Innovations in Renal Cell Carcinoma and Urothelial Cancer

Florida Society of Clinical Oncology Fall General Session 2023

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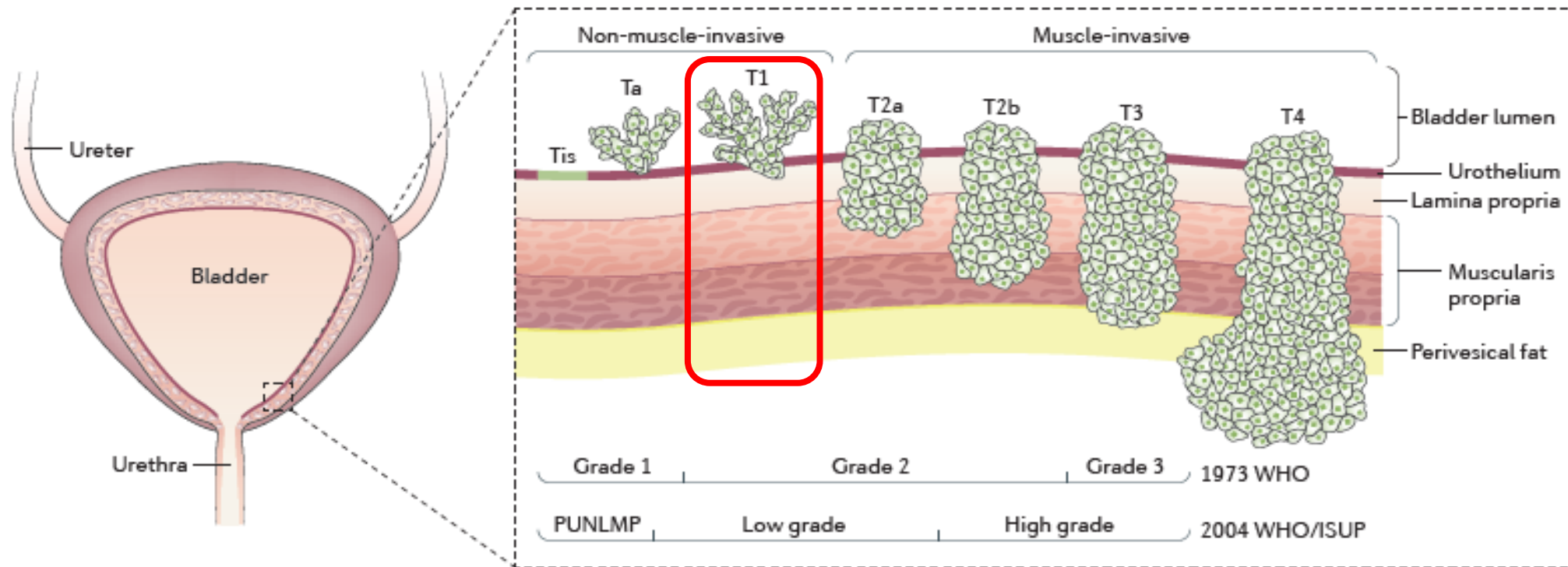
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MOFFITT
CANCER CENTER

# Recent suggestion for staging of bladder cancer
Subcategorization of pT1

Extent of lamina propria invasion (pT1) in transurethral specimens has prognostic value.

Nature Reviews | Disease Primers

Subcategorization of pT1

- Approaches for subcategorization of pT1
    1. *Micrometric measurements* (microscopic vs extensive invasion)
    2. *Histoanatomical landmarks* such as the muscularis mucosae and the vascular plexus of the lamina propria

- Higher subcategories (both approaches) correlate with recurrence and stage progression.

- Micrometric pT1 approach may better predict outcome.

- Pathologists are strongly encouraged to convey the extent of lamina propria invasion using any of the proposed approaches (2022 WHO GU tumors).

    - Example: urothelial carcinoma focally (*micrometric*) and superficially (*histoanatomically*) invades lamina propria.
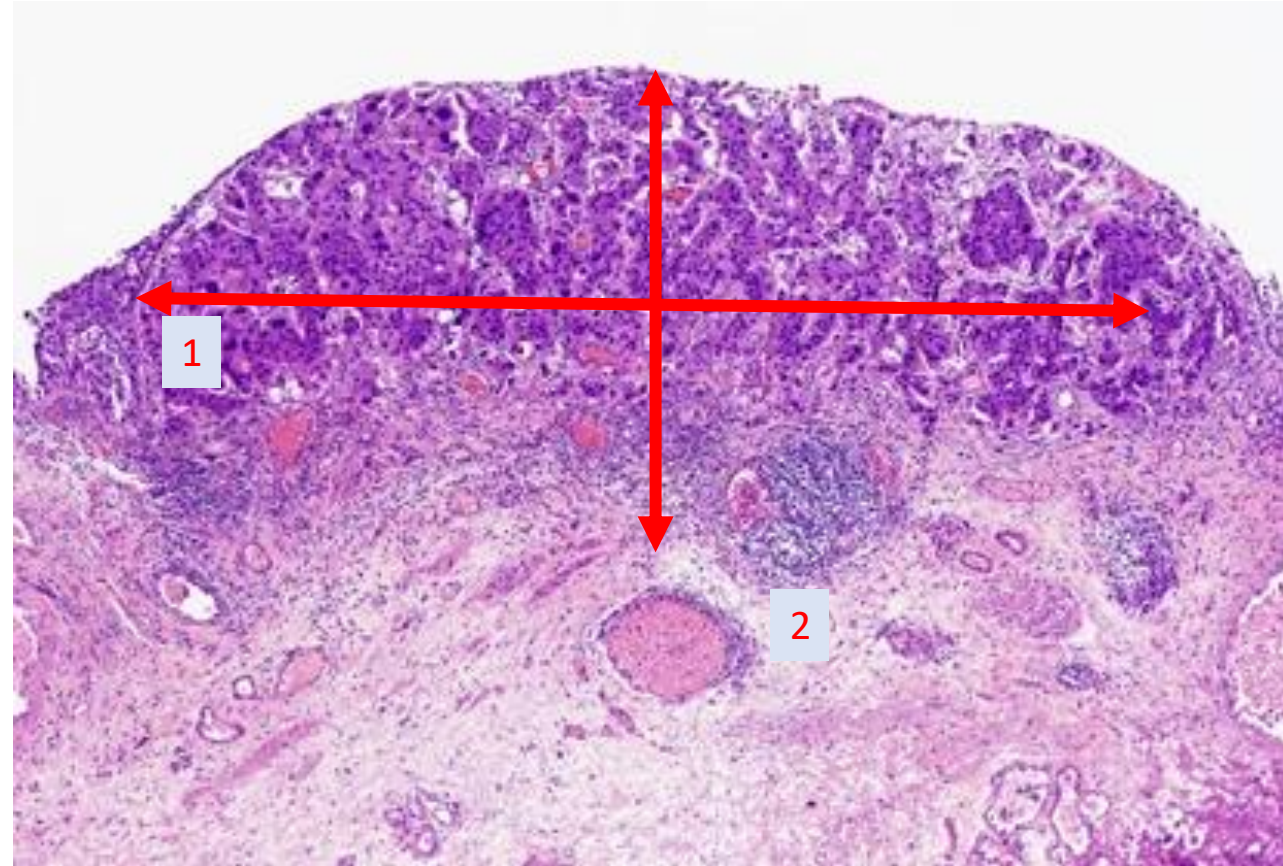
Heterogeneity in grade of papillary urothelial carcinoma

- Heterogeneity in grade is characteristic of non-invasive papillary urothelial carcinoma.

- Heterogeneity in grade occurs in one third of tumors and may impact outcome

- It is recommended to grade the tumor based on its highest-grade component (WHO GU tumors 2022).

