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JOHNS HOPKINS
M E D I C I N E

PD42-01

Clinical Restaging and Tumor DDR Mutation Analysis are Inaccurate Indicators of Response to Neoadjuvant Chemotherapy for Muscle Invasive Bladder Cancer

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Whose bladder can be spared?

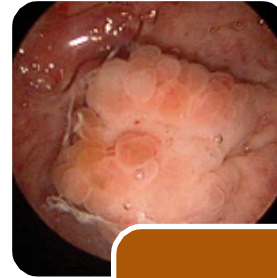
- Standard of care for MIBC: neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC)
- Some patients/tumors (~30%) show dramatic or complete pathologic response after NAC alone
 - Can we spare them from the morbidity of RC?

DNA Damage Response (DDR)

- DNA repair pathway genes
- Deleterious mutations → enhance cytotoxic effects
 - Improved pathologic responses & survival
- RETAIN trial (NCT02710734) & A031701 (NCT03609216)
 - DDR mutations part of criteria for bladder sparing
 - Post-NAC restaging

Post-NAC restaging

- Not universally performed
- Accuracy/prognostic value still uncertain
- Hopkins institutional standard:
 - Axial imaging C/A/P
 - Exam under anesthesia
 - Cystourethroscopy
 - Transurethral tissue sampling (TUR)



