Multiple Instance Learning of Large-scale DNA Organization to Characterize Prostate Cancer Aggressiveness

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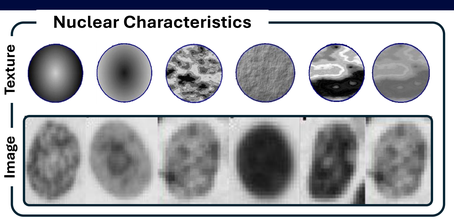
Background



Clinical Label	GS 6 Patients	GS 7 Patients	GS 8 Patients	GS 9Patients
Indolent (Train)	32	/	/	/
Indolent (Test)	2	5	/	/
Aggressive (Train)	/	/	/	20
Aggressive (Test)	/	/	7	1
A.S. (-)	2	5	/	/
A.S. (+)	13	4	/	/
Brachytherapy (-)	20	33	1	1
Brachytherapy (+)	7	19	/	/

Table 1: Patient demographic: **Indolent** = Gleason score (GS) 6 no progression; **Aggressive** = GS 9, dead within 2 years; **AS (-)** Active surveillance, no progression; **AS(+)** Active surveillance progression; **Brachytherapy (-/+)** = PSA recurrence after brachytherapy.

Background: Robust prognostic systems are a crucial element of prostate cancer (PCa) management. Despite improvements, precise prognostic systems which are widely available while offering –omics level granularity remain a challenge. Here, we introduce large-scale DNA organization (LDO) analysis, a form of pathomics analysis leveraging multiple-instance learning, as an effective prognostic system for PCa. LDO analysis quantifies nuclear morphology and texture as shown above.

Objective: Develop and validate a pipeline to analyze Feulgen-thionin stained prostate biopsy sections which will: (1) analyze LDO of cell nuclei to characterize the aggressiveness of the patient's prostate cancer and (2) act as a complementary system to the current PCa grading/prognosis system.

