

Oncology

The Effects of Enzalutamide Monotherapy on Multiparametric 3T MR Imaging in Prostate Cancer



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ABSTRACT

The effects of enzalutamide monotherapy on prostate tumor downsizing and multiparametric MRI are currently unknown. Here we present the first case in literature of a patient with high-grade prostate cancer who underwent 3 months of neoadjuvant enzalutamide, for which the effects on mpMRI and histology were determined. Tumor size reduction and downstaging were noted. Neoadjuvant enzalutamide resulted in an increase in ADC value on the DWI-MRI sequences. Histological changes were also observed.

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Introduction

Androgen ablation is the cornerstone of systemic prostate cancer treatment. This can either be achieved by (chemical) castration with GnRH/LH-RH-analogues alone or in combination with androgen receptor inhibitors. Over time, multiple androgen receptor inhibitors have been developed, with increasing efficacies in blocking androgen action. Initially, flutamide was developed as a non-steroidal antiandrogen. Subsequently, other non-steroidal antiandrogens such as nilutamide and bicalutamide were introduced, with longer half-lives and reduced toxicity.¹ Second generation antiandrogens such as enzalutamide (Xtandi, Astellas Pharma; Medivation) showed increased androgen receptor blockade, inhibition of receptor nuclear translocation and

diminished DNA-binding² that resulted in a survival benefit in men with castration resistant cancer.^{3,4} The effects of enzalutamide monotherapy on cell growth have not extensively been studied in hormone-naïve prostate cancer patients.

Neoadjuvant androgen ablation prior to prostatectomy has shown to result in tumor downstaging, reduction in surgical positive margin-rates, decreased lymph node invasion and reduced blood loss.^{5–7} Although generally found not to affect overall survival,⁶ in men with PSA > 20 ng/mL neoadjuvant cyproterone acetate treatment was found to improve recurrence-free survival.⁴ Therefore, we started a phase II window study on the efficacy of enzalutamide in hormone-naïve patients in the preoperative setting; tissue is analyzed before and after 3 months of neoadjuvant 160 mg daily enzalutamide monotherapy (NL47463.031.14). In this study, potential tumor downstaging is assessed in men who undergo prostatectomy for intermediate or high-risk prostate cancer.

Multiparametric (mp) MRI is presently used to grade and stage men with prostate cancer preoperatively. Androgen ablation was

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found to alter MRI-characteristics of the prostate.⁸ The effects of enzalutamide monotherapy on tumor downsizing and mpMRI are currently unknown. Here, we present the case of a patient with high-grade prostate cancer who underwent 3 months of neoadjuvant enzalutamide, and for whom treatment effects on mpMRI and histology were assessed.

Case report

A 62-year-old man was diagnosed with prostate cancer at a PSA of 8.5 ng/mL and Gleason score 4 + 4 = 8 in 4 of 6 biopsies on the left and Gleason score 3 + 3 = 6 in 3 of 6 biopsies on the right in a 36 cc prostate. Digital rectal examination revealed suspicion for a cT2b tumor in the right lobe. Transrectal ultrasound showed a tumor in the peripheral zone on the left side staged as cT2b. The patient participated in the above mentioned clinical study approved by the local ethical committee.

Pretreatment

Multiparametric 3T MRI was performed prior to enzalutamide treatment using a pelvic coil in combination with an endorectal coil (Achieva, Philips, the Netherlands) and included T2-weighted imaging, diffusion weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE-MRI). The apparent diffusion coefficient (ADC) was calculated from DWI-images using *b*-values 200, 600, and 1000 s/mm². Pharmacokinetic analysis with the Tofts model was performed of DCE-images (temporal resolution 2.7 s) resulting in *K*^{trans} maps (volume transfer constant from blood plasma to extravascular extracellular space). Imaging suggested extraprostatic extension (mcT3aN0Mx) in the left lobe with an ADC value of 0.75×10^{-3} mm²/s suspicious for high-grade prostate cancer. The tumor on the right was difficult to differentiate on MRI.

After treatment

After enzalutamide pretreatment PSA dropped to 1.2 ng/mL. The second mpMRI showed prostate size reduction of 27% and tumor size reduction of 83%. Interestingly, alterations were most markedly present in functional imaging data (Fig. 1): mean ADC increased

Table 1

Functional imaging data before and after enzalutamide monotherapy.

	Before enzalutamide monotherapy	After 3 months of enzalutamide monotherapy
ADC* (10 ⁻³ mm/s)		
Tumor	0.75 ± 0.13	1.28 ± 0.17
Healthy PZ'	1.83 ± 0.19	2.05 ± 0.32
<i>K</i> ^{trans} (min ⁻¹)		
Tumor	0.44 ± 0.08	0.13 ± 0.02
Healthy PZ	0.13 ± 0.02	0.08 ± 0.02

Data presented as mean ± standard deviation.

* = apparent diffusion coefficient; '(PZ) = peripheral zone; ' = volume transfer constant.

from 0.75×10^{-3} mm²/s in the pretreatment mpMRI compared to 1.28×10^{-3} mm²/s in the mpMRI after enzalutamide (Table 1). The ADC in a ROI (region of interest) in healthy peripheral zone did not change significantly. In DCE-MRI, a clear reduction in tumor perfusion and gadolinium washout was visible: *K*^{trans} reduced from 0.44 min⁻¹ pretreatment to 0.13 min⁻¹ after enzalutamide. A small reduction in perfusion was visible in healthy peripheral zone (from 0.13 to 0.08 min⁻¹).

