinical outcomes in the real-world community setting. As previously described, these aggressive variants are rarely isolated in their pure form, and typically co-exist with acinar adenocarcinoma. Whilst Liu et al. demonstrated promising findings in pure DAC, further studies into survival outcomes of different treatment modalities in other rare aggressive variants, such as mixed adenocarcinoma and IDC-P, are also important in improving prognostic stratification.

In conclusion, Liu and colleagues have provided us with valuable insights into cancer-specific and overall survival outcomes of DAC of the prostate treated with radical prostatectomy or radiotherapy. Their clinical data emphasise the need to further understand the mechanisms underpinning the aggressive nature of these uncommon variants of prostate cancer. There is a need for further large-scale prospective studies to help improve the precision in patient risk-stratification, as well as possibly developing new approaches in multi-modal, personalised therapy to improve prognosis in prostate cancer. We believe the time has come for the global community of scientists and clinicians treating prostate cancer to work together towards improving diagnostics and treatments, and welcome this inclusive approach.

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