EDITORIAL

Clinical Research

Screening of visceral metastasis in castration-resistant prostate cancer: a cornerstone in personalized patient's care

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In this issue of *Prostate Cancer and Prostatic Diseases*, van der Bergh et al. highlight the importance of screening for visceral metastasis (VM) in castration-resistant prostate cancer (CRPC) patients, as well as the prognostic impact of the presence and the localization of VM [1] in a real-world context.

Along with recent improvements in the treatment of metastatic prostate cancer, men diagnosed with CRPC have prolonged life expectancy. While up to 12% of patients with metastatic CRPC (mCRPC) present VM at screening [2], around 32% will be diagnosed with VM radiologically detected before death [3]. As per van der Bergh et al., the prevalence of VM in mCRPC is likely to be underestimated since their real-world population analysis shows that over 80% of patients are not screened for VM at CRPC diagnosis and about 40% did not undergo screening before starting systemic treatment [1]. As pointed out by the authors, during the study period ranging from 2010 to 2016, international guidelines did not recommend systematic screening of VM by mean of whole-body imaging. Conventional computed tomography (CT) is the most commonly used tool for the detection of VM in CRPC patients, however, has limited sensitivity. New imaging modalities (NIM) with potentially better accuracy have emerged, such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET), whole-body MRI with diffusion-weighted imaging, and single-photon emission CT. These were compared in the PROSTAGE trial, showing that PSMA-PET outperformed all other imaging methods studied for the detection of primary distant metastasis in high-risk prostate cancer [4]. However, the role of PET-CT scans in detection of progressing CRPC is still unclear, and the Radiographic Assessments for Detection of Advanced Recurrence III Group recommends the use of NIM in mCRPC only in presence of a negative conventional CT with clinical suspicion of disease progression [5]. The way in which NIM will be integrated into the standard pathway will be obviously key to further explore the importance and the prognostic implications of VM.

In the area of personalized medicine, advances in genetic research have recently played a significant role in the management of mCRPC, especially with the use of next-generation sequencing (NGS). NGS allows the analysis of many gene mutations in a short time frame and is increasingly used in clinical practice. At present, the European Guidelines of Urology suggest that all metastatic patients should be offered somatic genomic testing for homologous repair and *MMR* defects. This is also supported by the ESMO Precision Medicine Working Group that recommends to perform NGS on tumor samples to assess the mutational status of at least BRCA1/2 in selected mCRPC patients [6]. VM mostly occurs in the liver and lungs in mCRPC patients [3]. As previously described [7, 8], van der Bergh et al. found a significant difference in survival between patients with lung-only and liver-only metastases, with worse survival in the latter group. The greater genomic instability associated with liver metastases when compared to lung metastases could explain the worse survival of this subgroup of patients [1]. In this context, early NGS with a larger panel of gene mutation could potentially identify poor prognosis patients at diagnosis and trigger personalized systemic treatment. However, the cost-effectiveness of these new approaches will also be challenged by the limited overall survival (OS) of mCRPC patients having VM.

Regardless of the imaging modality and screening for genetic mutations, identification of VM in CRPC patients at diagnosis and assessment of VM's site seems crucial. In fact, among other factors such as lactate dehydrogenase, prostate-specific antigen, alkaline phosphatase, hemoglobin, performance status, Gleason score, age, albumin, presence of pain, number of metastatic sites, and circulating tumor cell enumeration, presence and localization of VM is a known prognostic marker of OS [9, 10]. This was underlined in the real-world study of van der Bergh et al., with a median OS of 8.6 months for patients with liver, 18.3 with lung, and 10.9 with both liver and lung metastases ($p < 0.001$) from the date of the first VM diagnosis [1]. Since metastatic disease distribution may affect survival and efficacy of systemic treatments in mCRPC, patients presenting with VM in the liver versus lung should be assessed independently [8]. In the context of an uncurable disease with limited therapeutic options, systemic treatment should be given as part of a personalized patient's care, with the aim of improving survival and quality of life, while avoiding overtreatment. In that way, van der Bergh et al. underline the necessity of identification of VM to initiate the appropriate treatment or best supportive care [1].

It is noteworthy that OS in the real-world analysis of van der Bergh et al. was shorter than in clinical trial populations, as reported in the meta-analysis of Halabi et al. including samples

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from multiple randomized clinical trials (RCT) [10]. Many factors could explain this discrepancy between real-life and RCT data. First, around one-third of patients did not benefit from a life-prolonging treatment in van der Bergh et al.'s cohort, while all patients were previously treated with docetaxel in the clinical trial populations included in Halabi et al.'s meta-analysis. Secondly, the absence of a protocol for radiologic assessment of VM in the real-life setting potentially leads to a delayed identification of VM, and longer survival reported in RCTs can be attributed to early detection of VM triggered by stringent protocols unapplied in daily practice. Finally, a selection bias may also explain this OS difference: while patients with unfavorable prognostic factors can be unfit for systemic treatments and are therefore excluded from RCT, real-world populations show worse prognostic factors at the diagnosis of VMs, as shown by van der Bergh et al. [1].

In conclusion, although the presence of VM is a known important prognostic factor of mCRPC, real-population study shows a lack of VM screening in CRPC patients. Onco-urologists need guidelines for better screening of VM in CRPC patients in clinical practice. NIM and NGS could potentially improve the detection of VM, leading to earlier adequate and personalized treatment.

REFERENCES

1. van den Bergh GPA, Kuppen MCP, Westgeest HM, Mehra N, Gerritsen W, Aben KKH, et al. Incidence and survival of castration-resistant prostate cancer patients with visceral metastases: results from the Dutch CAPRI-registry. Prostate Cancer Prostatic Dis. 2022.
2. Alumkal JJ, Chowdhury S, Loriot Y, Sternberg CN, de Bono JS, Tombal B, et al. Effect of visceral disease site on outcomes in patients with metastatic castration-resistant prostate cancer treated with enzalutamide in the PREVAIL trial. Clin Genitourin Cancer. 2017;15:610–7.e3.
3. Pezaro C, Omlin A, Lorente D, Rodrigues DN, Ferraldeschi R, Bianchini D, et al. Visceral disease in castration-resistant prostate cancer. Eur Urol. 2014;65:270–3.
4. Anttinen M, Ettala O, Malaspina S, Jambor I, Sandell M, Kajander S, et al. A prospective comparison of 18F-prostate-specific membrane antigen-1007 positron emission tomography computed tomography, whole-body 1.5 T magnetic resonance imaging with diffusion-weighted imaging, and single-photon emission computed tomography/computed tomography with traditional imaging in primary distant metastasis staging of prostate cancer (PROSTAGE). Eur Urol Oncol. 2021;4:635–44.
5. Crawford ED, Koo PJ, Shore N, Slovin SF, Concepcion RS, Freedland SJ, et al. A clinician's guide to next generation imaging in patients with advanced prostate cancer (RADAR III). J Urol. 2019;201:682–92.
6. Mosele F, Remon J, Mateo J, Westphalen CB, Barlesi F, Lolkema MP, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020;31:1491–505.
7. Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol. 2014;65:3–6.
8. Loriot Y, Fizazi K, de Bono JS, Forer D, Hirmand M, Scher HI. Enzalutamide in castration-resistant prostate cancer patients with visceral disease in the liver and/or lung: outcomes from the randomized controlled phase 3 AFFIRM trial. Cancer. 2017;123:253–62.
9. Halabi S, Lin CY, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2014;32:671–7.
10. Halabi S, Kelly WK, Ma H, Zhou H, Solomon NC, Fizazi K, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol. 2016;34:1652–9.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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