IMPACT OF VARIANT HISTOLOGY ON UPSTAGING AND SURVIVAL IN PATIENTS WITH NON MUSCLE INVASIVE BLADDER CANCER UNDERGOING RADICAL CYSTECTOMY

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Introduction

- Histological heterogeneity in bladder cancer has significant impact on outcomes
- Efforts to identify variant histology (VH) urothelial carcinoma has increased for 2 reasons:

1. Prognostic value
2. Under-recognized in the community

- 17-20 % in TURBT specimens and 33% in RC
- VH NMIBC (non muscle invasive bladder cancer) categorized as high risk as per practice guidelines due to aggressive behaviour
- Early RC (radical cystectomy) for high and very high risk pure urothelial NMIBC, there is limited data on patients with VH NMIBC

Aims

- To examine the rate of upstaging and overall survival for patients with VH NMIBC against patients with pure urothelial MNIBC who underwent RC, to help clarify the optimum treatment strategy for these patients
- Hypothesis of this article : VH NMIBC compared to pure urothelial NMIBC would demonstrate higher upstaging and worse overall survival after RC

Methods

- Indiana University bladder cancer database was used to identify cases between 2004 – 2020.
- 42 patients with VH (micropapillary, plasmacytoid, squamous, sarcomatoid, glandular)
- 42 pts. with pure urothelial carcinoma over the same period to perform a matched pair analysis
- Upstaging was defined as any shift from lower clinical stage to higher pathologic stage

Table 1
Demographic and clinical variables

	VH NMIBC ($n = 42$)	Pure UC NMIBC ($n = 42$)	*P*-value	OR	95% CI
Age (*median, range*)	66 (31–92)	62 (37–83)	0.84		−5.11 to 6.26
Gender					
– Male	30	33	1	0.857	0.238–2.979
– Female	12	9			
Race					
– White	41	41	0.48	1	0.013–78.497
– Nonwhite	1	1			
Smoking history					
– Yes	29	30	1	0.857	0.238–2.979
– No	13	12			
Prior pelvic radiation			0.62	0.33	0.006–4.151
– Yes	1	3			
– No	41	39			
Multifocal disease presence					
– Yes	18	21	0.51	0.75	0.317 – 1.772
– No	24	21			
Maximum documented tumor burden on TURBT					
– <2cm	14	17	0.77		
– 2 to 5cm	17	16			
– >5cm	11	9			
Number of TURBTs prior to RC (*median, range*)	2 (1–5)	2 (1–5)	0.13		−0.77 to 0.10
Prior intravesical therapy					
– Yes	15	15			
– No	27	27			
MP presence on final TURBT					
– Yes	17	17			
– No	25	25			
CIS presence on prior TURBTs					
– Yes	11	11			
– No	31	31			
Clinical T-stage					
– pT1	41	41			
– pTa	1	1			
Days from final TURBT to RC (*median, range*)	48 (21–239)	49 (2–268)	0.6188		−29.93 to 18.02
Upstaged at RC					
– Yes	31	22	**0.0244**	**4.33**	1.191–23.707
– No	11	20			
Lymph node staging					
– pN0	23	30	**0.0389**	**4**	1.079–22.088
– pN+	17	9			

Table 2
Distribution of pathologic staging after radical cystectomy

	VH	Pure UC	*P*-value
pT0	4	5	0.72
pTis	3	4	0.69
pTa	0	0	
pT1	5	12	0.057
pT0–pT1	*12*	*21*	**0.044**
pT2	2	1	0.287
– pT2a	1	5	
– pT2b	4	5	
pT3			**0.0078**
– pT3a	3	2	
– pT3b	11	2	
pT4	1	1	0.39
– pT4a	7	5	
– pT4b	1	0	
pT3–pT4	*23*	*10*	**0.0037**

Abbreviations: VH = variant histology; pure UC = pure urothelial carcinoma.

Bold values in Table 1 and 2 reflect statistically significant values ($p < 0.05$).

