

Supplementary Materials:

The Immunoscore in Localized Urothelial Carcinoma Treated with Neoadjuvant Chemotherapy: Clinical Significance for Pathologic Responses and Overall Survival

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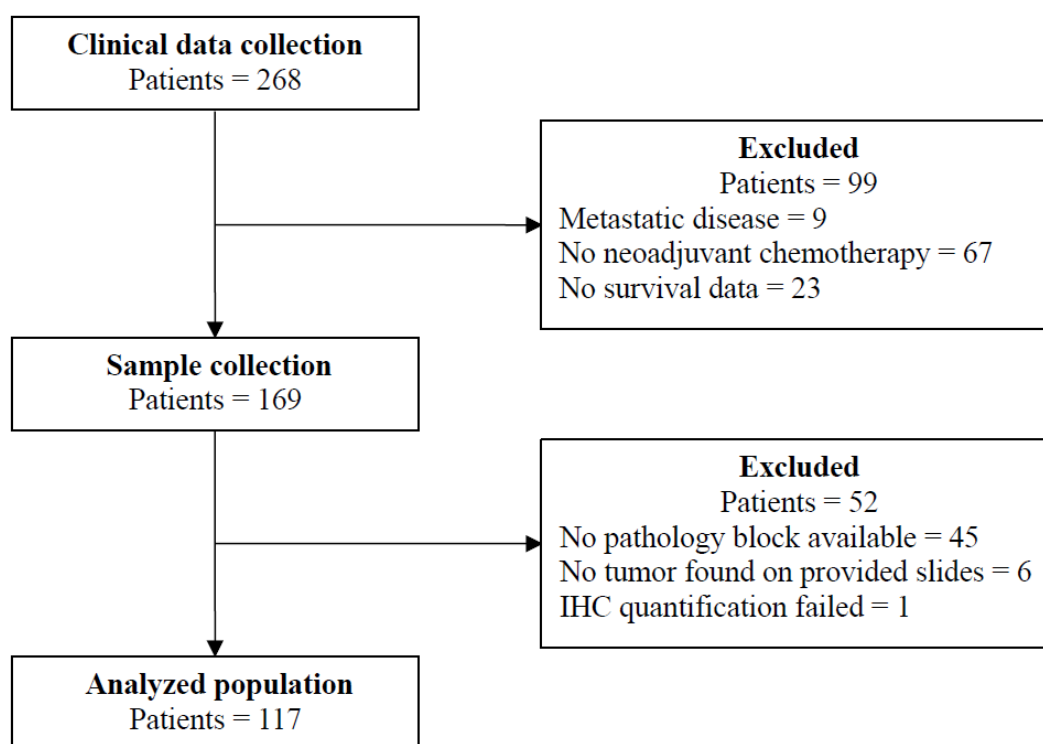


Figure S1. The localized UC study design. Biomarker exclusion and clinical a data exclusion prior to analysis.