MIBC

NAC

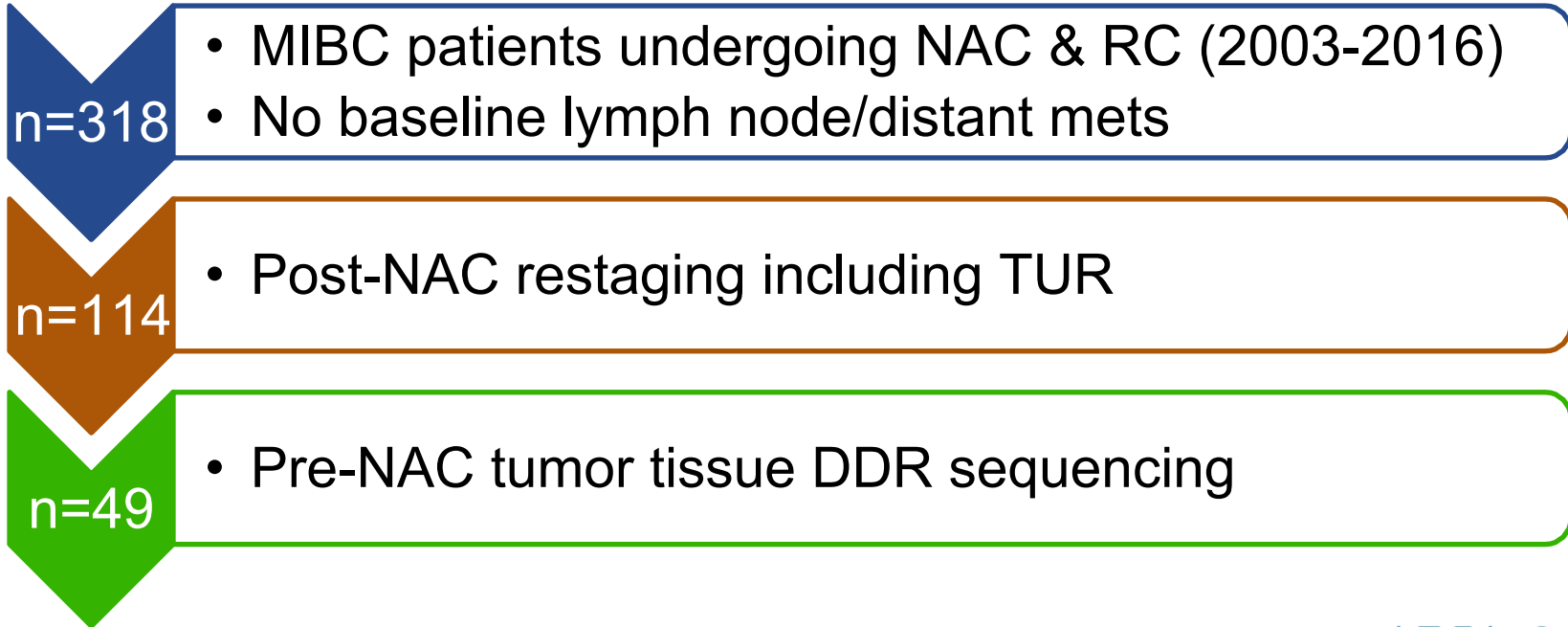
Restage

RC

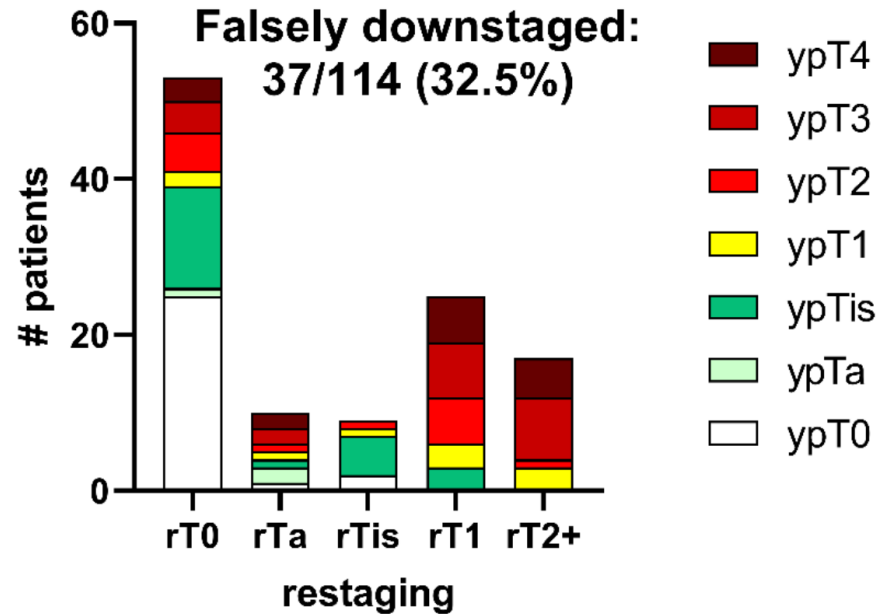


Tumor DDR sequencing

Institutional RC database



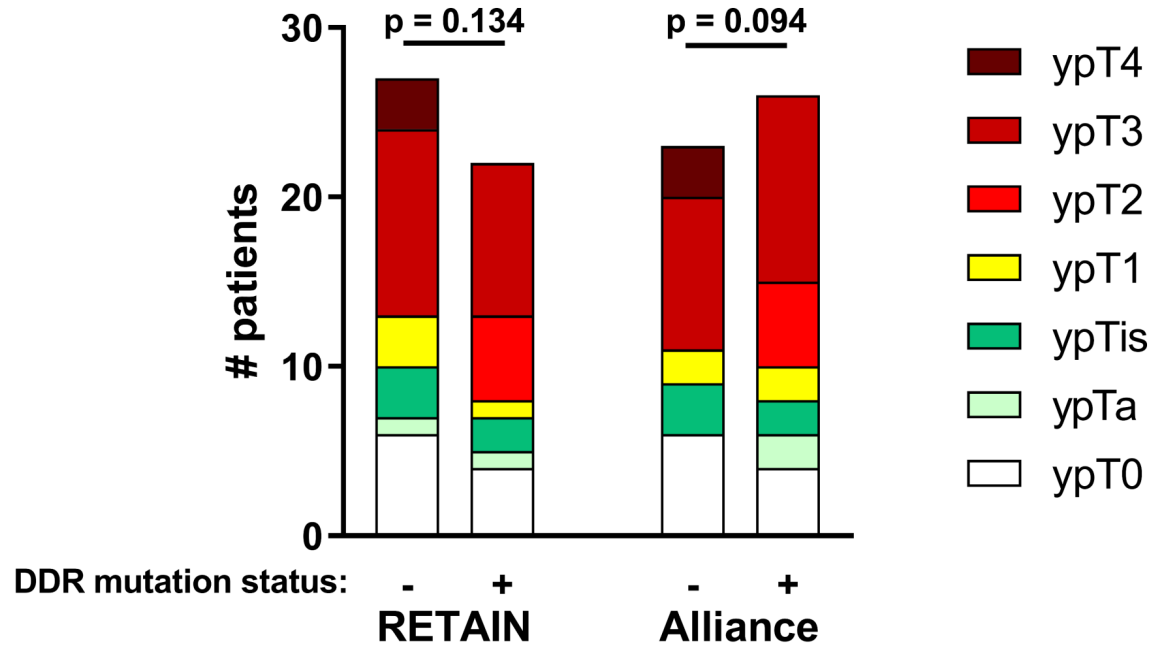
All patients with TUR restaging (N=114)