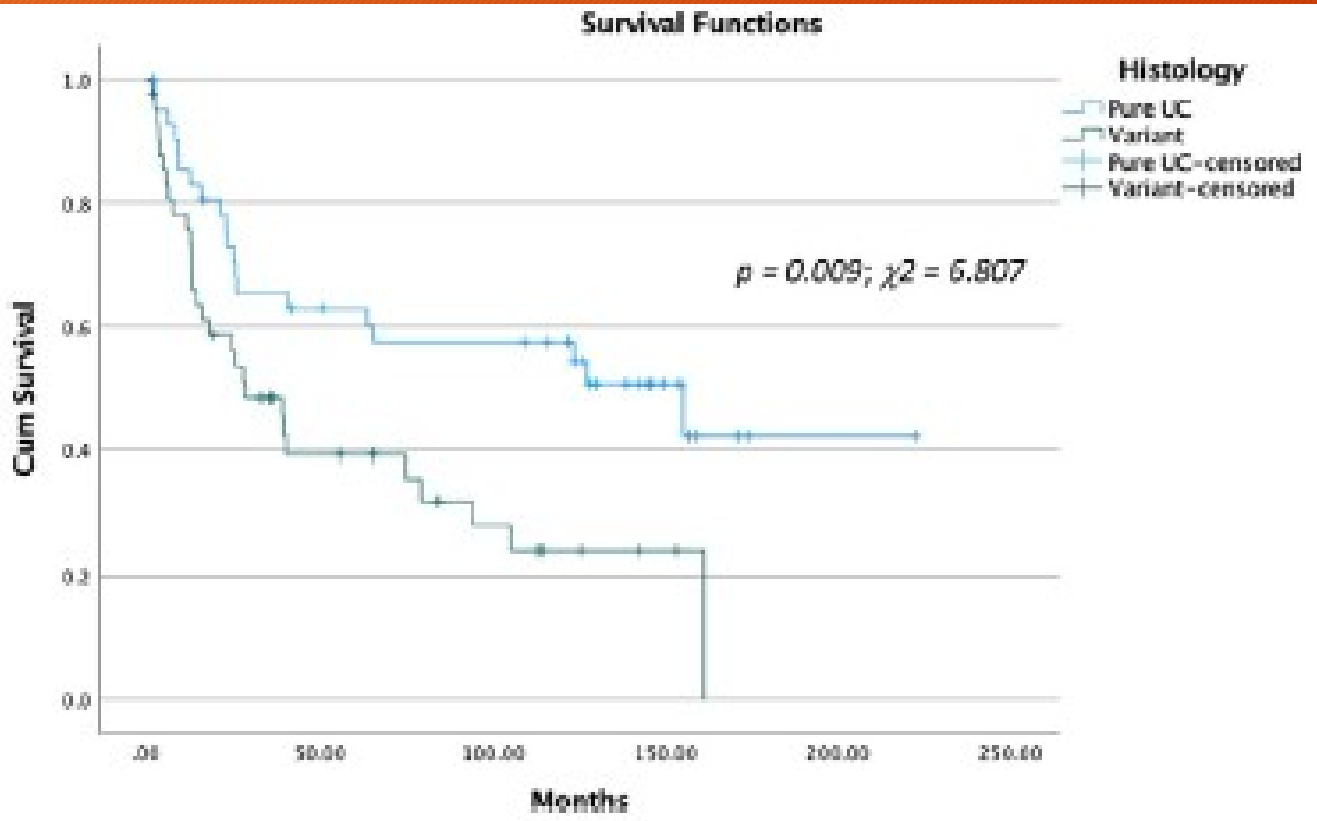

Fig. 1. Overall survival using Kaplan Meier estimates for patients with variant histology ("Variant") vs. pure urothelial ("Pure UC") nonmuscle invasive bladder cancer undergoing radical cystectomy. Statistically significant difference in survival estimates between groups was observed ($P = 0.009$). UC = urothelial carcinoma.