For histologic evaluation, prostate base and apex were laminated parasagittally after formalin fixation overnight. Remaining prostate parts were laminated transversely in whole mount 4 mm slices. Hematoxylin and eosin stained slides were evaluated by a urogenital pathologist (JdJ). The neoadjuvant treatment effect was heterogeneous, with only focal areas of tumor cells with severe treatment effect consisting of cells with pyknotic nuclei and abundant xanthomatous cytoplasm (Fig. 1). Residual tumor was scattered multifocal with dominant lesions at the apex on the left and in central slides ventral on the right. TNM (7th edition) stage was ypT2cN0Mx. Because of treatment effect, no Gleason score was assigned.

Discussion

Androgen ablation was earlier found to be of limited value in a neoadjuvant setting prior to prostatectomy.^{5–7,9} Although positive margin-rates were found decreased in men with neoadjuvant

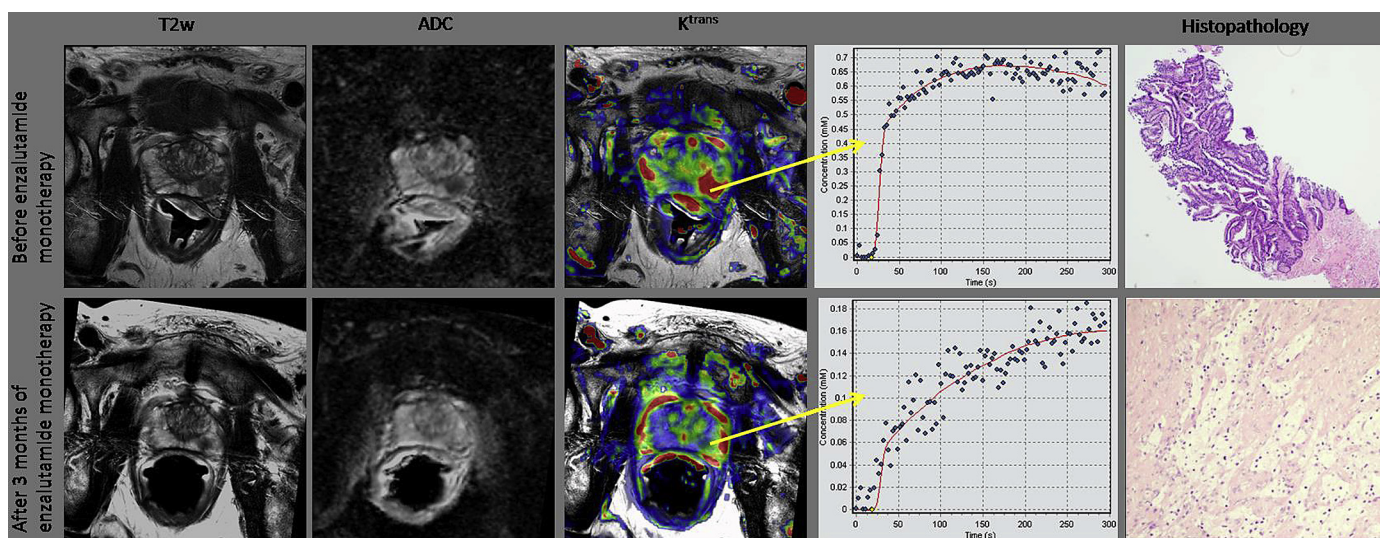


Figure 1. MpMR images and histology before and after 3 months of enzalutamide monotherapy. Subsequently, transversal T2-weighted image, ADC map from DWI, *K*^{trans} map with contrast uptake curve in tumor area, and corresponding histology of the left prostate lobe.

treatment, oncological outcome was not improved. Since novel antiandrogen treatment options were found to improve survival in men with metastasized disease³ and are effective in a monotherapy setting,⁴ it may be of value to re-explore their role in localized disease.

We present the first case in literature depicting the effects of neoadjuvant enzalutamide in high-risk prostate cancer using mpMRI and histological evaluation. Surprisingly, little is known on histopathological characteristics that are causative of altered mpMRI-findings so well studied in the detection of prostate cancer. The neoadjuvant setting provides an interesting opportunity to correlate histology with mpMRI-findings in relation to androgen ablation. Earlier studies after chemotherapy indicated that marked MRI changes were associated with partial tumor responses in 27%, although MRI response was not clearly predictive of postoperative recurrence-free survival.¹⁰ Alterations on mpMRI after enzalutamide monotherapy and correlation with histology have not been thoroughly studied. In the presented case a tumor size reduction of 83% was noted after enzalutamide use. This downsizing was associated with downstaging on MRI from T3a to T2c. Interestingly, neoadjuvant enzalutamide also resulted in an ADC value increase on DWI-MRI sequences suggestive of reduction in cell density. Histological changes were also observed. Both tumor downsizing and downstaging was achieved in this case by means of neoadjuvant enzalutamide.

This case shows, for the first time, the effects of enzalutamide monotherapy on primary prostate cancer using MRI. The alterations on mpMRI parameters were remarkably more pronounced in tumor compared to normal prostate tissue.

Conflicts of interest

The authors declare no conflicts of interest.

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