

Aureon Laboratories' Systems Pathology - Prostate Cancer

Prediction of Duration of Response to Androgen Deprivation Therapy

Challenge: To determine if Androgen Receptor (AR) levels from the primary prostate tumor tissue may be predictive of therapeutic response to androgen deprivation therapy (ADT) in terms of elapsed time from initial treatment with ADT after prostatectomy, to castrate rise in PSA levels. By utilizing quantitative immunofluorescence (IF) and spectral imaging, we evaluated AR content as an independent predictor of therapeutic outcome.

Methods: 63 of 881 patients treated by radical prostatectomy had received ADT for a biochemical rise in PSA and/or clinical progression of their disease. 32 of 63 patients had progressed post-ADT with a castrate rise in PSA. Tissue microarrays with triplicate patient cores were stained with a multiplex immunofluorescent assay (IF) which contained the nuclear marker DAPI, along with the following antibodies: Androgen Receptor (AR), Racemase (AMACR), CK-18, HMWCK and p63. IF images were acquired with spectral un-mixing employed to develop antibody-cell-specific gray scale images. Utilizing image analysis algorithms, quantitative features including intensity and area for selected antigens was generated.

Results: Eleven IF antigen features were evaluated after feature selection and filtering using the concordance index (CI) with respect to outcome. A total of five (5) features were statistically significant for predicting time to progression post-therapy of which two (2) features (AR intensity within AMACR (+) and (-) epithelial cells; $p=0.0003$ and $p=0.0021$, respectively) demonstrated that elevated levels of AR were associated with a shortened time to castrate rise in PSA post-ADT. Clinical features alone were not found to be statistically significant with respect to predicting outcome.

Conclusions: AR levels in the prostatectomy sample appears to be a useful indicator for determining therapeutic ADT response and potentially guiding future treatment decision and patient monitoring. Further research on a larger cohort is needed to conduct a properly powered study, which then needs further validation.

Clinical Features	CI	Chi Square	p-value
Clinical Stage	0.50	0.00	0.9689
Pre-Op PSA	0.48	0.26	0.6107
Dominant Biopsy Gleason Grade	0.49	0.05	0.8223
Biopsy Gleason Sum	0.46	0.54	0.4608
Dominant Prostatectomy Gleason Grade	0.43	0.87	0.3499
Prostatectomy Gleason Sum	0.49	0.04	0.8462
Seminal Vesicle Invasion Status	0.44	1.67	0.1956
Lymph Node Status	0.53	0.32	0.5731
Surgical Margin Status	0.51	0.21	0.6476
Extra Capsular Extension Status	0.51	0.23	0.6335
Aureon Multivariate Model for ADT Response	0.68	11.00	0.0009

Note: Chi-squared and p-values calculated according to the Log-Rank test.

Table 2. Comparison of univariate analysis of various clinical-pathological attributes used to risk stratify patients for duration of ADT response and a multivariate model developed by Aureon Laboratories utilizing morphometric image analysis of Androgen Receptor. The CI and p-values generated using Aureon's Systems Pathology show promise in being able to more accurately risk stratify these patients in terms of ADT response than clinical features alone.

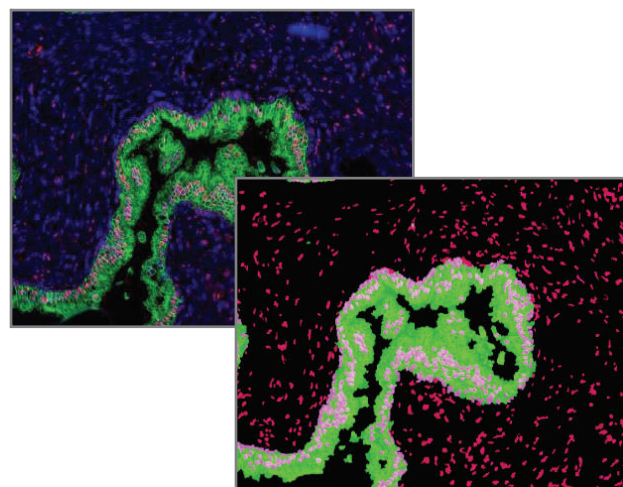


Figure 2. Aureon image capture of prostate gland: Original multiplex IF assay is in the background, Aureon segmented and classified image is in the foreground. Patients who have a predominance of Androgen Receptor (AR) expressed in epithelial nuclei are at higher risk for biochemical recurrence and/or clinical failure. Aureon's technology utilizes object-based quantitation of AR (or any other biomarker of interest) in gland units, vessels, cytoplasm and/or the nuclei of a variety of cell types (e.g., epithelial, stroma, proliferative). Epithelial nuclei is in green, AR+ epithelial nuclei is in light pink, AR+ stromal nuclei is dark pink.

Patient Demographics	63 Patients
Clinical Stage	T1c (17), T2a-c (38)
Average PSA	14.34ng/ml
Dom Biopsy Grade	GG 3 (37), GG4 (25)
Biopsy Gleason Score	GS 6(23), 7(21) 8>(16)
Dom Prostatectomy Grade	3(32), 4(29)
Prostatectomy Gleason Score	6(19), 7(24), 8>(20)
SVI	0(41), 1(22)
LN	0 (52), 1(11)
Margins	0 (27), 1(34)
ECE	0 (33), 2(29)

Table 1. Patient demographics for study.

