HISTOLOGICAL CHARACTERIZATION OF LYMPH NODES METASTASIS IN MIXED UROTHELIAL-SQUAMOUS HISTOLOGICAL VARIANT AT RADICAL CYSTECTOMY.

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Introduction & objectives:

- Bladder urothelial histological variants (BHV) at final pathological report after radical cystectomy (RC) are a frequent event, about 20% of cases. Moreover, as reported in literature, histological variants are more aggressive diseases, with a high rate of lymph node invasion (LNI). Indeed about 43% of patients with BHV have a LNI compared to the 24% of pure urothelial variants.
- No data are available in literature about the characterization of lymph node histology in BHV.
- **Aim of our study was to investigate the presence or not of histological variant into the lymph node in N+ patients and evaluate if oncological outcomes are affected by the node histology.**

Materials & methods:

- We evaluated **34 consecutive non metastatic patients with BHV, treated with RC and diagnosed with lymph node invasion at final pathological repor**t at a single tertiary referral centre between 2008 and 2015.
- Specimens were evaluated by a dedicated uro-pathologist. Descriptive statistic was used to identify characteristics of the population.
- Univariable and multivariable Cox proportional hazards regression analyses model was used to predict cancer specific mortality (CSM), overall mortality (OM) and recurrence rate.
- Covariates included age at surgery, gender, pathological T stage, pathological N stage, pathological grade, surgical margins and lymph vascular invasion (LVI).

Results:

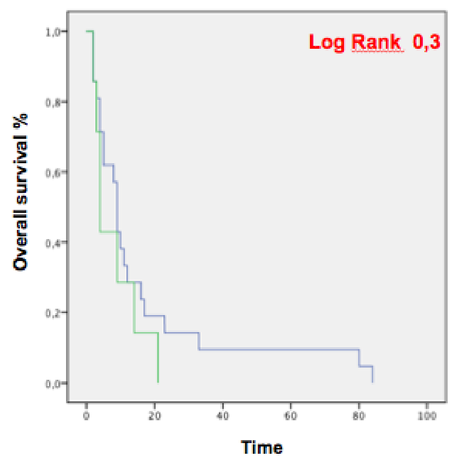
Descriptive characteristics

Variables	OVERALL (n=391)	MIXED UROTHELIAL (N= 72; 18%)	PURE UROTHELIAL (N= 319; 82%)	P value
Age at surgery, years Median (IQR)	71 (40-90)	71 (48-84)	70 (40-90)	0.5
Gender, n (%) Male Female	322 (82) 69 (18)	57 (79) 15 (21)	265 (82) 54 (18)	0.06
ASA score, n (%) 1 2 3 4	36 (9) 183 (47) 145 (37) 27 (6)	5 (7) 34 (47) 28 (39) 5 (7)	31 (9) 149 (47) 117 (37) 22 (7)	0.1
Tumor stage, n (%) 2 3-4	217 (55.5) 174 (44.5)	36 (50) 36 (50)	181 (56.7) 138 (43.3)	0.03
Margins, n (%) Positive Negative	51 (13) 340 (87)	14 (19.5) 58 (80.5)	37 (11.5) 282 (88.5)	0.01
Pathologic nodal stage, n (%) pN0 pN +	250 (63.9) 141 (36.1)	38 (52.7) 34 (47.3)	212 (66.5) 107 (33.5)	0.01
Number of LN removed, n (%)	23 (10-73)	25 (10-63)	22 (10-73)	0.05
LVI, n (%) Yes No	127 (32.4) 264 (67.6)	34 (47) 38 (53)	93 (29) 226 (71)	0.01
Adjuvant chemotherapy, n (%) Yes No	57 (14.6) 334 (85.4)	12 (16.6) 60 (84.4)	45 (14.1) 274(85.9)	0.06
Adjuvant radiotherapy, n (%) Yes No	25 (6.4) 366 (93.6)	5 (6.9) 67 (93.1)	20 (6.3) 299 (93.7)	0.2
Postoperative follow-up, months Median (IQR)	30 (5-130)	28 (5-110)	31 (5-109)	0.1

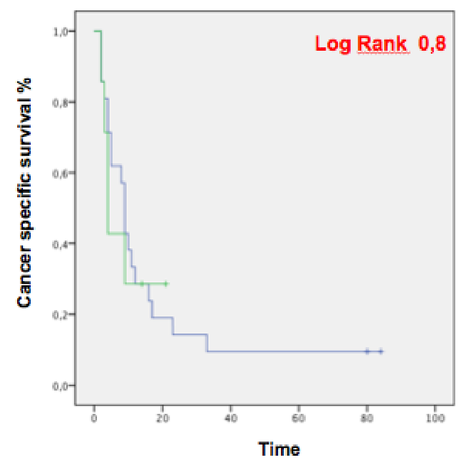
Variables	BHV N + Overall (N 34)	LNI Variant (N 8; 23.5%)	LNI Urothelial (N 26; 76.5%)	P value
Age at surgery, years Median (IQR)	72 (50-84)	71 (48-84)	70 (40-90)	0.8
Gender, n (%) Male Female	25 (73) 9 (27)	6 (75) 2 (25)	19 (73) 7 (27)	0.09
ASA score, n (%) 1 2 3 4	3 (9) 21 (62) 8 (23) 2 (6)	1 (13) 4 (50) 2 (24) 1 (13)	2 (8) 17 (65) 6 (23) 1 (4)	0.2
Tumor stage, n (%) 2 3-4	14 (41) 20 (59)	3 (38) 5 (62)	11 (42) 15 (58)	0.2
Margins, n (%) Positive Negative	8 (23) 26 (77)	2 (25) 6 (75)	6 (23) 20 (77)	0.1
Number of LN removed, n (%)	24(10-63)	25 (10-63)	22 (10-73)	0.4
LVI, n (%) Yes No	20 (53) 14 (47)	5 (60) 3 (40)	15 (57) 11 (43)	0.08
Percentage of Histological Variant Median (IQR)	60 (5-95)	60 (5-95)	60 (5-95)	1
Postoperative follow-up, months Median (IQR)	16 (5-84)	16 (5-110)	37 (5-109)	0.9