  - If high grade component ≥ 5% ⟶ High grade
  - If high grade component < 5% ⟶ Low-grade
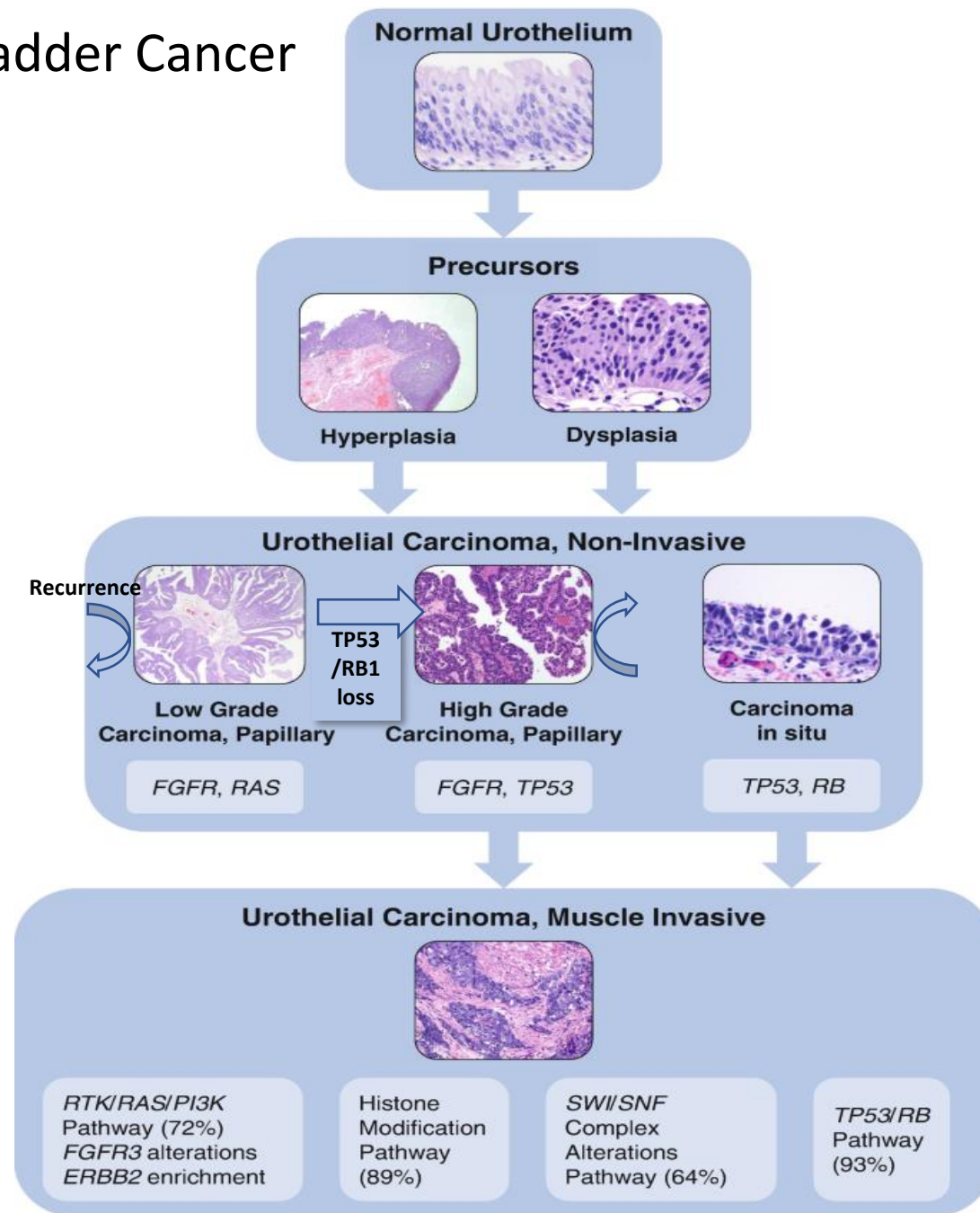   with < 5% high-grade component
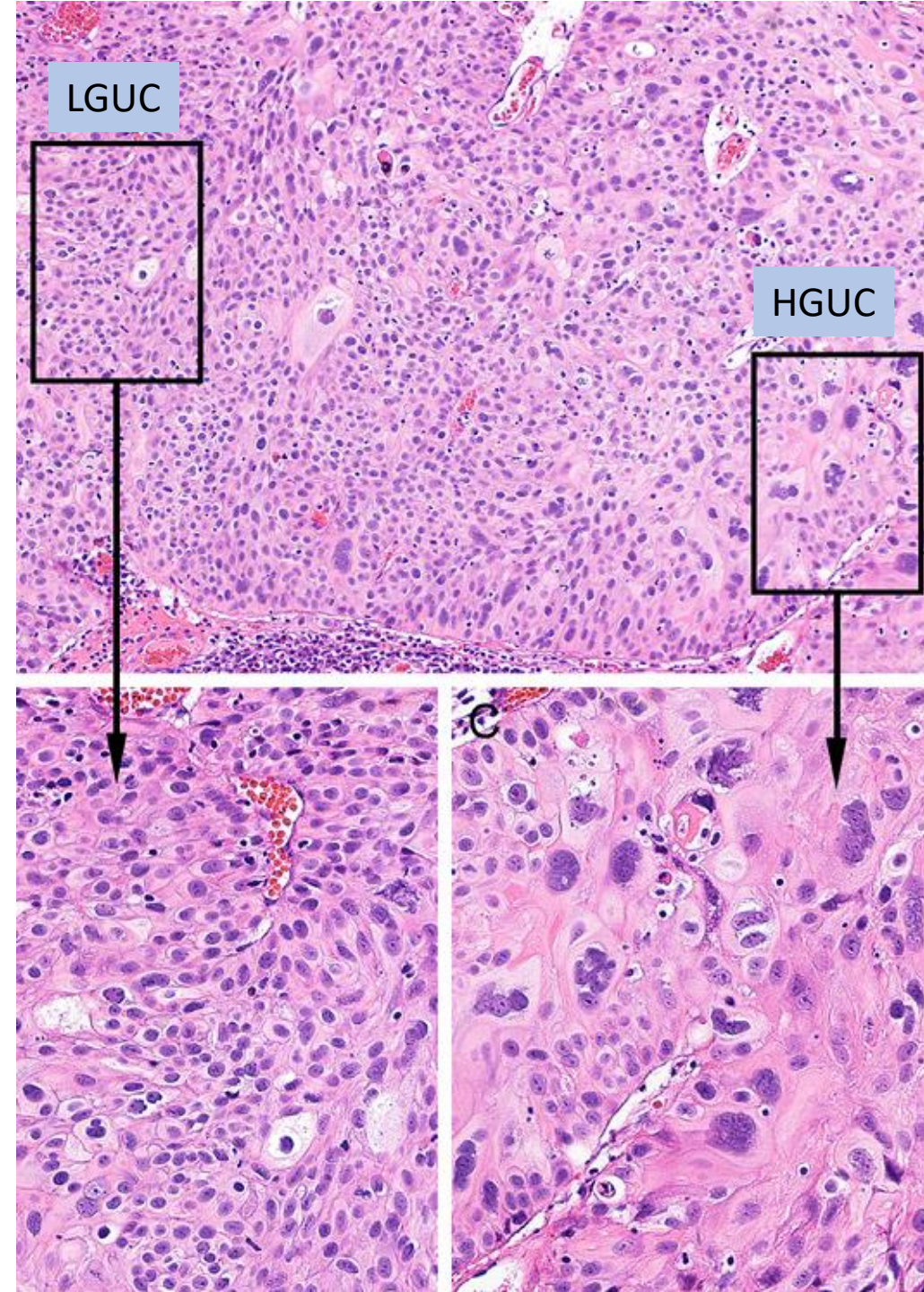
Application of AI (Artificial Intelligence) for evaluation of heterogeneity of urothelial carcinoma

