# Metastatic prostate cancer: a wealth of data to put into practice

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Over the last decade, the management of advanced and metastatic prostate cancer (PCa) has remarkably evolved from a disease treated primarily by androgen deprivation therapy (ADT) into a complex landscape with now multiple therapies with demonstrated survival benefit. These advances correspond with a better understanding of PCa biology and the mechanisms underlying castration resistance.

Following the work of visionary Nobel prize laureates C. Huggins and A. Schally, metastatic PCa was once considered a uniform disease, typically responding to ADT in eugonadal men. Hormone responsiveness, unfortunately, is consistently transient and patients progress into a castration-resistant state wherein further therapeutic options were scarce and mostly palliative. Clinical trials were limited to fine-tuning the timing and duration of ADT and evaluating combination with available antiandrogens. PCa was considered insensitive to chemotherapy, and disease classification was simple, dichotomized into local and metastatic, hormone naive and hormone resistant.

Starting in 2005, a series of discoveries profoundly changed the PCa landscape. The start of this new era can certainly be fixed by the publication of two seminal studies establishing that taxane chemotherapy is active against PCa, hence promoting a multidisciplinary approach of a disease traditionally managed by a urologist. Together with results of the initial studies on bisphosphonates, hopes of longer and better life were brought to patients progressing on ADT. Metastatic castration resistant prostate cancer (CRPC) was then classified into pre and post-docetaxel states. From this, four events further profoundly impacted the PCa landscape.

Extensive dissection of the androgen receptor (AR) pathway led to the development of more potent second-generation AR-pathway inhibitors, including the antiandrogen enzalutamide and the steroidogenesis inhibitor abiraterone. With these agents, the AR axis could be further manipulated beyond ADT, extending the duration of life, with minimal toxicity, while preserving quality of life. Initially confined to patients progressing on docetaxel, they rapidly became the reference first-line treatment for metastatic CRPC.

Work on new imaging techniques such as whole-body MRI and PET have challenged the definition of localized and metastatic PCa, demonstrating that traditional imaging with thoraco-abdominal computed tomography (CT) and bone scintigraphy were grossly underestimating the natural history and extent of metastatic disease. Identifying with limited metastatic deposits more precision, coined as 'oligo-metastatic', is now creating opportunities for further attempts to apply localized treatment, to delay or enhance systemic treatment.

An in-depth understanding of the molecular landscape of Pca revealed that, apart from the AR and its extensive adaptative capacity, other alternative pathways could drive the disease, often leading to an even more aggressive path. One of the most important observations is the role of homologous recombination repair (HRR) genes. Somatic and germline loss-of-function DNA aberrations in the HRR pathway occur in up to 20% of metastatic Pca. This has led to successfully unveil the efficacy of PARP inhibitors for this subset of patients, already well studied in ovarian and breast cancer.

But the most important advances came from studies investigating early treatment intensification as an alternative to the 'sequence' approach starting when patients were progressing to metastatic CRPC setting. Three studies, enrolling 4224 patients with nonmetastatic CRPC with rapid PSA progression, have demonstrated that initiation of AR-pathway inhibitors should not be delayed until the appearance of metastases on conventional imaging. More

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importantly, nine trials, including more than 13 000 metastatic hormone-naive patients, have consistently demonstrated that early intensification of ADT with AR pathway inhibitors, chemotherapy and local treatment significantly increases overall survival and maintains quality of life.

These great developments, however, increase the complexity for treating physicians and effort must be made to transform these study results into practice. In this special issue of *Current Opinion in Urology*, we have invited key opinion leaders to summarize present knowledge on these series of critical topics.

Hopefully, these will help physicians in the field to better interpret and apply these rapidly emerging data to deliver the most effective treatments for patients with advanced prostate cancer.

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