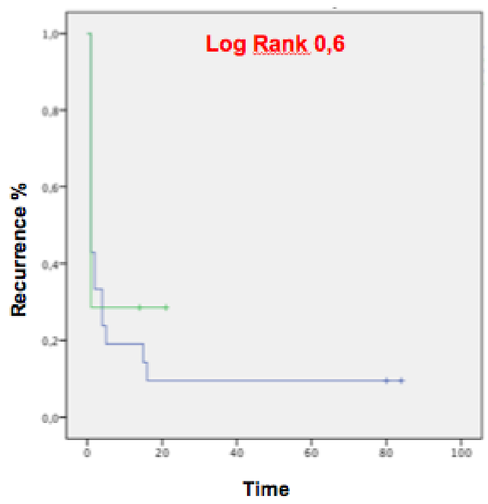
Kaplan Meier analysis assessing survival and recurrence in patients stratified according to Lymph Node Histology

PURE UROTHELIAL NODE METASTASIS



UROTHELIAL-SQUAMOUS HISTOLOGICAL VARIANT NODE METASTASIS





Univariable and Multivariable Cox Regression predicting CSM, OM and Recurrence

	CANCER SPECIFIC MORTALITY		OVERALL MORTALITY		RECURRENCE	
	Univariable		Univariable		Univariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at surgery	1.2 (0.89-1.12)	0.2	1.57 (1.37-3.16)	<0.001	1.01 (0.99-1.02)	0.3
ASA	1.47 (0.91-1.65)	0.3	1.23 (1.12-1.47)	<0.001	1.04 (0.91-1.25)	0.4
Gender	1.5 (0.96-2.47)	0.5	1.12 (0.93-1.79)	0.2	1.54 (0.97-3.67)	0.2
Pathologic tumor stage T2 vs T3-T4	4.7 (2.45-6.63)	<0.001	0.93 (0.43-1.37)	0.3	3.4 (2.29-5.43)	0.01
Surgical margins	1.6 (0.96-3.37)	0.3	1.21 (0.53-1.59)	0.3	1.98 (1.27-2.37)	0.03
LVI	1.37 (1.08-3.15)	0.01	1.12 (0.69-1.27)	0.5	1.21 (1.11-3.25)	0.05
Adjuvant Chemotherapy	6.17 (3.88-11.34)	<0.001	1.16 (0.52-1.47)	0.09	8.3 (4.88-21.34)	<0.001
Histological variant in LND	1.42 (0.95-3.94)	0.5	1.21 (0.59-1.27)	0.2	1.19 (0.52-2.52)	0.6

	CANCER SPECIFIC MORTALITY		OVERALL MORTALITY		RECURRENCE	
	Multivariable		Multivariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at surgery	1.2 (0.99-1.02)	0.7	1.29 (1.07-1.93)	0.02	1,7 (0.97-1.52)	0.5
ASA	1.17 (0.91-1.25)	0.4	1.33 (1.22-2.47)	<0.001	1.12 (0.61-3.165)	0.4
Gender	1.25 (0.82-3.67)	0.3	1.52 (0.83-3.79)	0.3	1.55 (0.7-2.67)	0.3
Pathologic tumor stage T2 vs T3-T4	3.6 (2.29-4.73)	<0.001	0.98 (0.63-2.37)	0.7	3.3 (2.49-6.63)	0.01
Surgical margins	2.5 (0.86-3.67)	0.6	1.12 (0.83-1.99)	0.3	1.3 (0.87-4.57)	0.1
LVI	1.27 (0.95-2.25)	0.4	1.14 (1.09-1.37)	0.3	3.12 (1.45-5.15)	0.01
Adjuvant Chemotherapy	13.27 (6.88-25.34)	<0.001	1.11 (0.82-1.56)	0.4	13.12 (4.68-23.24)	<0.001
Histological variant in LND	1.17 (0.93-1.42)	0.5	1.13 (0.88-1.92)	0.3	1.26 (0.78-1.64)	0.5

Conclusions: **Literature data about the frequency of histological variants at RC are confirmed in our study. Moreover we show for the first time the histological characterization of lymph node metastasis in BHV. Furthermore bladder percentage of histological variant is not associated with the presence of variant in node metastasis. In the end the presence of histological variant in lymph node metastasis does not affect survival outcomes**

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