Improving Bladder Cancer Grading with AI-Enabled Computer Vision: Externally Validating Grading Models and Incorporating Highly Prognostic Nuclear Features

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Background:

- Bladder cancer grading is crucial for treatment decisions, but the existing ISUP 2004 system is subjective, compromising its reliability and prognostic utility[1].

- By mathematically defining well-established WHO 2004 grading criteria as quantitative nuclear features (QNFs) and employing AI-driven image analysis to extract QNFs, we previously developed precise, reproducible models for expert consensus grading[2].

- QNFs serve as excellent building blocks for prognostic classifiers.

- Using QNFs, we externally validate grading models and create recurrence-free survival (RFS) models that outperform grades assigned by pathologists.

Design:

- All patients were stage Ta. Grading was centrally reviewed as described[2].

- CNIO Madrid validation cohort comprised 581 images (403 cases). Kingston cohort contained 267 images (163 cases).

- QNFs were extracted using Visiopharm image analysis software (Hoersholm, Denmark).

- Our published univariate, decision tree, regression, and random forest models[2] were applied to the CNIO cohort to predict consensus pathologist grade.

- Cox Proportional Hazards (CPH) and Random Survival Forest (RSF) models for time-to-first bladder cancer recurrence were trained and cross-validated in the Kingston cohort using holdout testing.

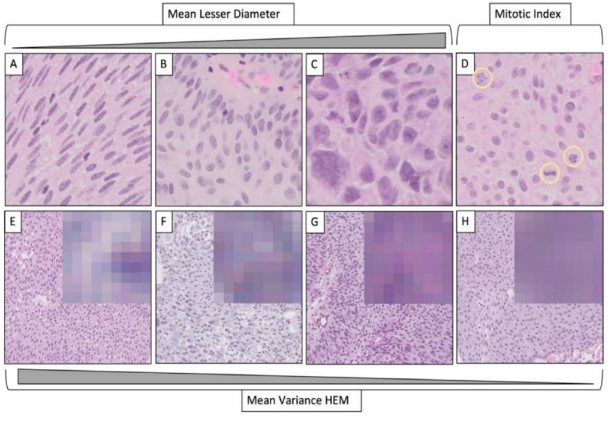

Figure 1. Top three quantitative nuclear imaging feature indicating higher risk of recurrence. A-C. Low to high mean lesser diameter, a measure of nuclear size and shape. D. High mitotic index, a marker of proliferation. E-H. High to low mean variance HEM, a measure of staining intensity for nuclear texture. For A-C and E-H, QNFs are displayed from left to right according to their association with slower (left) or faster (right) recurrence.

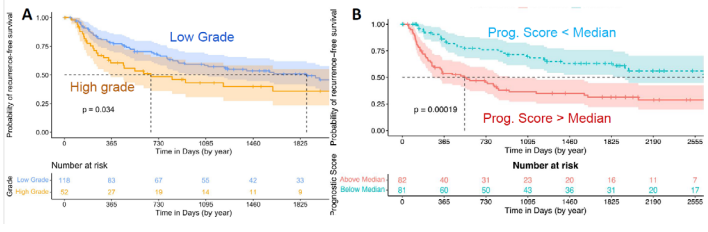

Figure 2. Kaplan-meier curves for the Kingston nonmuscle invasive bladder cancer survival cohort (n=163) split by A. 3-Pathologist Consensus Grade for the case, and B. Median QNF prognostic score above or below the median. Features included in the model: mitotic index, mean variance of hematoxylin intensity, and mean lesser diameter.

Results:

- Random forest grading yielded 80% balanced accuracy in external validation, outperforming all other models.

- For survival models, mitotic index, mean lesser diameter (size and shape), and mean-variance in hematoxylin intensity (chromatin texture) (Fig 1) were most correlated with recurrence-free survival. The CPH model achieved a C-index of 0.73 (95% CI: 0.56-0.88) compared to only 0.55 (95% CI: 0.40-0.69) using consensus grading by 3 GU pathologists.

- The RSF model achieved a C-index of 0.70 (95% CI: 0.66-0.70) (Fig. 2).

Conclusion:

- The external validation results show that models derived from objective and explainable QNFs can be reliably extracted and applied to diverse cohorts, highlighting an opportunity to improve the reliability and accuracy of grading.

- QNFs can be further leveraged to more accurately identify patients with early and late recurrence, providing an opportunity to identify patients for intensified or relaxed treatment and surveillance.

- We are currently adapting these models to whole slide image analysis.

References:

[1]. Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non-muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. *Eur Urol.* 2017 Nov;72(5):801-813. PMID: 28457661.

[2]. Quantitative Nuclear Grading: An Objective, Artificial Intelligence-Facilitated Foundation for Grading Noninvasive Papillary Urothelial Carcinoma. *Lab Invest.* 2023 Jul;103(7):100155. PMID: 37059267.

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