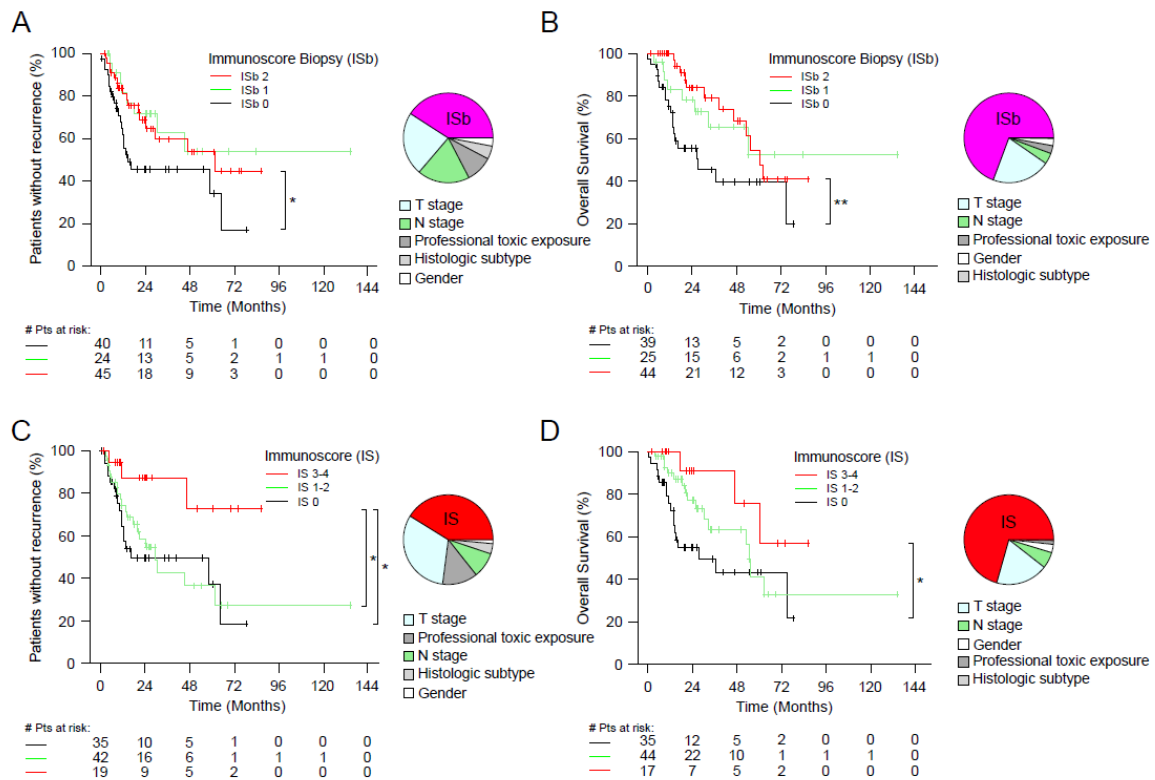


Figure S2. The impact of Immunoscore on the patient outcome. Kaplan-Meier curves for Immunoscore (IS) are shown for TTR (A, C) and OS (B, D). Pie chart indicates the contribution of X2 proportion of ISb and IS among other variables for influencing survival in multivariate analysis. (A-B) Immunoscore three categories for Immunoscore biopsy: ISb 0 (black), ISb 1 (green) and ISb 2 (red). (C-D) Immunoscore three categories for Immunoscore: IS 0 (black), IS 1-2 (green) and IS 3-4 (red). * P<0.05; ** P < 0.01.