Methodology

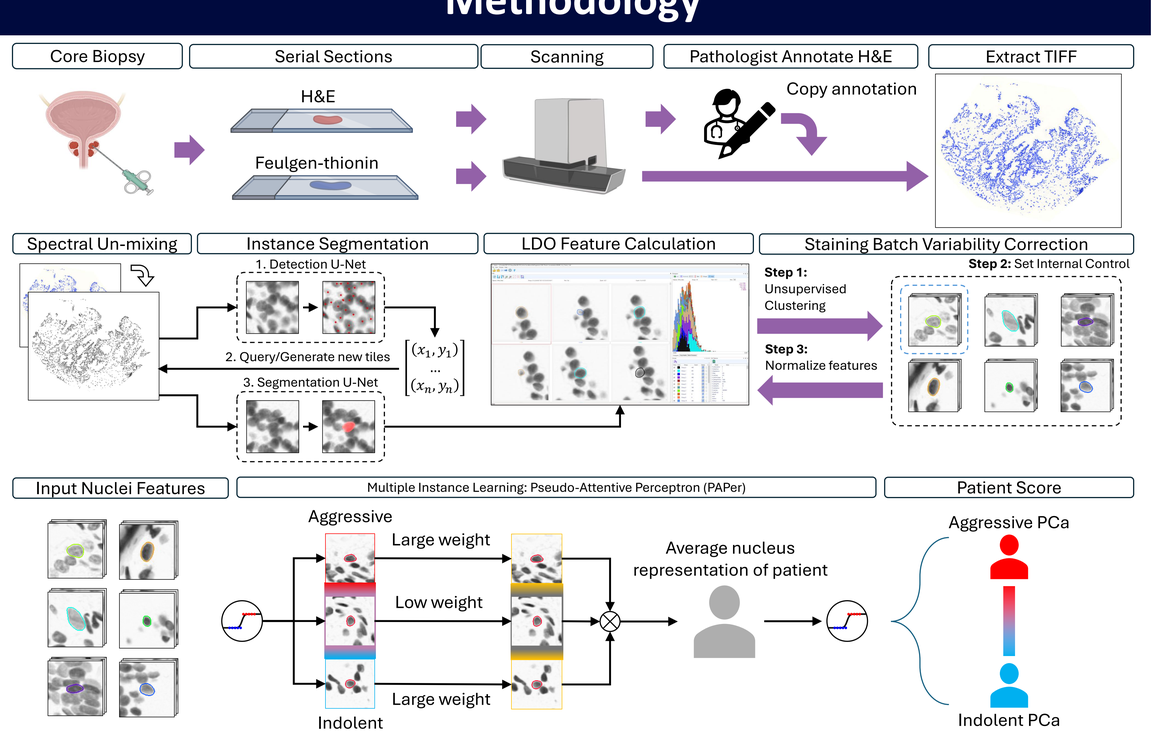


Figure 1: Row 1) Illustrates the clinical specimen collection. A core needle biopsy is formalin fixed, and paraffin embedded. Serial sections of 4 µm are cut and stained with hematoxylin and eosin (H&E) and Feulgen-thionin. Pathologist annotations of diagnostic regions on H&E are copied onto Feulgen-thionin and extracted as a TIFF image. **Row 2)** Extracted images are spectrally unmixed to generate a DNA concentration image. Nuclei on the unmixed image are segmented by the sequential U-Net instance segmentation algorithm. For each segmented object, 140 LDO features are calculated. To correct for staining batch variability, LDO features are re-normalized using the mean integrated optical density (IOD) of an internal control population generated by unsupervised clustering. **Row 3)** Nuclear features are analyzed with a pseudo-attentive perceptron (PAPer) model which assigns higher weights to nuclei which are highly likely to be indolent or highly likely to be aggressive, and lower weights to ambiguous nuclei. The weighted mean of nuclear features is input to the same PAPer model to generate an LDO score for the patient.

Results

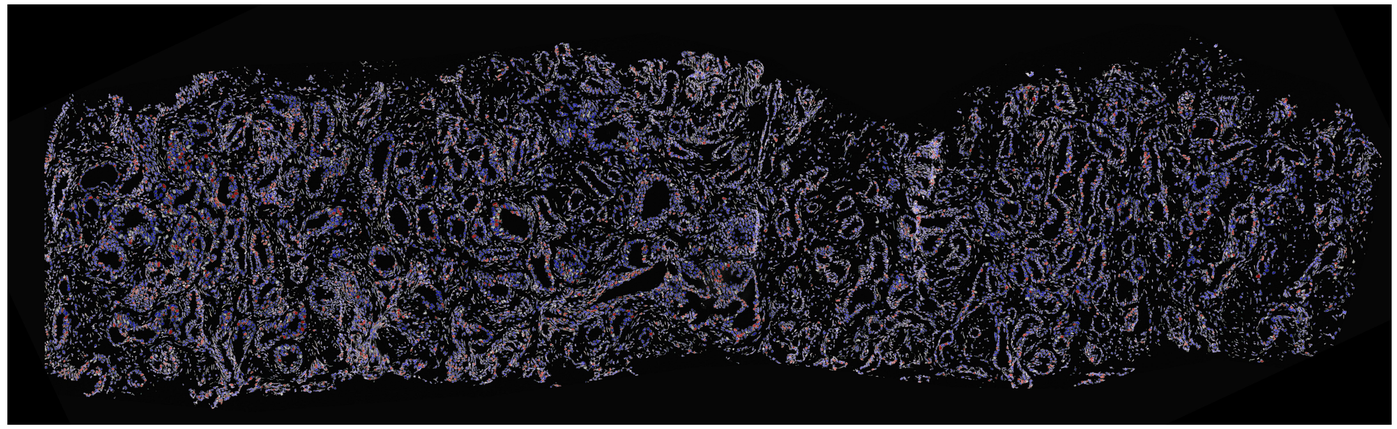


Figure 1: Prostate core needle biopsy (inverted color image) with attention values mapped to each nucleus. Red = positive attention, likely aggressive. Blue = negative attention, likely indolent cell. White = ambiguous (probability 0.45 – 0.55).