$\geq rT2$ as predictor of $\geq ypT2$: specificity 95.2%, sensitivity 27.5%

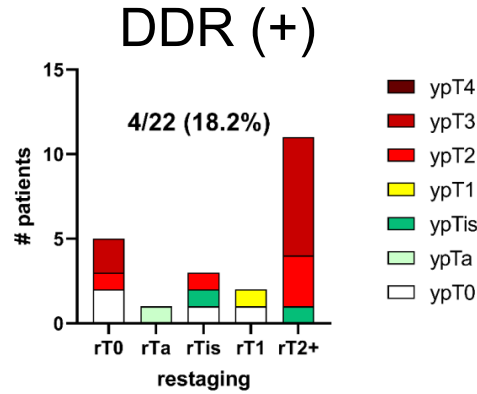
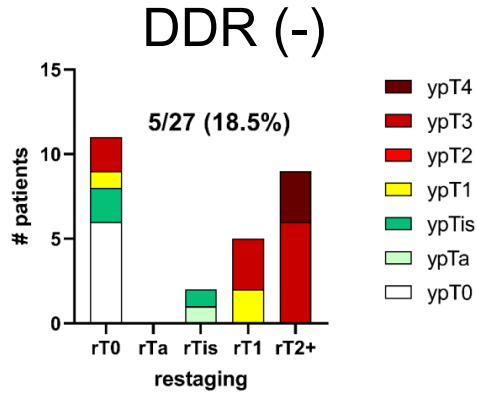
	Study population (N=49)	TCGA Pan-Cancer Atlas: Bladder Urothelial Carcinoma (N=411)
DDR+ (Fox Chase panel)	22 (44.9%)	178 (43.3%)
DDR+ (modified Alliance panel)	26 (53.1%)	220 (53.5%)
DDR+ (any sequenced DDR gene)	32 (65.3%)	255 (62.0%)

DDR status not correlated with NAC response



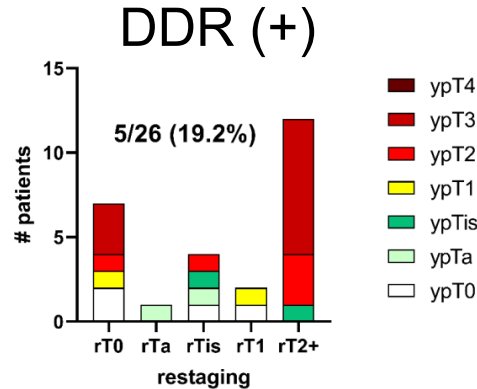
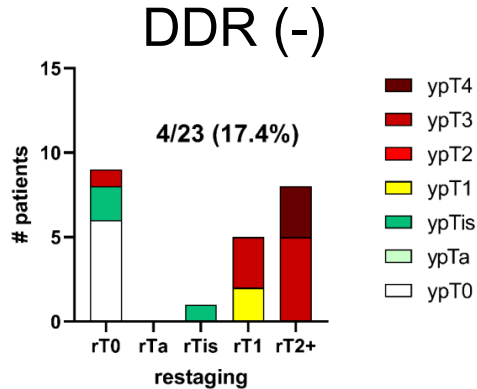
DDR and post-NAC restaging

RETAIN



p = 1.000

A031701



p = 1.000

DDR and post-NAC restaging

- “Most favorable” subset
 - Restaging <rT2
 - DDR+ mutated tumor
- **Missed \geq ypT2 rate 36.4% (RETAIN) or 35.7% (A031701)**

Limitations

- Retrospective analysis, small cohort
- Heterogeneous NAC (65% Gem/Cis)
- 38% patients underwent restaging TUR
- DDR mutation credentialing

Conclusions

- Post-NAC restaging unreliable (sens. 27.5%)
- Tumor DDR mutations not correlated with:
 - Pathologic response
 - Rate of false downstaging
- “Best-selected candidates” for bladder sparing: **35% rate of missed residual MIBC**

Thank you!

- Alexa Meyer
- Max Kates
- Jean Hoffman-Censits
- Noah Hahn
- Alex Baras
- Trinity Bivalacqua

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