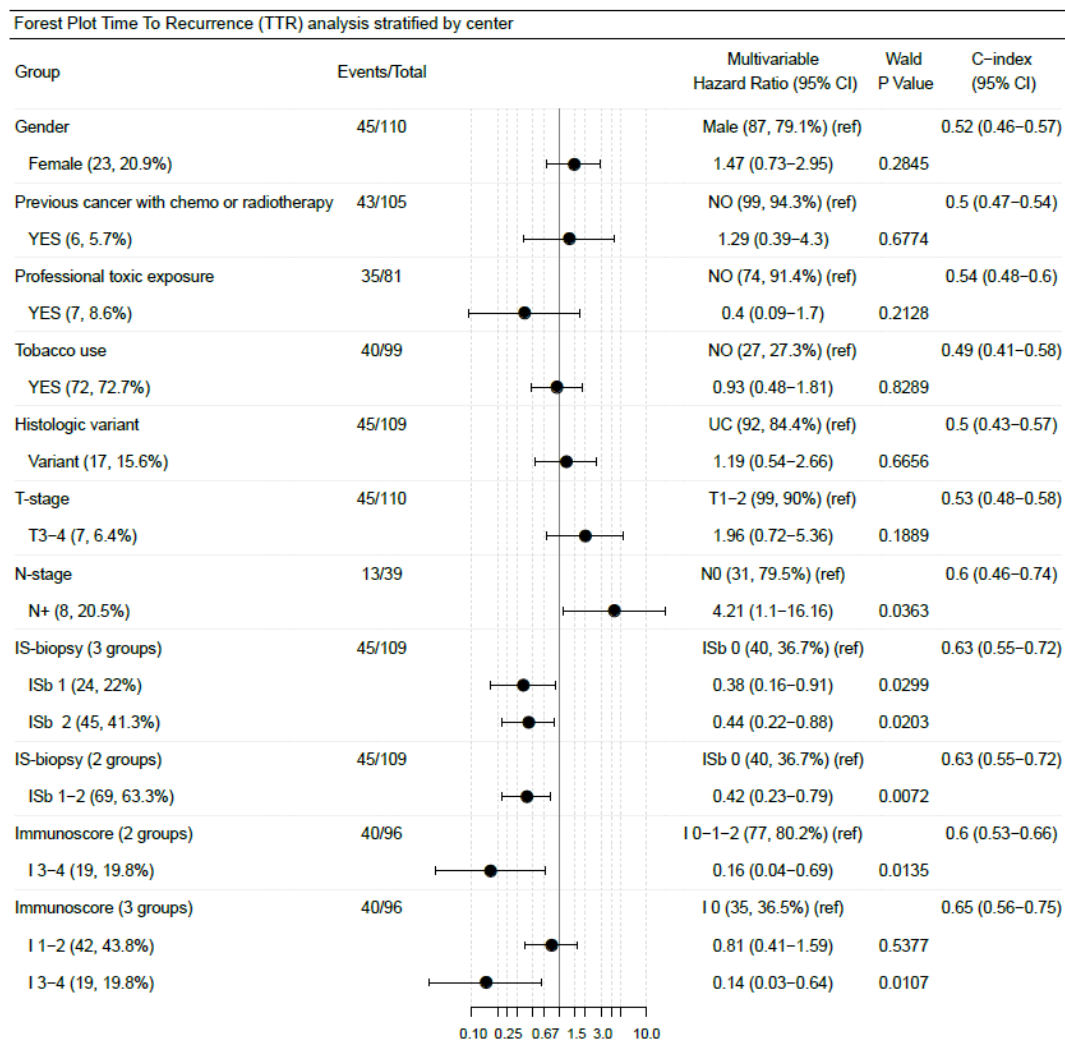
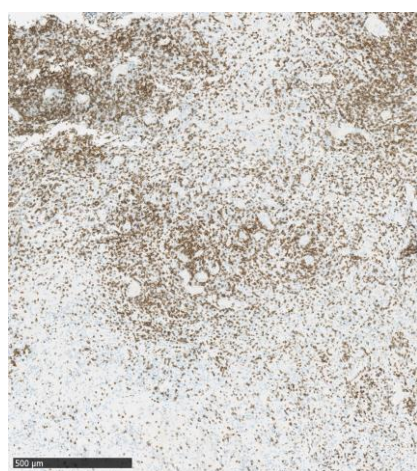
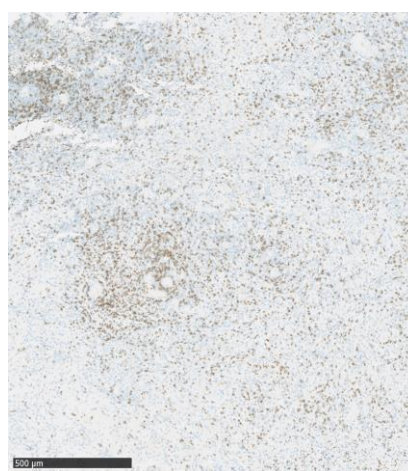


Figure S3. Forest plot for the impact of clinical parameters and Immunoscore on the patient outcome. Bi-variate Cox models stratified by participating center for clinical parameters and Immunoscore.



