

***HSD3B1* Genotype and Response to Androgen Deprivation Therapy for Biochemical Recurrence after Radiotherapy for Localized Prostate Cancer**

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Background

The variant *HSD3B1*(1245C) allele enhances dihydrotestosterone synthesis and predicts resistance to androgen deprivation therapy (ADT) for biochemically recurrent prostate cancer after prostatectomy and for metastatic disease. Whether the same is true after radiotherapy is unknown. We sought to determine whether the *HSD3B1*(1245C) allele predicts worse clinical outcomes in men receiving ADT for biochemical recurrence after RT.

Methods

We used the Prostate Clinical Research Information System at Dana-Farber Cancer Institute to identify the study cohort, which included men treated with ADT for biochemical recurrence after primary radiotherapy. We retrospectively determined *HSD3B1* genotype and then analyzed time to progression, time to metastasis, and overall survival according to *HSD3B1* genotype using an additive genetic model. Multivariable analyses were performed to adjust for known prognostic factors with Cox regression.

Results

We identified 218 eligible men, of whom 213 (98%) were successfully genotyped. Of these, 97/213 (46%), 96/213 (45%) and 20/213 (9%) carried 0, 1, and 2 variant alleles. Overall variant allele frequency was 136 of 426 alleles (32%). Median age (interquartile range) at ADT initiation was 69 (63-74), 72 (65-78), and 69 (65-77) years for 0, 1, and 2 variant alleles (P=0.03). Demographic and treatment factors were otherwise similar. With a median follow-up of 7.9 years, median time to progression was 2.3 (95% CI: 1.6, 3.1) years in men who inherited 0 variant alleles, 2.3 (1.5, 3.3) years with 1 variant allele, and 1.4 (0.7, 3.3) years with 2 variant alleles (P=0.683). Median time to metastasis diminished with the number of variant alleles inherited (7.4 [6.7, 9.7], 5.8 [4.9, 6.5] and 4.4 [3.0, 5.7] years, respectively (P=0.030). No difference in overall survival was detected (P=0.305). On multivariable analysis with 0 variant alleles as the reference, the adjusted hazard ratio (HR) for metastasis was (1.19 [0.74, 1.92]; P=0.480) for 1 allele and (2.01 [1.02, 3.97]; P=0.045) for 2 alleles. Multivariable analysis did not demonstrate significant differences in time to progression or overall survival.

Conclusions

The *HSD3B1*(1245C) allele predicts more rapid development of metastases in men treated with ADT for biochemical recurrence after primary radiation therapy for prostate cancer. Notably, 105/213 (49%) of men had received prior ADT as part of local therapy and 119/213 (56%) received an anti-androgen during salvage treatment, both of which may blunt the effect of the variant allele.

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Conflict of Interest

None.