Predicting tumor recurrence of low grade papillary urothelial carcinoma
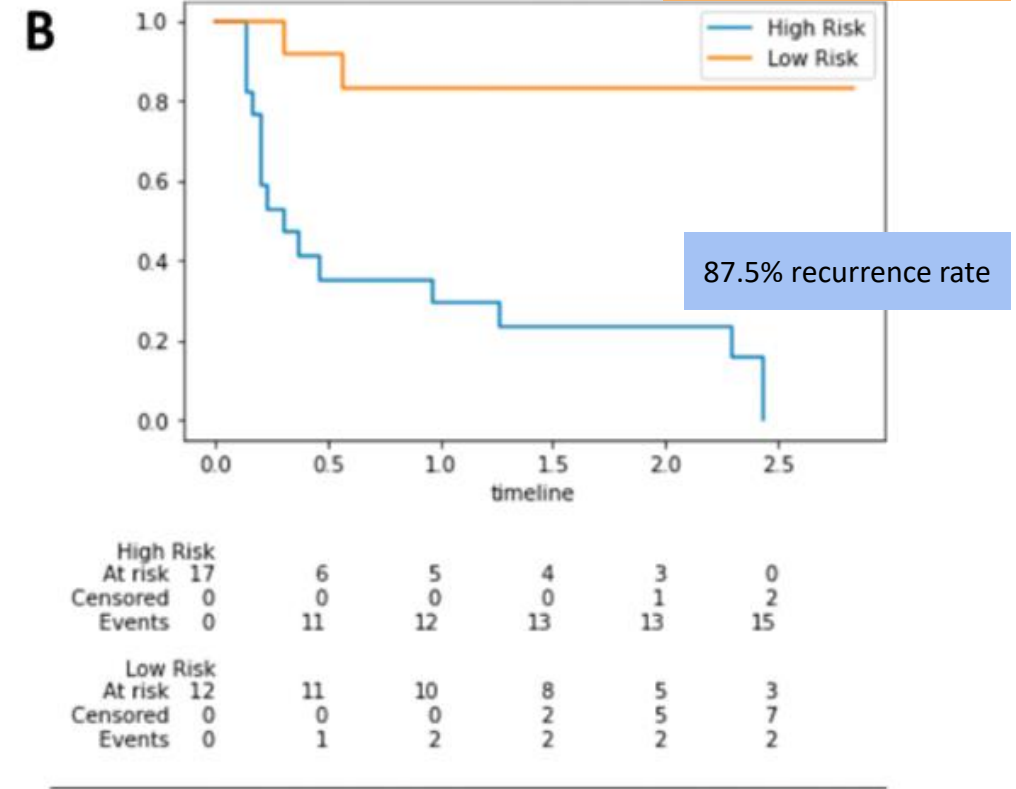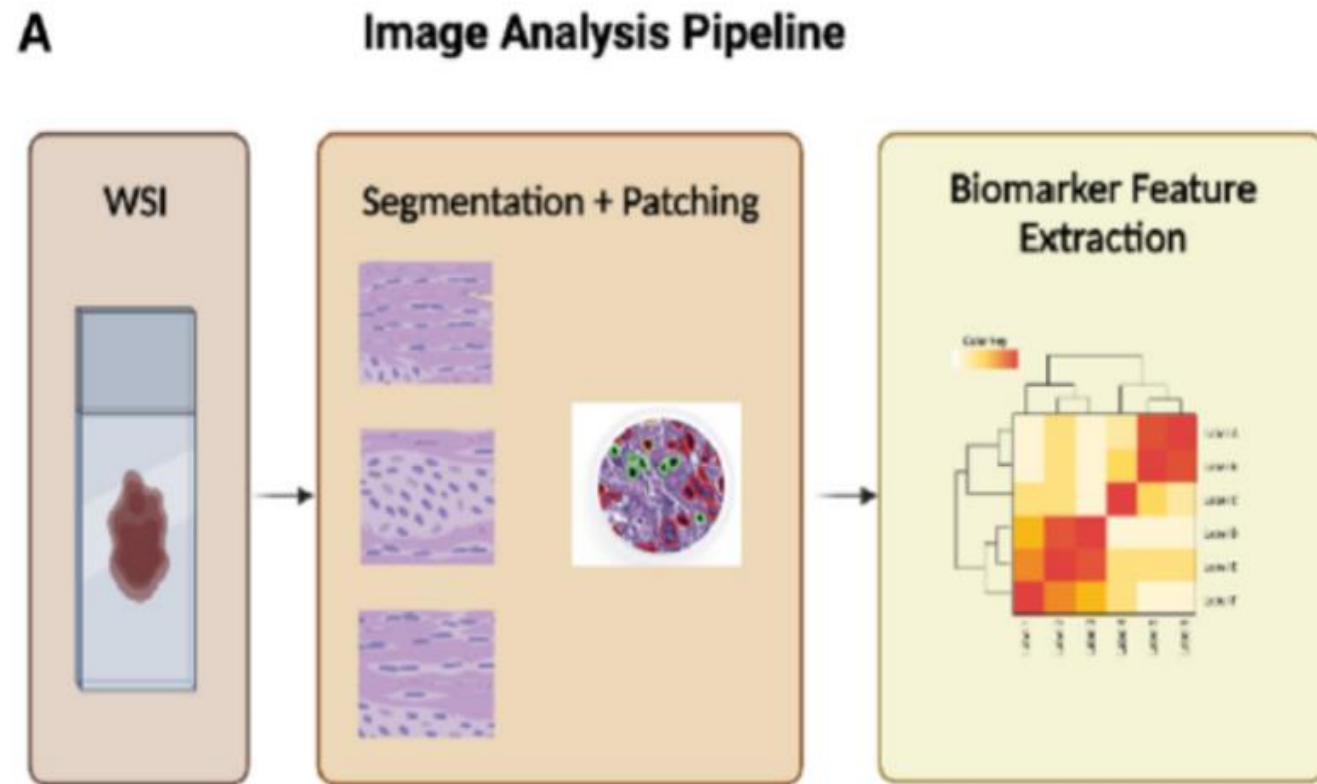
HR: 5.43 (95% CI 1.1, 26.27)
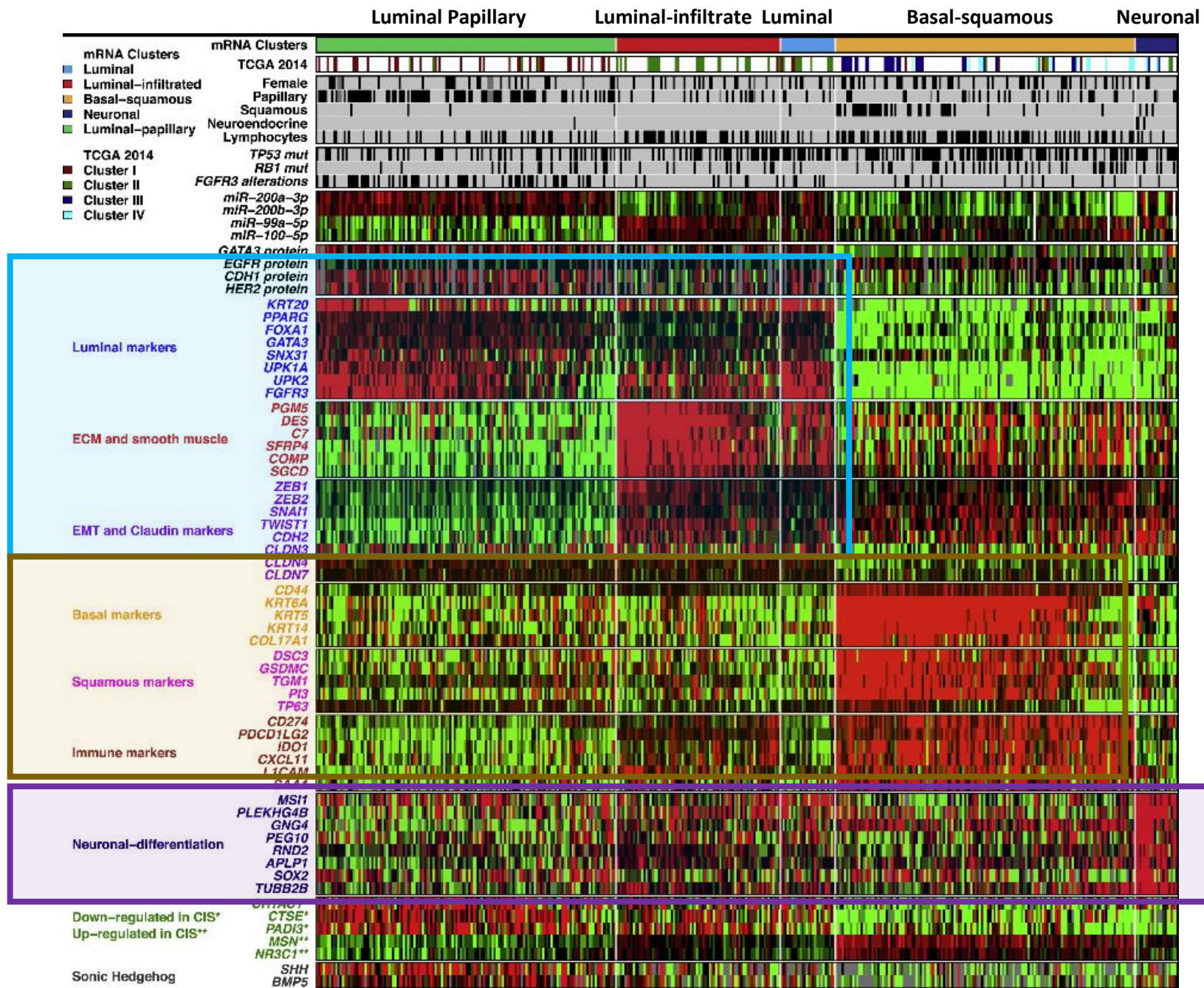
Molecular Pathways in Bladder Cancer

