

Basal and Luminal Markers in Non-Muscle Invasive Bladder Urothelial Carcinoma

Preliminary Results

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Methology

The following markers were evaluated

- CK5/6
- CK20
- CD44
- GATA3
- ER
- HER2
- Uroplakin

For each marker, the percentage of positive cells (extent) was recorded. Markers were also categorized as High/Low expression using the mean as the cutoffpoint

Outcome endpoints

The analysis was carried out using paired events. For any case, the paired event consisted in the pair formed by 2 consecutive diagnoses during follow up. Thus, a case could have one or more paired events. For each marker, the considered outcomes included:

- **Tumor recurrence at next diagnosis:** Tumor reappeared showing a similar or lower-grade/stage lesion.
- **Tumor recurrence at any time:** Tumor had recurred at least once during follow-up.
- **Tumor grade progression at next diagnosis:** Tumor reappeared showing a higher-grade lesion.
- **Tumor grade progression at any time:** Tumor had showed grade progression at least once during follow-up.
- **Tumor stage progression at next diagnosis:** Tumor reappeared showing a higher-stage lesion.
- **Tumor stage progression at any time:** Tumor had showed stage progression at least once during follow-up.

Statistical analysis

For the association and outcome analysis we used the Student's t-test and the Pearson's Chi-squared test. Data was analyzed and plots were generated using R version 3.3.1 (2016-06-21).

Results

Marker Extent and Level by Tumor Recurrence

Table 1: Recurrence at next diagnosis

Descriptive Statistics by 'rec_next_time'			
	No tumor recurrence (N=167)	With tumor recurrence (N=243)	p
ck56	36.6 ± 31.6	26.7 ± 29.6	0.005
ck20	23.8 ± 33.5	26.9 ± 34.5	0.436
cd44	61.8 ± 31.8	47.4 ± 34.8	0.000
gata3	98.5 ± 6.7	99.3 ± 3.9	0.226
er	2.0 ± 7.6	1.5 ± 6.4	0.506
her2	33.2 ± 35.0	44.0 ± 35.0	0.007
uoplakin	12.4 ± 24.6	17.2 ± 25.5	0.110
ck56_cat			0.001
- High CK5/6	69 (56.6%)	72 (36.4%)	
- Low CK5/6	53 (43.4%)	126 (63.6%)	
ck20_cat			0.889
- High CK20	42 (34.4%)	71 (35.9%)	
- Low CK20	80 (65.6%)	127 (64.1%)	
cd44_cat			0.002
- High CD44	76 (66.7%)	86 (47.3%)	
- Low CD44	38 (33.3%)	96 (52.7%)	
gata3_cat			0.675
- High GATA3	116 (94.3%)	191 (96.0%)	
- Low GATA3	7 (5.7%)	8 (4.0%)	
er_cat			0.409
- High ER	16 (13.1%)	19 (9.5%)	
- Low ER	106 (86.9%)	181 (90.5%)	
her2_cat			0.002
- High HER2	44 (35.2%)	108 (53.2%)	
- Low HER2	81 (64.8%)	95 (46.8%)	
uoplakin_cat			0.065
- High Uoplakin	24 (20.9%)	58 (31.4%)	
- Low Uoplakin	91 (79.1%)	127 (68.6%)	

Table 2: Recurrence at any time

Descriptive Statistics by 'rec_any_time'			
	No tumor recurrence (N=54)	With tumor recurrence (N=407)	p
ck56	34.8 ± 28.7	29.0 ± 30.2	0.242
ck20	22.7 ± 34.4	28.9 ± 35.3	0.291
cd44	61.2 ± 33.7	50.7 ± 33.7	0.053

