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Heterogeneity of 68Ga-prostate-specific membrane antigen positron emission tomography/computed tomography in metastatic castration-resistant prostate cancer: Genomic characteristics and association with enzalutamide/abiraterone response

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Introduction & Objectives: In prostate cancer, both ^{68}Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and circulating tumor DNA (ctDNA) could act as a dynamic tool for 'real-time' reflection of tumor characteristics. The aim of this study was to evaluate the impact of spatial heterogeneity of the PSMA uptake on the ctDNA characteristics and response rate to new hormonal agent (NHA) treatment.

Materials & Methods: This retrospective study included 153 patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing ^{68}Ga-PSMA PET/CT and 72 targeted genes ctDNA sequencing with a less than 2-week interval. Patients with >1 PSMA-positive lesions were eligible for SUVhetero (as measured by the variance of average SUV) calculation. Patients receiving abiraterone treatment after enrollment and with complete follow-up record were included into prostate-specific antigen (PSA) response rate analysis. PSA response was defined as a reduction of greater than 50% from baseline. Correlations and comparisons by Spearman and Mann-Whitney tests, respectively.

Results: Overall, 118 patients were eligible for SUVhetero calculation. And the ctDNA detection rate was 65% (100/153). Higher SUVhetero value contributed to higher ctDNA% (Spearman's rho = 0.278, $p < 0.002$). A total of 60 patients were included in PSA response rate analysis. Compare to patients with higher SUVhetero value, patients with not available SUVhetero value had a higher PSA response rate (52% vs. 90%, $p = 0.036$). We further discovered a higher SUVmax-mean value was strongly correlated with higher SUVhetero value (Spearman's rho = 0.833, $p < 0.0001$). Patients with higher SUVmax-mean value also had a higher PSA response rate compared to patients with lower SUVmax-mean value (83.3% vs. 53.3%, $p = 0.024$). An external cohort confirmed baseline SUVmax-mean value was associated with enzalutamide treatment response rate. In overall population, a higher SUVmax-mean value was found to be correlated with higher ctDNA% (Spearman's rho = 0.357, $p < 0.0001$), higher TTV (Spearman's rho = 0.549, $p < 0.0001$), and higher TLU (Spearman's rho = 0.679, $p < 0.0001$). In addition, patients with alterations in AR, DNA damage repair pathway, TP53, and WNT pathway had higher SUVmax-mean value compared to those without ($p < 0.05$).

Conclusions: SUVhetero and SUVmax-mean, which was associated with ctDNA characteristics and response rate to NHA treatment, both reflect the Spatial heterogeneity of the PSMA uptake. Our findings supported the implementation of 68Ga-PSMA PET/CT testing in clinical management of NHA-treated patients with mCRPC.