Molecular Subtypes of muscle invasive urothelial carcinoma (transcriptomic profile classification)
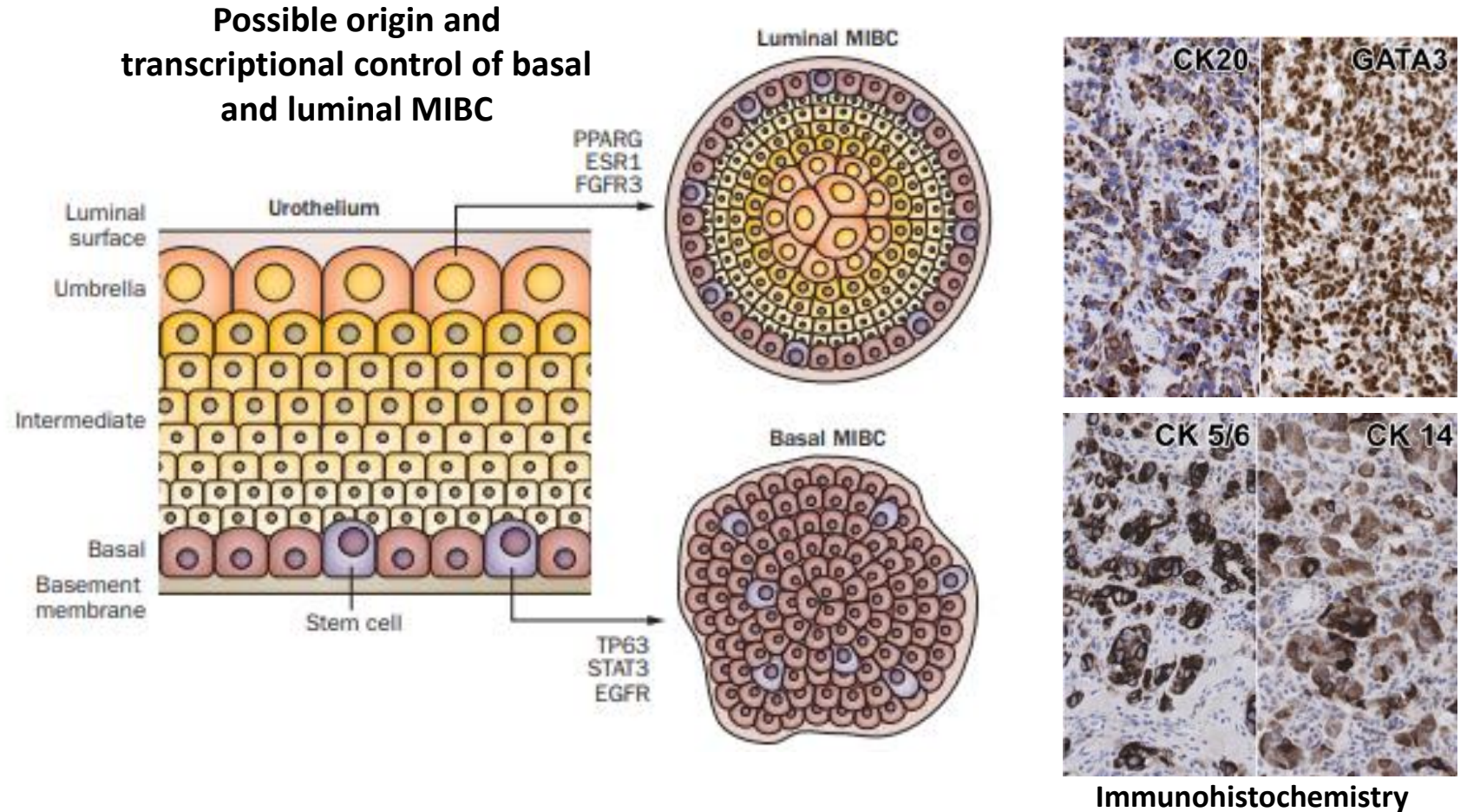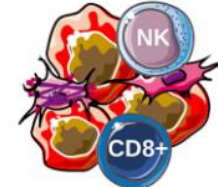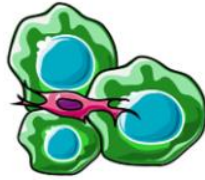
Basal and Luminal subtypes of muscle invasive urothelial carcinoma

Possible origin and transcriptional control of basal and luminal MIBC

Immunohistochemistry

Nature Reviews. Urology. Choi, Woonyoung. et. al. 2014

Molecular Subtype Of Muscle Invasive Urothelial Carcinoma

% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)

Basal was enriched in PDL1 expression tumor cells

Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	FGFR3 (40%), KDM6A (38%)	ELF3 (35%)	TP53 (76%), ERCC2 (22%) TMB +, APOBEC +		TP53 (61%), RB1 (25%)	TP53 (94%) RB1 (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

* 94% of these tumors present either RB1 mutation or deletion
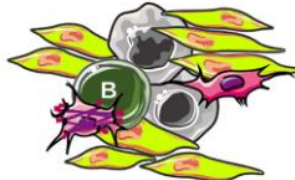
Clinical Application Of Molecular Subtypes Of Urothelial Carcinoma

- lowest rate of upstaging was seen in patients with luminal tumors without systemic therapy as compared with non-luminal tumors (34% versus 51%)

- The luminal-papillary subtype was strongly associated with FGFR3 alterations ⟶ FGFR3 inhibitor

- The luminal-infiltrated subtype featured PD1 and PD-L1 and expression of other immune cell-related genes

- Basal subtype was enriched in PD-L1 expression tumor cells.

- Basal subtypes of MIBC tumors show the best overall survival benefit from NAC (77.8% versus 49.2%) at 3-year follow-up.

Summary

- Available data support combining pathology reports incorporating both standardized pathologic data, such as histologic grade, AJCC/TNM stage, and other risk parameters, with relevant molecular information.

- Providing luminal-basal phenotype may provide data on the need to perform additional testing, such as PD-L1 or FGFR3 mutation/translocation analysis, thus serving as quick screening of cases necessitating extra workup.
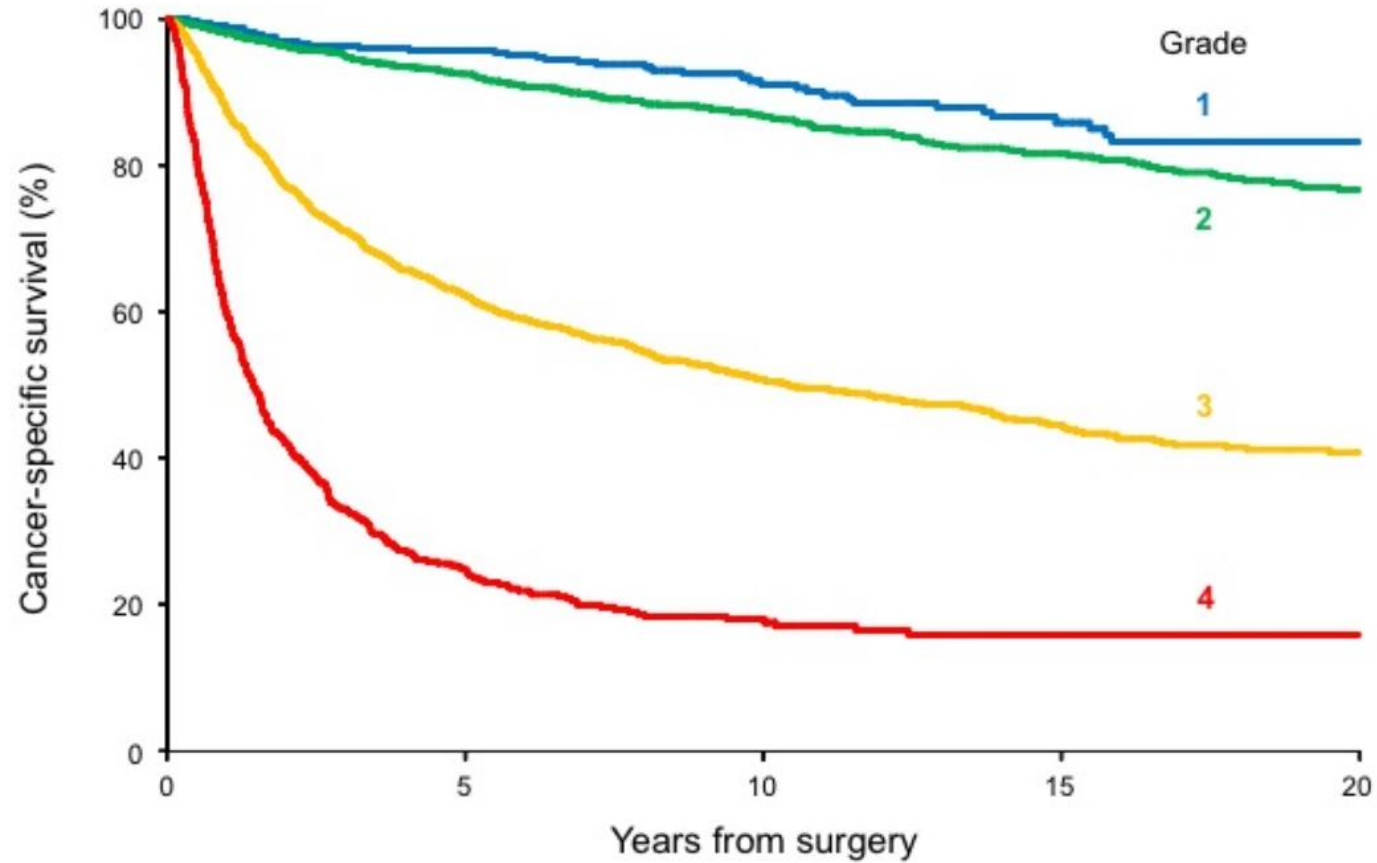
Care Presentation