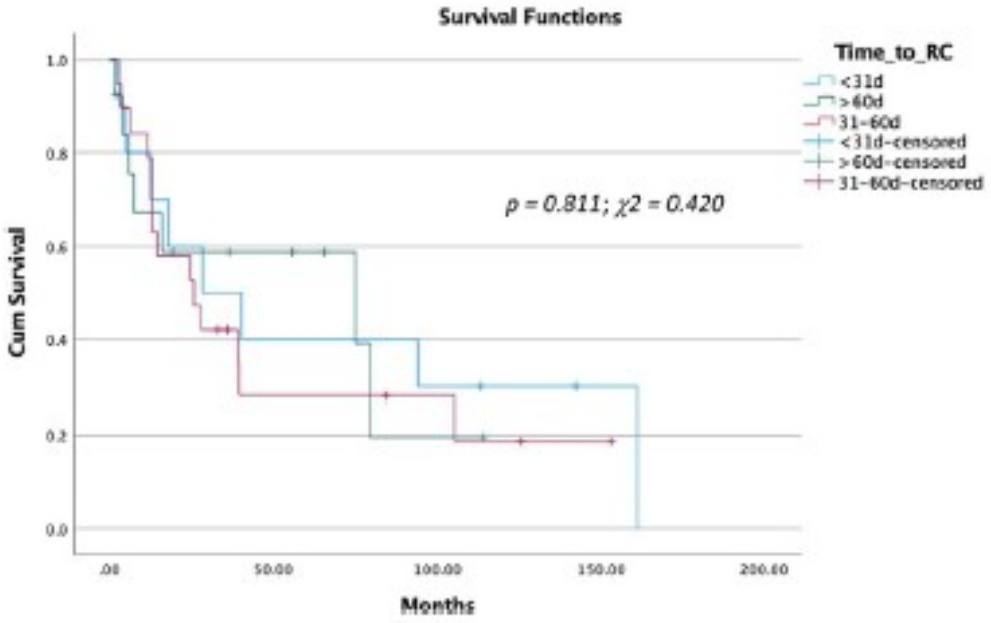

Fig. 2. Impact of time from final TURBT to RC among patients with variant histology nonmuscle invasive bladder cancer. Overall survival using Kaplan Meier estimates for patients that underwent RC within 30 days ("<31 days") of final TURBT, between 31−60 days after final TURBT ("31−60 days"), and greater than 60 days from final TURBT (">60 days"). Statistically significantly difference in survival estimates between groups was not observed. TURBT = transurethral resection of bladder tumor; RC = radical cystectomy.

Table 3

Variant-specific pathologic outcomes

	Total	pN+	Upstaged	Percent upstaged	Fisher's exact test, upstaging vs. pure UC	Fisher's exact test, upstaging vs. all other VH
Squamous differentiation	12	2	9	75%	$P = 0.20$	$P = 1$
Plasmacytoid	8	7	7	87.5%	$P = 0.12$	$P = 0.66$
Micropapillary	8	3	5	62.5%	$P = 0.71$	$P = 0.42$
Nested	5	2	4	80%	$P = 0.36$	$P = 1$
Glandular differentiation	5	0	2	40%	$P = 0.67$	$P = 0.10$
Sarcomatoid	4	3	4	100%	$P = 0.12$	$P = 0.56$

Abbreviations: VH = variant histology; pure UC = pure urothelial carcinoma.

Discussion

- This study reports a higher incidence of upstaging in VH NMIBC following RC compared to pure urothelial NMIBC and underscores the aggressive behaviour of variant histology in the NMIBC setting with poorer overall survival.
- Shapur et al found higher rates of disease progression in VH NMIBC v/s pure urothelial NMIBC (31.8% vs 12.5%).
- Gofrit et al. observed significantly worse progression free (60 vs. 82.5%) and overall survival (66 vs. 89.5%) at 5 years when comparing 41 VH NMIBC patients that received BCG to 140 patients with conventional high-grade UC

Discussion

- Shift in diagnostic and therapeutic strategy to improve outcomes for VH NMIBC
- Recommendations:

1. Improved classification schemes- clarity on treatment strategy
2. Adjunct molecular profiling and mutational signatures to optimize the timing and type of treatment

Strength of the study

- Matched –pair case-control study design
- VH on TURBT confirmed by experienced genitourinary pathologists
- RC is performed by experienced high volume surgeons
- Broadly inclusive study population – real world scenarios and provide value for patient counselling and determination of treatment course

Limitations of the study

- Retrospective design- inherent bias,
- Small sample size
- Limitations in follow up , prevented adequate capture of timing of diseases progressions
- Not all TURBTs were performed in parent institution - inadequate resection may affect true clinical staging and upstaging rates

Conclusions

- Meaningful contribution to the understanding of behaviour of VH NMIBC with a matched pair study design
- Compelling evidence for strong consideration of upfront RC when VH NMIBC is encountered
- Future studies are warranted to establish the role of neoadjuvant systemic therapy

THANK YOU