##	gata3	98.6 ± 5.7	99.2 ± 4.8	0.431
##	er	4.7 ± 12.2	1.2 ± 5.3	0.074
##	her2	23.4 ± 36.5	41.0 ± 34.9	0.002
##	uroplakin	9.2 ± 19.0	15.5 ± 24.6	0.127
##	ck56_cat			0.143
##	- High CK5/6	23 (54.8%)	132 (41.5%)	
##	- Low CK5/6	19 (45.2%)	186 (58.5%)	
##	ck20_cat			0.644
##	- High CK20	14 (33.3%)	122 (38.4%)	
##	- Low CK20	28 (66.7%)	196 (61.6%)	
##	cd44_cat			0.018
##	- High CD44	31 (70.5%)	144 (50.0%)	
##	- Low CD44	13 (29.5%)	144 (50.0%)	
##	gata3_cat			0.607
##	- High GATA3	39 (92.9%)	307 (95.9%)	
##	- Low GATA3	3 (7.1%)	13 (4.1%)	
##	er_cat			0.035
##	- High ER	9 (20.9%)	29 (9.1%)	
##	- Low ER	34 (79.1%)	290 (90.9%)	
##	her2_cat			0.002
##	- High HER2	9 (20.9%)	155 (47.7%)	
##	- Low HER2	34 (79.1%)	170 (52.3%)	
##	uroplakin_cat			0.138
##	- High Uroplakin	6 (15.0%)	81 (27.4%)	
##	- Low Uroplakin	34 (85.0%)	215 (72.6%)	
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Marker Extent and Level by Grade Progression

Table 3: Tumor grade progression at next diagnosis

##	Descriptive Statistics by 'grade_prog_next_time'			
##	-----			
##		No grade progression	With grade progression	p
##		(N=402)	(N=21)	
##	-----	-----	-----	-----
##	ck56	29.0 ± 30.2	47.5 ± 33.1	0.026
##	ck20	27.4 ± 35.1	27.7 ± 35.8	0.975
##	cd44	52.1 ± 34.0	70.0 ± 34.6	0.143
##	gata3	99.0 ± 5.2	100.0 ± 0.0	0.001
##	er	1.8 ± 6.9	0.0 ± 0.0	0.000
##	her2	38.9 ± 35.7	51.9 ± 32.8	0.196
##	uroplakin	14.7 ± 24.7	22.7 ± 28.2	0.293
##	ck56_cat			0.162
##	- High CK5/6	133 (41.7%)	9 (64.3%)	
##	- Low CK5/6	186 (58.3%)	5 (35.7%)	
##	ck20_cat			1.000
##	- High CK20	118 (36.9%)	5 (38.5%)	
##	- Low CK20	202 (63.1%)	8 (61.5%)	
##	cd44_cat			0.393
##	- High CD44	160 (53.3%)	6 (75.0%)	

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##   - Low CD44          140 (46.7%)          2 (25.0%)
## gata3_cat                                0.873
##   - High GATA3       306 (95.0%)         13 (100.0%)
##   - Low GATA3        16 ( 5.0%)          0 ( 0.0%)
## er_cat                                0.439
##   - High ER          37 (11.5%)          0 ( 0.0%)
##   - Low ER           286 (88.5%)         12 (100.0%)
## her2_cat                                0.141
##   - High HER2        146 (44.5%)          9 (69.2%)
##   - Low HER2         182 (55.5%)          4 (30.8%)
## uroplakin_cat                        0.259
##   - High Uroplakin    77 (25.5%)          5 (45.5%)
##   - Low Uroplakin     225 (74.5%)         6 (54.5%)
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Table 4: Tumor grade progression at any time

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##
##      Descriptive Statistics by 'grade_prog_any_time'
## -----
##               No grade progression With grade progression   p
##               (N=428)              (N=33)
## -----
## ck56                29.3 ± 30.0          34.4 ± 30.8       0.390
## ck20                27.6 ± 34.7          35.2 ± 41.2       0.281
## cd44                51.5 ± 33.7          62.5 ± 35.1       0.179
## gata3               99.1 ±  5.1          100.0 ±  0.0       0.001
## er                   1.6 ±  6.8           1.2 ±  3.0       0.528
## her2                37.9 ± 35.3          51.7 ± 35.9       0.053
## uroplakin           14.9 ± 24.3          12.7 ± 21.8       0.689
## ck56_cat                                0.724
##   - High CK5/6       142 (42.6%)         13 (48.1%)
##   - Low CK5/6        191 (57.4%)         14 (51.9%)
## ck20_cat                                0.592
##   - High CK20        124 (37.2%)         12 (44.4%)
##   - Low CK20         209 (62.8%)         15 (55.6%)
## cd44_cat                                0.329
##   - High CD44        163 (51.9%)         12 (66.7%)
##   - Low CD44         151 (48.1%)          6 (33.3%)
## gata3_cat                                0.520
##   - High GATA3       320 (95.2%)         26 (100.0%)
##   - Low GATA3        16 ( 4.8%)          0 ( 0.0%)
## er_cat                                0.554
##   - High ER          34 (10.1%)          4 (16.0%)
##   - Low ER           303 (89.9%)         21 (84.0%)
## her2_cat                                0.321
##   - High HER2        149 (43.7%)         15 (55.6%)
##   - Low HER2         192 (56.3%)         12 (44.4%)
## uroplakin_cat                        0.921
##   - High Uroplakin    82 (26.1%)          5 (22.7%)
##   - Low Uroplakin     232 (73.9%)         17 (77.3%)
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Marker Extend and Level by Stage Progression