RCC session

WHO Classification of Tumors / International Society of Urological Pathology (WHO/ISUP) histological grading
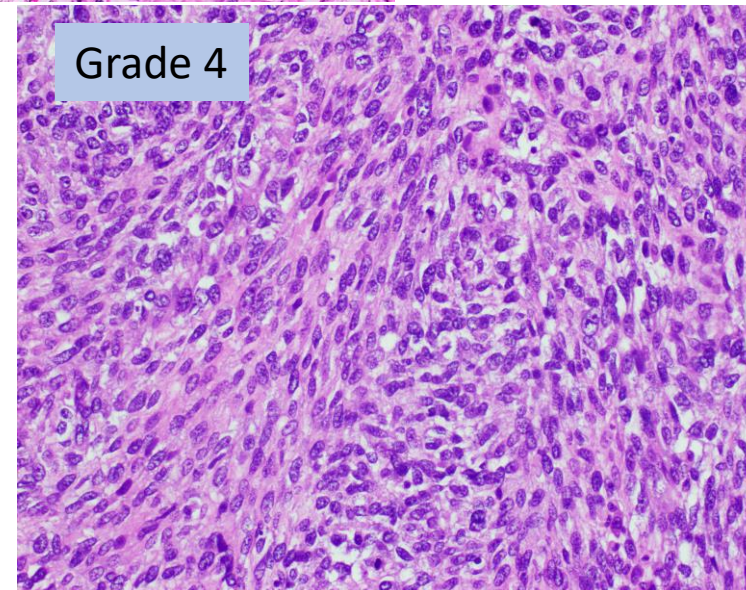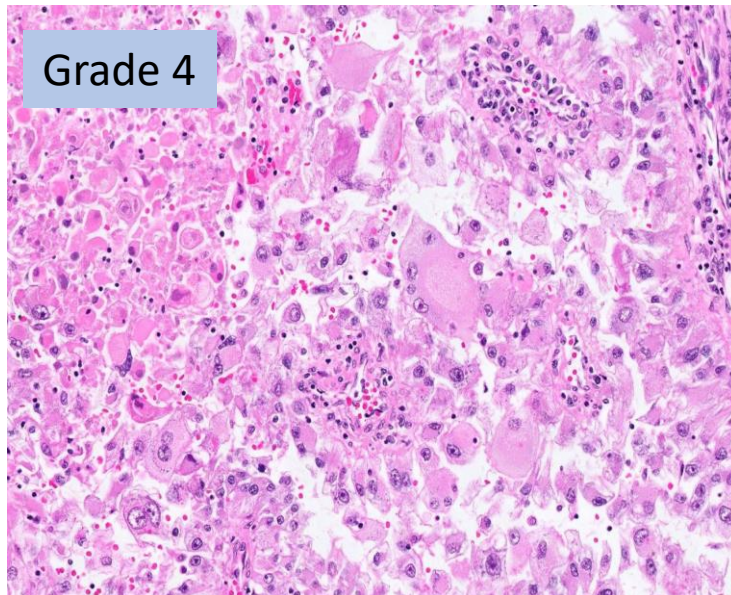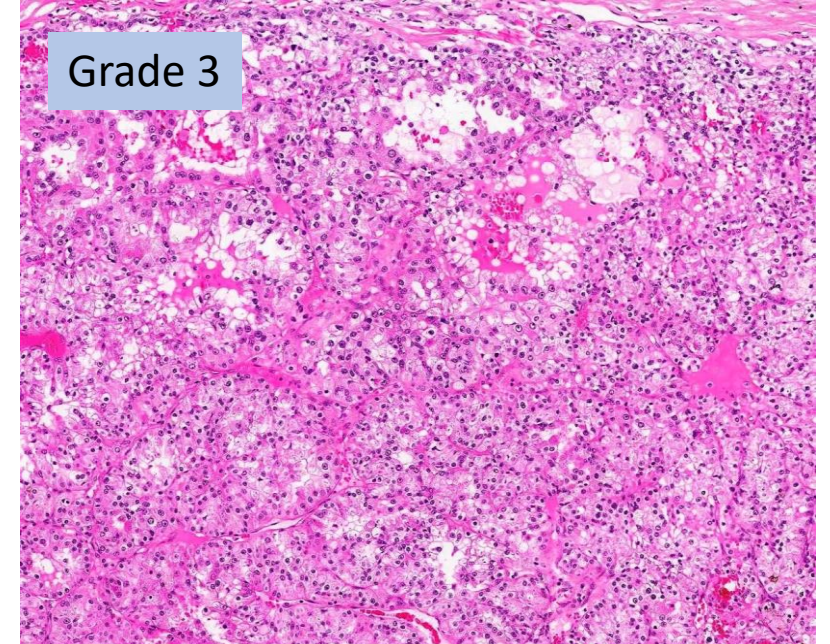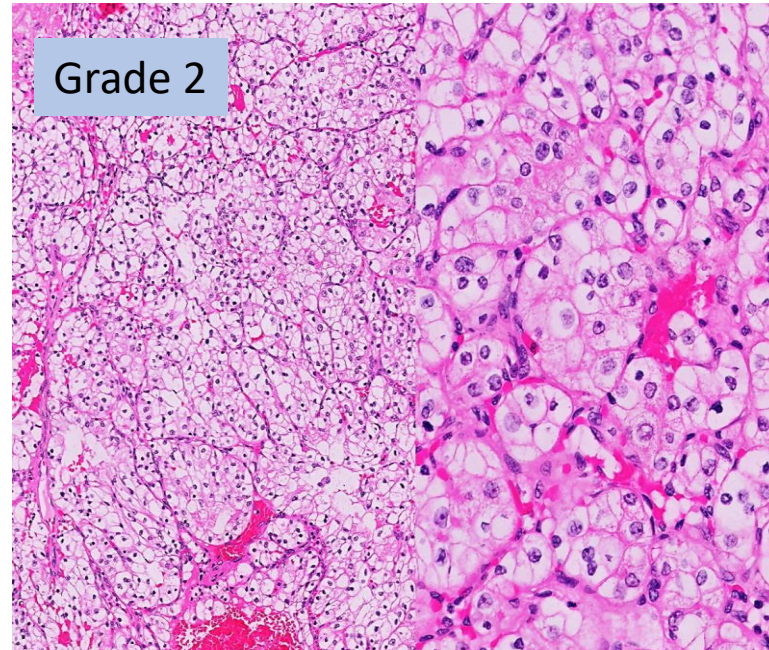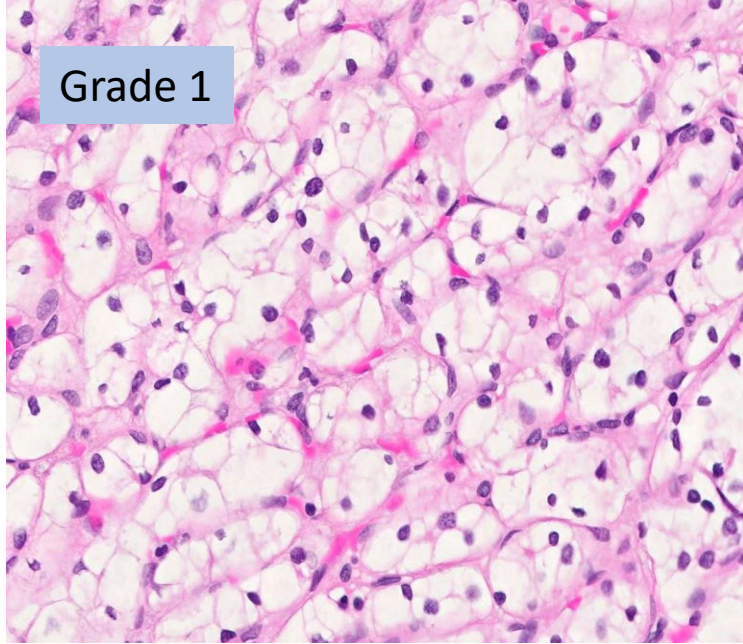