A



B

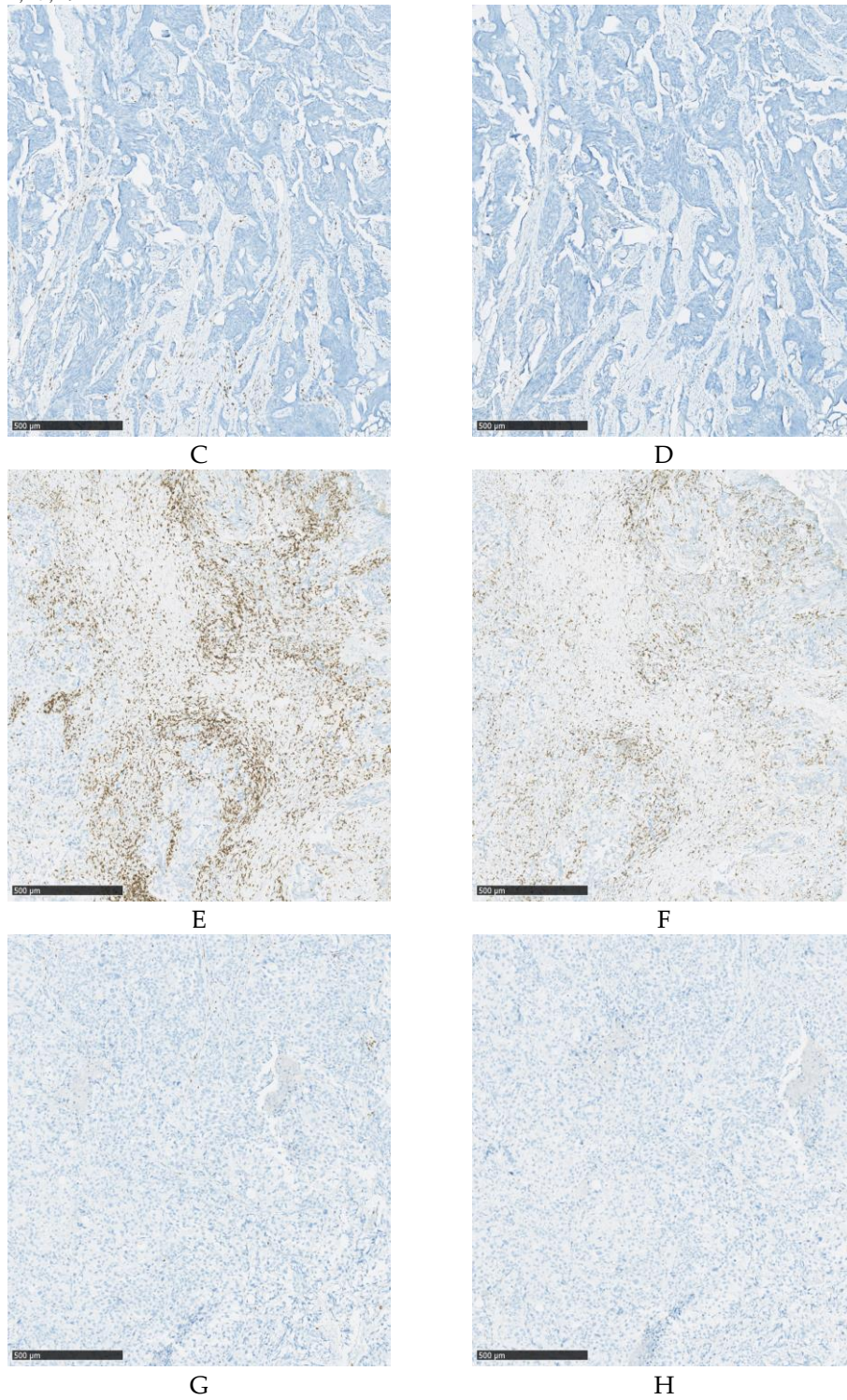


Figure S4. Pathology slides for Immunoscore determination (A) CD3 immunohistochemistry (IHC) in IS-4 patient (B) CD8 IHC in IS-4 patient (C) CD3 IHC in IS-0 patient (D) CD8 IHC in IS-0 patient (E) CD3 IHC in ISb-2 patient (F) CD8 IHC in ISb-2 patient (G) CD3.