Table 5: Tumor stage progression at next diagnosis

Descriptive Statistics by 'pT_upstage_next_time'			
	No stage progression (N=384)	With stage progression (N=26)	p
ck56	28.7 ± 29.3	67.8 ± 32.6	0.000
ck20	26.2 ± 34.2	19.4 ± 31.9	0.435
cd44	52.5 ± 34.5	61.7 ± 30.4	0.367
gata3	99.1 ± 5.0	96.7 ± 7.8	0.300
er	1.7 ± 6.7	0.0 ± 0.0	0.000
her2	39.1 ± 35.3	42.8 ± 35.9	0.681
uroplakin	15.3 ± 25.4	10.0 ± 17.7	0.455
ck56_cat			0.002
- High CK5/6	128 (42.5%)	15 (83.3%)	
- Low CK5/6	173 (57.5%)	3 (16.7%)	
ck20_cat			0.531
- High CK20	109 (36.0%)	4 (25.0%)	
- Low CK20	194 (64.0%)	12 (75.0%)	
cd44_cat			1.000
- High CD44	155 (54.4%)	7 (58.3%)	
- Low CD44	130 (45.6%)	5 (41.7%)	
gata3_cat			0.190
- High GATA3	296 (95.8%)	10 (83.3%)	
- Low GATA3	13 (4.2%)	2 (16.7%)	
er_cat			0.420
- High ER	34 (11.0%)	0 (0.0%)	
- Low ER	274 (89.0%)	13 (100.0%)	
her2_cat			0.914
- High HER2	141 (45.3%)	8 (50.0%)	
- Low HER2	170 (54.7%)	8 (50.0%)	
uroplakin_cat			1.000
- High Uroplakin	77 (26.8%)	3 (23.1%)	
- Low Uroplakin	210 (73.2%)	10 (76.9%)	

Table 5: Tumor stage progression at any time

Descriptive Statistics by 'pT_upstage_any_time'			
	No stage progression (N=389)	With stage progression (N=72)	p
ck56	27.9 ± 28.5	38.2 ± 35.9	0.038
ck20	29.2 ± 35.3	22.8 ± 34.6	0.195

##	cd44	54.2 ± 33.9	39.1 ± 30.9	0.005
##	gata3	99.2 ± 4.9	98.5 ± 4.9	0.319
##	er	1.3 ± 5.7	3.2 ± 10.3	0.206
##	her2	38.2 ± 34.9	42.8 ± 38.4	0.373
##	uroplakin	15.5 ± 25.3	10.6 ± 15.2	0.064
##	ck56_cat			0.359
##	- High CK5/6	125 (41.8%)	30 (49.2%)	
##	- Low CK5/6	174 (58.2%)	31 (50.8%)	
##	ck20_cat			0.037
##	- High CK20	121 (40.3%)	15 (25.0%)	
##	- Low CK20	179 (59.7%)	45 (75.0%)	
##	cd44_cat			0.009
##	- High CD44	159 (55.8%)	16 (34.0%)	
##	- Low CD44	126 (44.2%)	31 (66.0%)	
##	gata3_cat			0.129
##	- High GATA3	297 (96.4%)	49 (90.7%)	
##	- Low GATA3	11 (3.6%)	5 (9.3%)	
##	er_cat			0.975
##	- High ER	33 (10.7%)	5 (9.4%)	
##	- Low ER	276 (89.3%)	48 (90.6%)	
##	her2_cat			0.634
##	- High HER2	136 (43.9%)	28 (48.3%)	
##	- Low HER2	174 (56.1%)	30 (51.7%)	
##	uroplakin_cat			0.919
##	- High Uroplakin	73 (25.6%)	14 (27.5%)	
##	- Low Uroplakin	212 (74.4%)	37 (72.5%)	
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