APCRC-Q Australian Prostate Cancer Research Centre Queensland
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Monitoring Tumour Growth and Oxygen Distribution of Prostate Cancer Xenografts *in vivo* Using Ultrasound and Photoacoustic Imaging

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Introduction

Prostate cancer is the second leading cause of cancer-related death in men. Androgen-targeted therapies (**ATTs**) are administered to treat prostate cancer, and the tumour microenvironment has long been recognised to modulate the response of tumours to therapies. However, the impact of ATTs on the tumour microenvironment and its contribution to ATT resistance has not been fully investigated longitudinally *in vivo*.

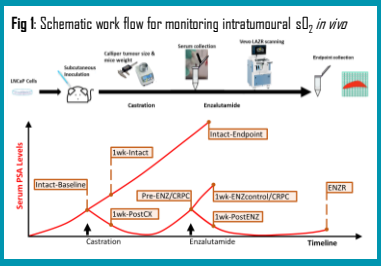
Research objectives

- To evaluate the potential of non-invasive combined photoacoustic ultrasound imaging to assess alterations in tumour hypoxia during treatment of prostate cancer xenografts with ATTs *in vivo*.
- To reveal the potential of oxygen saturation level derived from photoacoustic ultrasound imaging to predict tumour responses to ATTs.

Methods

The Vevo LAZR (FUJIFILM Visual Sonics) system was used to perform photoacoustic ultrasound imaging at intervals during the progression of subcutaneous LNCaP xenografts, prior to and during treatment with ATTs, i.e. castration and enzalutamide oral gavage (**Fig 1**). Tumour volumes, morphology, and intratumoural oxygen saturation (sO_2) were simultaneously monitored using photoacoustic ultrasound imaging. Changes of sO_2 were compared with the results from conventional endpoint assessments (immunohistochemistical analyses and RNA sequencing gene signature scores).

Fig 1: Schematic work flow for monitoring intratumoural sO_2 *in vivo*



Results

- sO_2 increased acutely in response to castration and enzalutamide and subsequently decreased during the development of ATT resistance (**Fig 2A**). This correlated with changes in hypoxia indicated via HIF1-α protein expression (**Fig 2B**) and transcriptional levels (**Fig 2C**; shown in heatmap of the hypoxic gene signature variation analysis scores).
- A higher pre-castration sO_2 level was associated with a better tumour response to castration (**Fig 3A**).
- Lower pre-enzalutamide sO_2 levels were associated with better tumour response to enzalutamide (**Fig 3B**).
- Sustained hypoxia indicated poor response to both castration and enzalutamide.

Fig 2: sO_2 levels and hypoxia response to ATTs

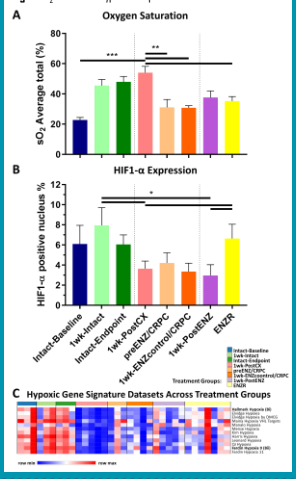
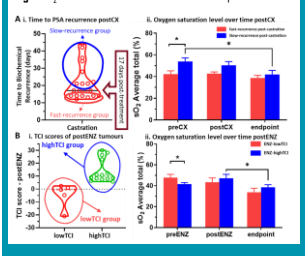


Fig 3: sO_2 levels in context of different tumour responses to ATTs



Discussion

Both castration and enzalutamide therapies inhibited intratumoural hypoxia and demonstrated that this effect was reversed with progression of castration and enzalutamide resistance. The study also revealed the potential of sO_2 as a predictor of prostate cancer resistance to ATTs.

Limitations

While use of photoacoustic-ultrasound imaging is well-established in pre-clinical models, its application for clinical imaging requires further optimisation. In this study, only subcutaneous LNCaP xenografts were investigated, and orthotopic xenografting using additional cell lines will be required for validation. Further pre-clinical studies using patient-derived tumour xenografts will be helpful in validating the prognostic value of sO_2 in predicting therapy responses.

Conclusion

The information gained from this study provided a holistic view of prostate tumour hypoxia responses to ATTs, suggesting that novel combination therapies targeting the androgen axis and hypoxia may be of clinical benefit in the management of prostate cancer. Furthermore, photoacoustic-ultrasound imaging-derived tumour sO_2 levels may have the potential to assist clinical decision-making.

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