Survival outcome of RCC bases on WHO Classification of Tumours / International Society of Urological Pathology (WHO/ISUP) histological grading
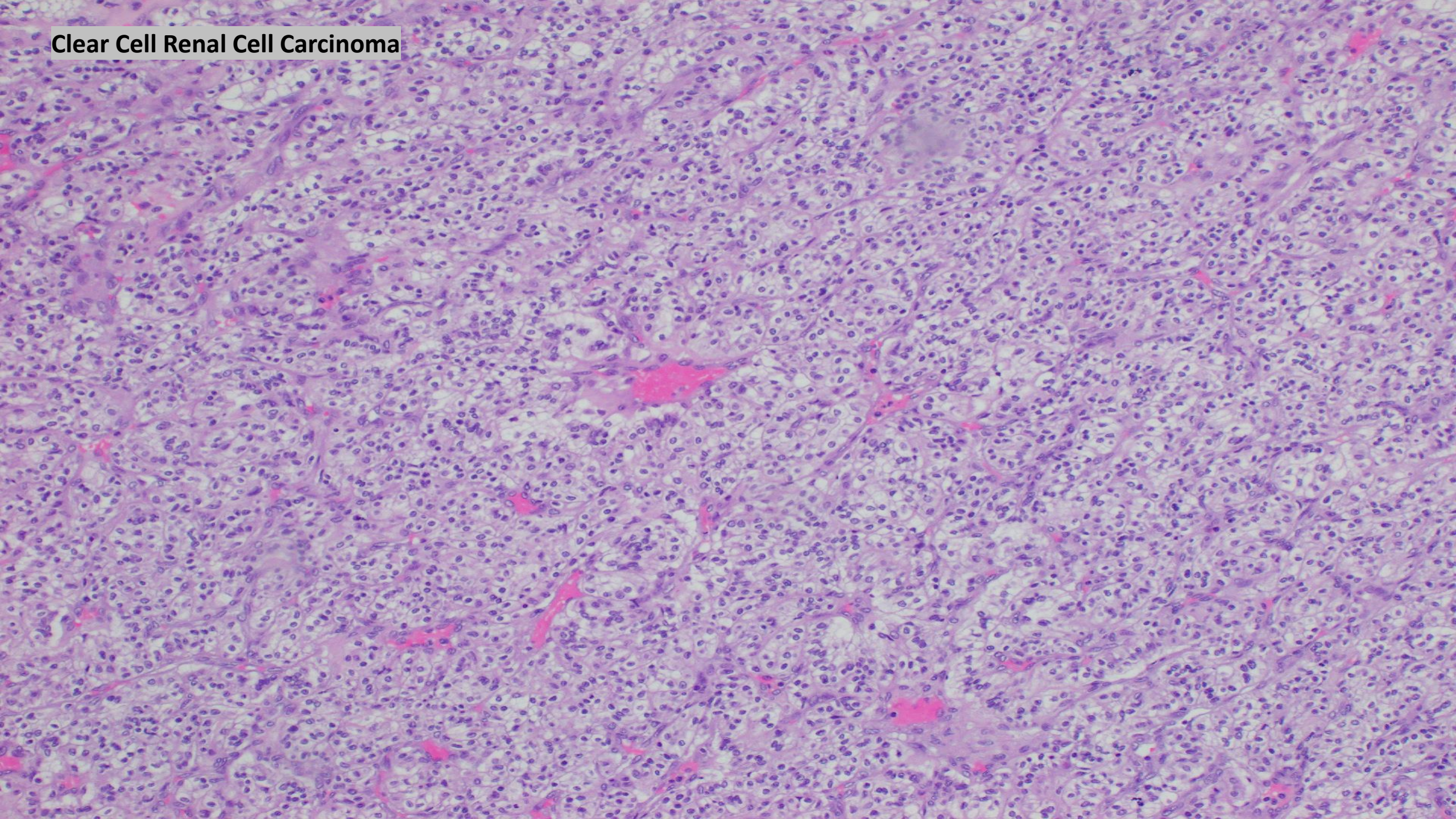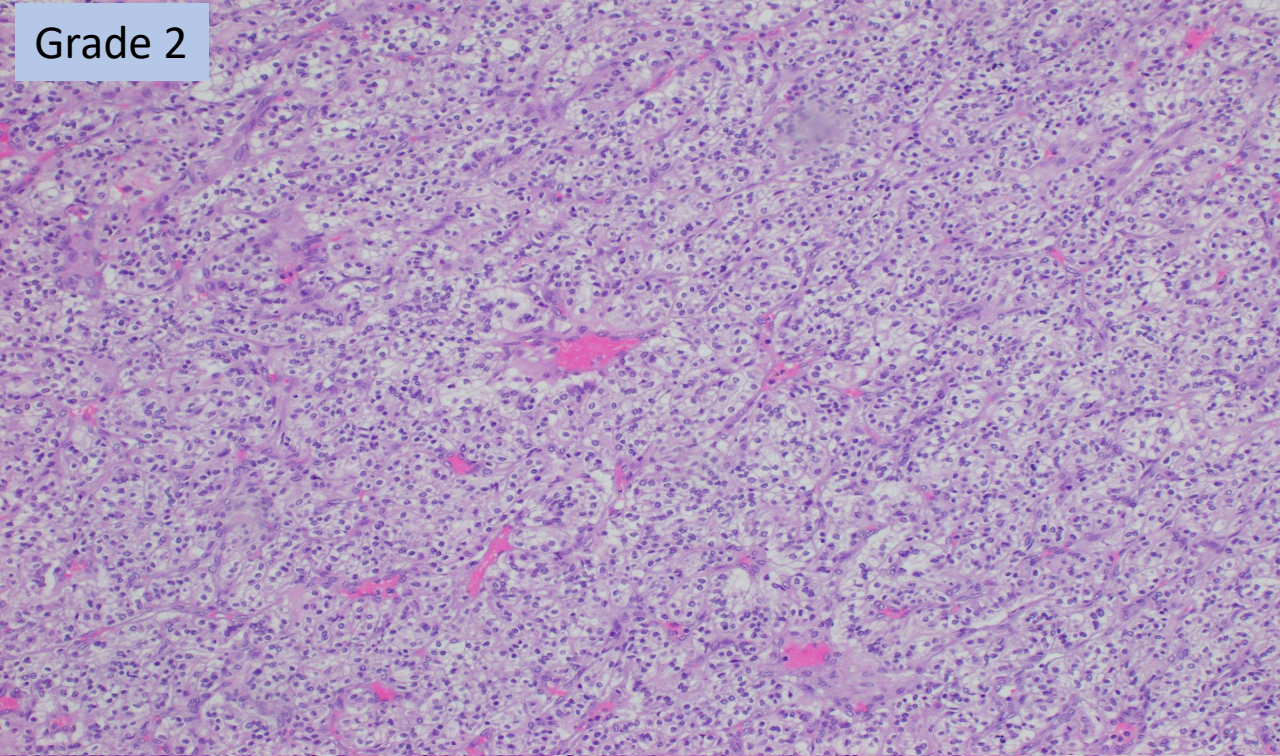

Clear cell renal cell carcinoma , grade 4 with sarcomatoid and rhabdoid feature showed response to immune checkpoint inhibitor (pembrolizumab)