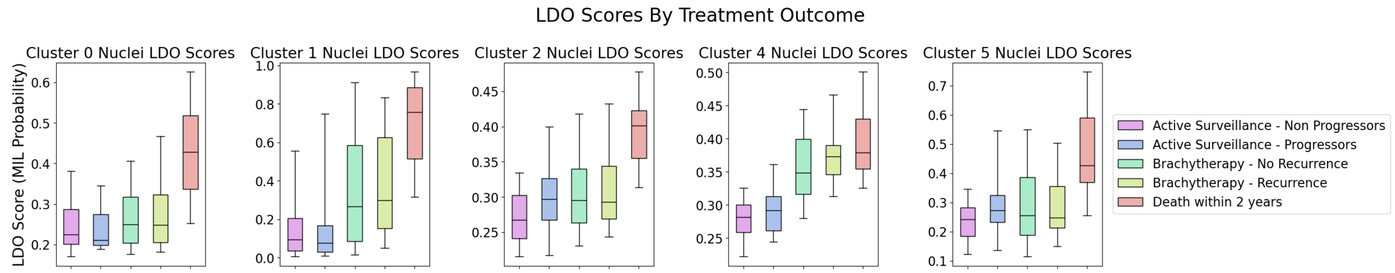


Figure 2: Of six clusters (subtypes of nuclei), cluster 0, cluster 1, cluster 2, cluster 4 and cluster 5 are selected for display. Cluster 3 is removed as it was used to normalize the LDO features. LDO scores per cluster exhibit different patterns – all clusters demonstrate clear separation between 'Death within 2 years' (aggressive PCa) patients and Active surveillance – Non progressors (indolent PCa). Mild separation can be seen in LDO score distributions of patients who respond differently to treatment.

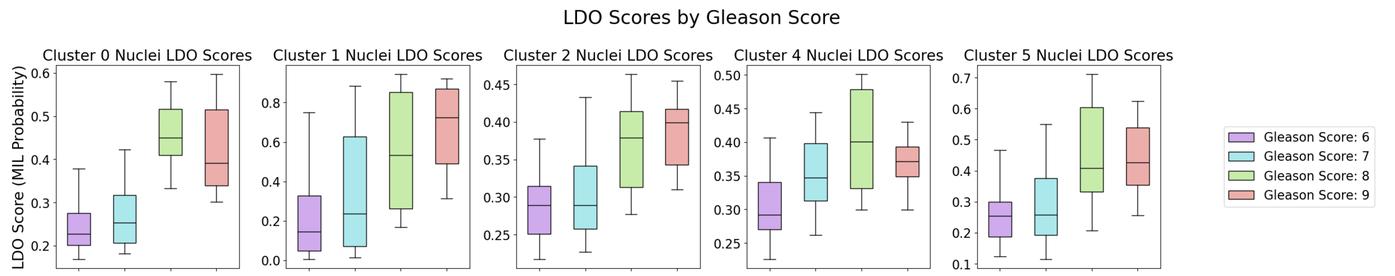


Figure 3: The LDO scores were highly correlated to Gleason score. LDO features are strictly limited to nuclear morphology and texture and contain no information regarding its architectural organization. Our results suggest there is a nuclear phenotypic change that occurs when upgrading in Gleason score. Training was done on patients with Gleason score 6 and Gleason score 9. All patients with Gleason score 7 and 8 are independent of training/testing.

Conclusion

We've demonstrated that nuclear phenotypes can be quantified and used to generate a score. This score was highly correlated with Gleason score despite not being trained to identify Gleason score, and to a lesser extent, correlated with treatment outcomes. This study aimed to characterize PCa aggressiveness on a spectrum by training a classifier on the extremes – indolent and aggressive PCa. Further work will elucidate the possibility of using the LDO scores for predicting specific therapy outcomes, such as by using a nomogram of clinical variables. Our work ultimately will become a quantitative tool for pathologists for more consistent, reproducible and accurate patient prognoses. .