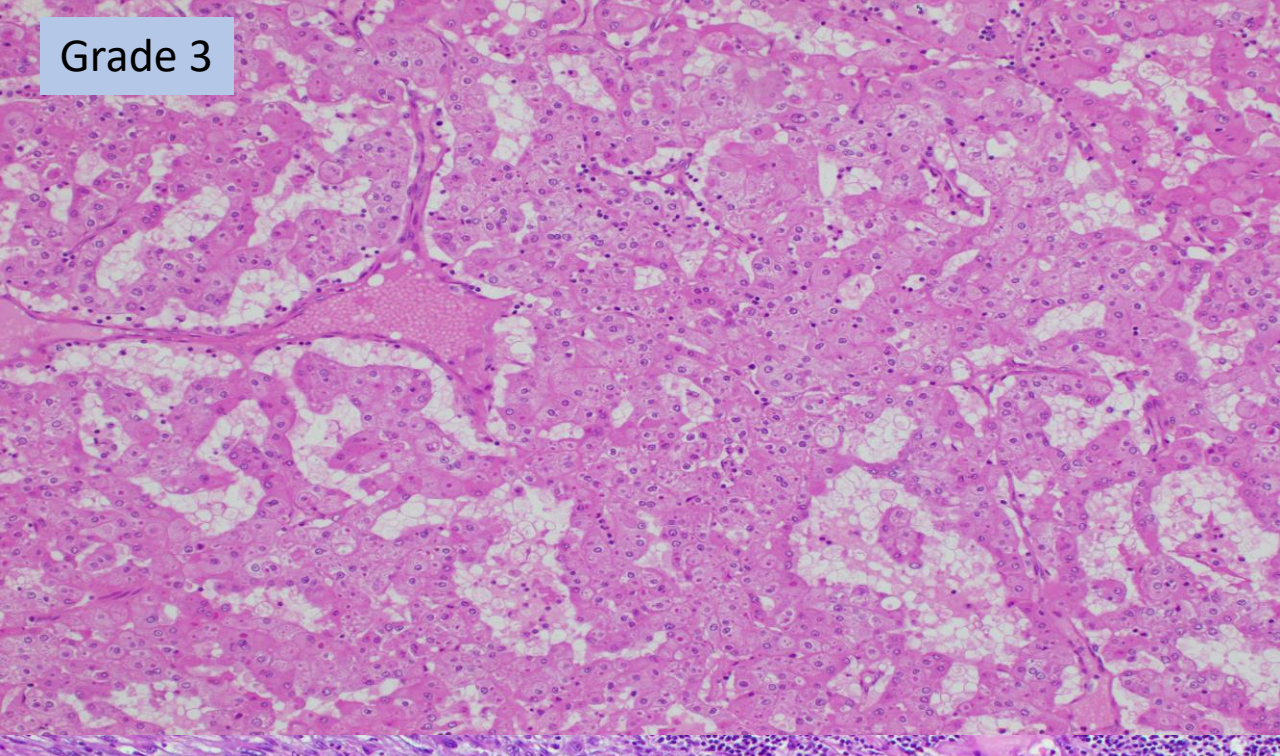# Radical nephrectomy (4/2018)

CASE# SP18-4923 SPECIMEN A   DATE 4|15|18
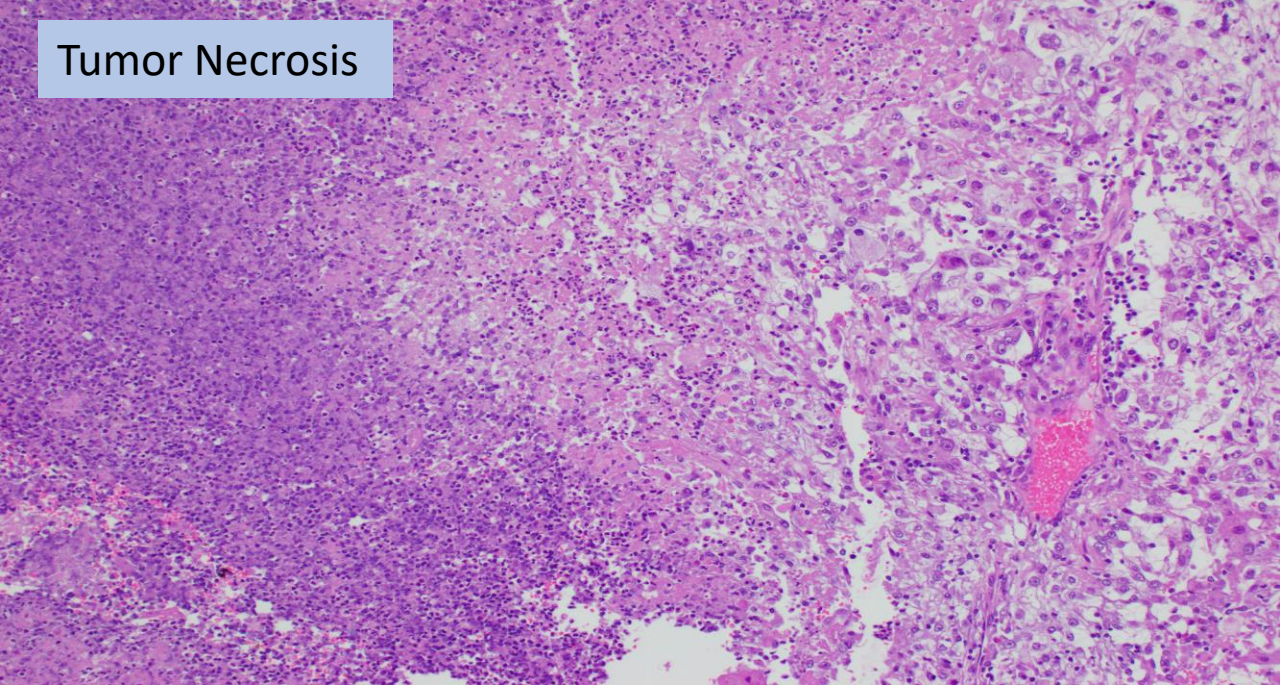
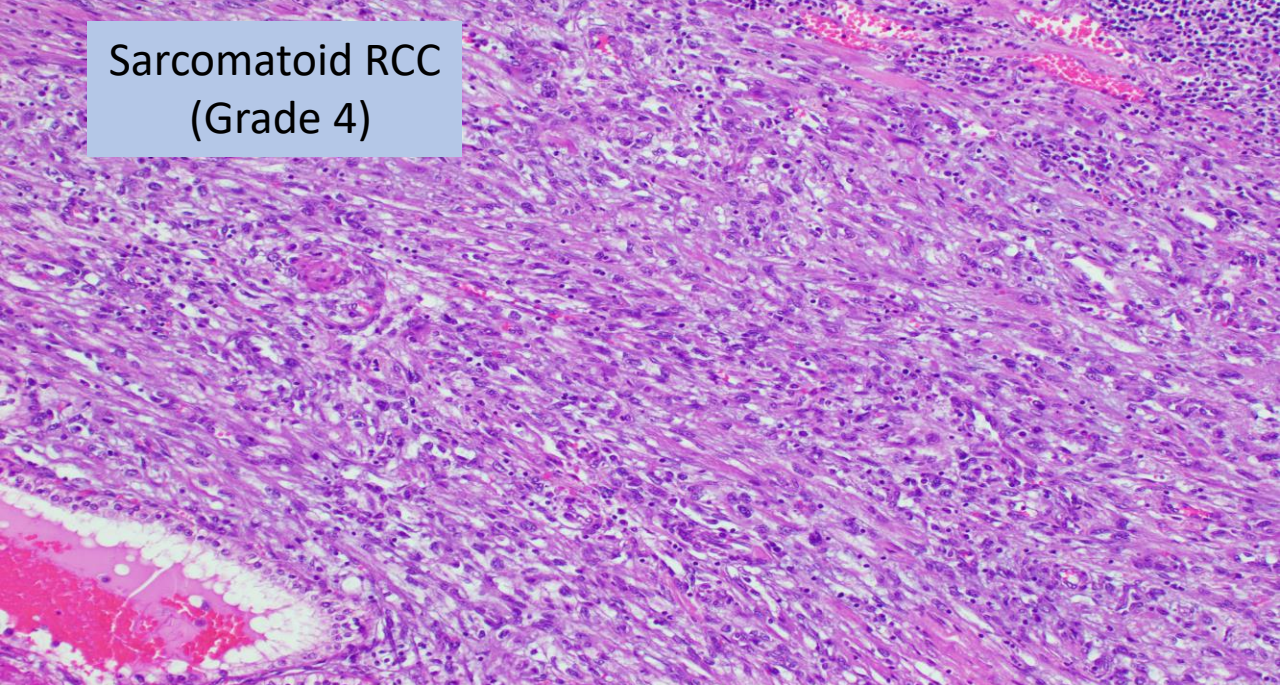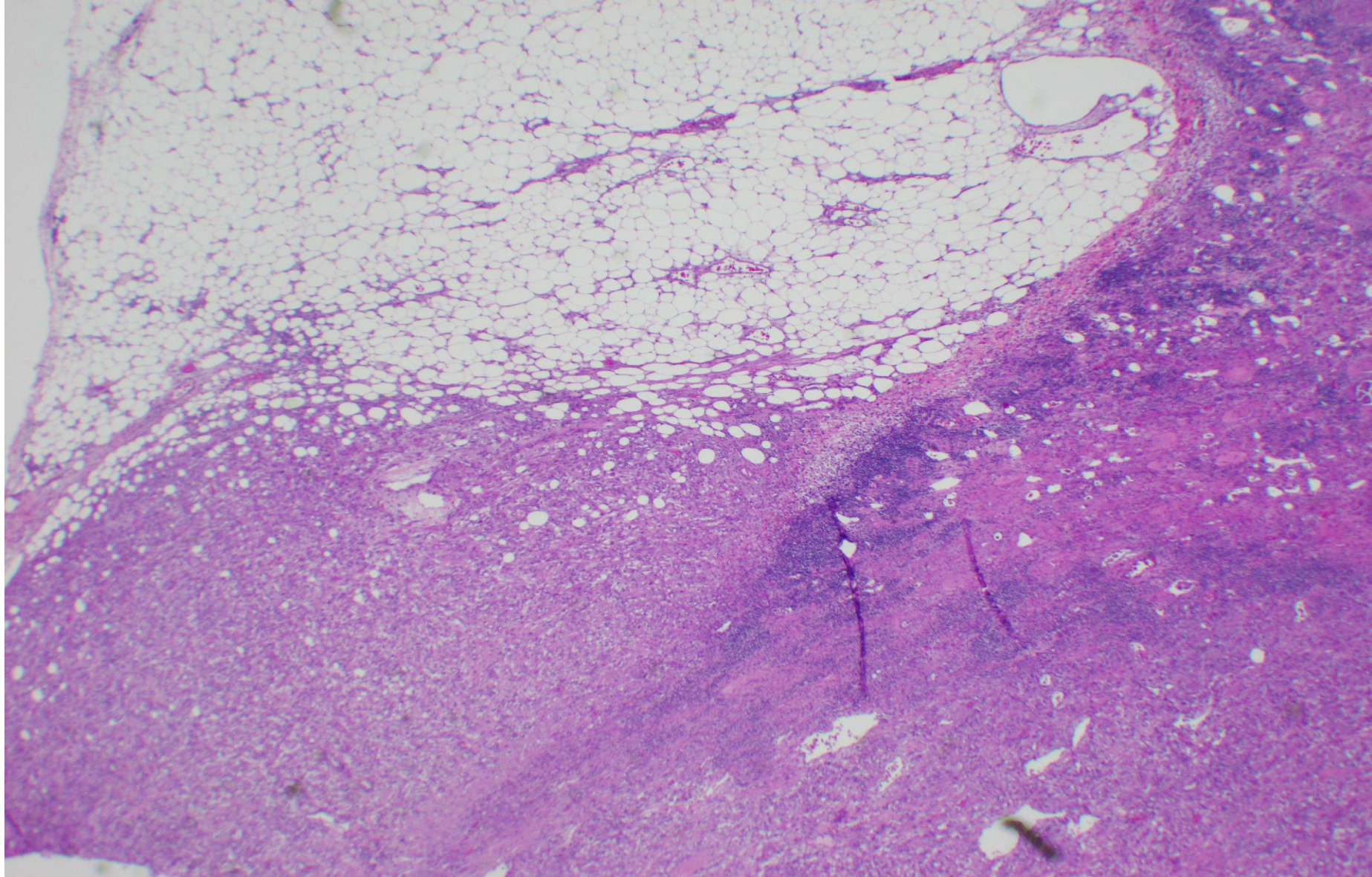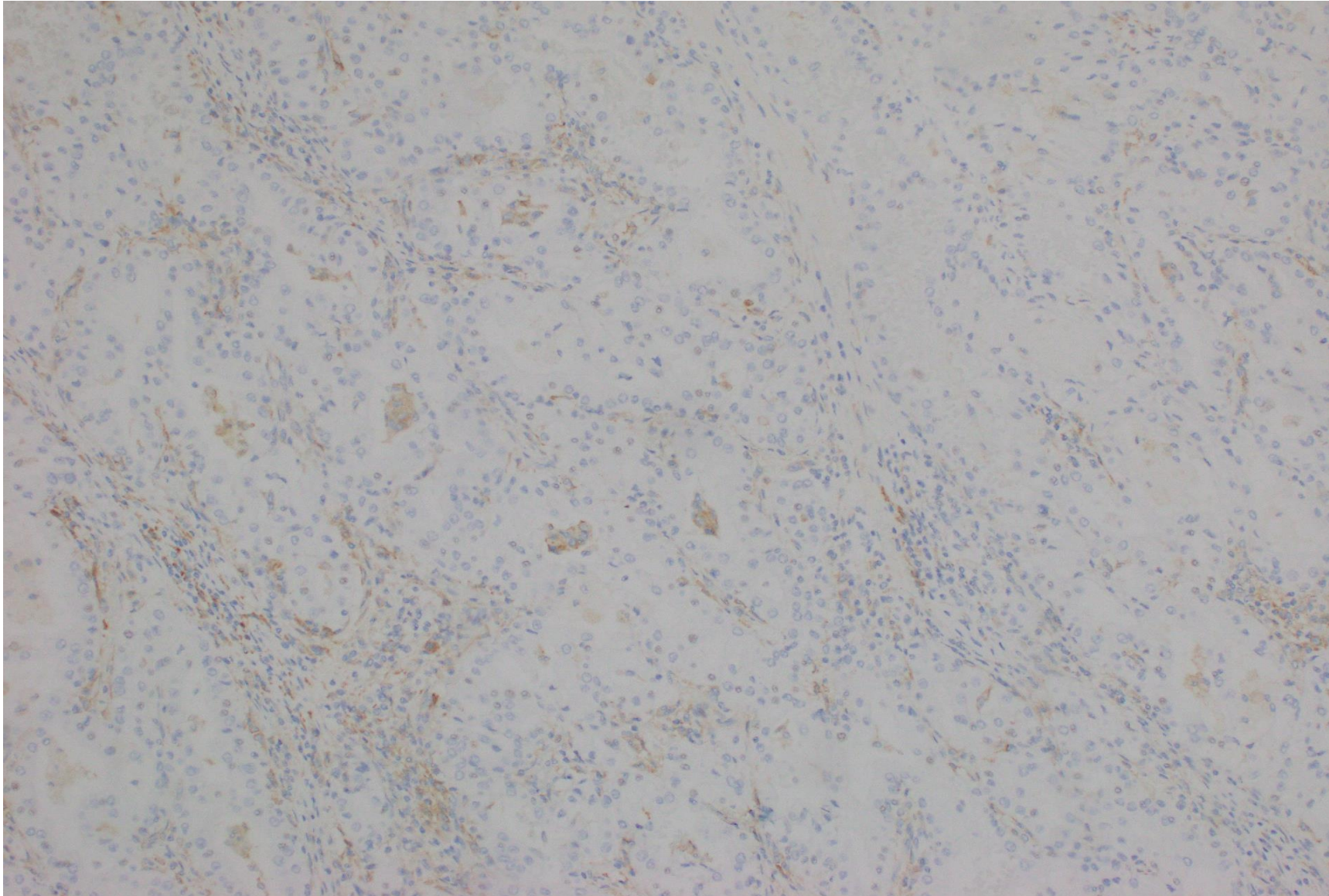Clear Cell Renal Cell Carcinoma

Grade 2

Grade 3

Tumor Necrosis

Sarcomatoid RCC
(Grade 4)

Perinephric Invasion (pT3a)

PDL1 Immunostain
Combined Positive Score (CPS) : 5

Chest wall biopsy (7/2022)