B

Table S1: Bivariable analysis for Clinical Parameters for OS

	Number of patients (%)	Median months (95% CI)	Rate at		Overall Survival (OS)			RMST Rel. Months (95% CI)	P value**
			3 yr % (95% CI)	5 yr % (95% CI)	Unadjusted stratified by center HR (95% CI)	P value*	C-index (95% CI)		
Sex							0.51 (0.43–0.58)		
Male	86 (78.9)	60.5 (32.9-NR)	62.7 (51.5-76.4)	50.2 (37.3-67.5)	1.0 (reference)			0.0 (reference)	
Female	23 (21.1)	53.1 (5.9-74.8)	64.3 (44.5-92.8)	37.5 (15-94)	0.99 (0.44–2.22)	0,9828		-2.3 (-17.9-13.2)	0,7683
Previous cancer with chemotherapy or pelvic radiotherapy							0.5 (0.45–0.54)		
No	100 (95.2)	55.3 (32.9-74.8)	64.1 (53.8-76.3)	48.1 (35.8-64.5)	1.0 (reference)			0.0 (reference)	
Yes	5 (4.8)	NR	80 (51.6-100)	NR (NR-NR)	0.76 (0.1–5.72)	0,7914		6.5 (-9.4-22.4)	0,4242
Professional toxic exposure							0.52 (0.43–0.6)		
No	73 (89)	55.3 (27.4-NR)	60.7 (48.6-75.7)	46.3 (32.5-65.9)	1.0 (reference)			0.0 (reference)	
Yes	9 (11)	NR	77.8 (54.9-100)	77.8 (54.9-100)	0.64 (0.19–2.16)	0,4688		9.8 (-13.1-32.7)	0,4001
Tobacco use							0.54 (0.44–0.63)		
No	24 (24.7)	74.8 (5.2-NR)	63.9 (45.2-90.3)	63.9 (45.2-90.3)	1.0 (reference)			0.0 (reference)	
Yes	73 (75.3)	55.3 (30.6-NR)	63 (50.8-78)	46.3 (31.7-67.6)	1.51 (0.67–3.44)	0,3220		-8.4 (-24.5-8.2)	0,3202
Histologic variant							0.51 (0.43–0.58)		
UC	93 (85.3)	55.3 (32.9-NR)	64.9 (54.1-77.8)	47.7 (34.2-66.6)	1.0 (reference)			0.0 (reference)	
Variant	16 (14.7)	36.8 (12.4-74.8)	53.4 (31.3-91.2)	42.7 (21.4-85.3)	1.4 (0.64–3.08)	0,3990		-7.8 (-24.5-8.8)	0,3557
T-stage							0.49 (0.47–0.51)		
T2	99 (90.8)	60.5 (36.8-NR)	66.2 (56.2-78)	52.4 (40.2-68.4)	1.0 (reference)			0.0 (reference)	
T3-4	6 (5.5)	25.8 (17.5-30.6)	NR (NR-NR)	NR (NR-NR)	1.85 (0.52–6.58)	0,3421		1.3 (-3.7-6.3)	0,6124
N-stage							0.55 (0.38–0.73)		
N0	26 (76.5)	36.8 (0.1-NR)	74.6 (53-100)	37.3 (8.9-100)	1.0 (reference)			0.0 (reference)	
N+	8 (23.5)	25.8 (9.9-NR)	41.7 (14.7-100)	NR (NR-NR)	1.96 (0.31–12.36)	0,4734		-4.7 (-20.4-11)	0,5575
IS-biopsy (2 groups)							0.7 (0.61–0.78)		
ISb 0	39 (36.1)	27.4 (13.9-74.8)	45.4 (29.9-68.8)	39.7 (24.3-64.9)	1.0 (reference)			0.0 (reference)	
ISb 1-2	69 (63.9)	60.5 (38.8-NR)	73.8 (62-87.8)	53.2 (37.8-74.8)	0.3 (0.15–0.59)	0,0005		15.8 (2.1-29.6)	0,0244
IS-biopsy (3 groups)							0.73 (0.65–0.8)		
ISb 0	39 (36.1)	27.4 (13.9-74.8)	45.4 (29.9-68.8)	39.7 (24.3-64.9)	1.0 (reference)			0.0 (reference)	
ISb 1	25 (23.1)	NR	65.4 (46.9-91.2)	52.4 (30.2-90.7)	0.34 (0.14–0.82)	0,0167		14.6 (-2.9-32)	0,1018
ISb 2	44 (40.7)	60.5 (38.8-NR)	79.2 (65.3-95.9)	54.6 (35.9-83)	0.27 (0.12–0.6)	0,0013		17.2 (2.5-31.8)	0,0216
Immunoscore (2 groups)							0.59 (0.53–0.65)		
IS 0-1-2	79 (82.3)	54.4 (27.4-74.8)	57.3 (45.5-72.3)	41.9 (28.3-62)	1.0 (reference)			0.0 (reference)	
IS 3-4	17 (17.7)	NR	90.9 (75.4-100)	75.8 (50.6-100)	0.35 (0.1–1.19)	0,0936		21.2 (3.3-39.1)	0,0200
Immunoscore (3 groups)							0.71 (0.62–0.79)		
IS 0	35 (36.5)	27.4 (12.4-74.8)	49.5 (33.7-72.6)	43.3 (27.2-68.9)	1.0 (reference)			0.0 (reference)	
IS 1-2	44 (45.8)	54.4 (21.2-NR)	63.4 (47.5-84.7)	41.1 (23.1-73.3)	0.43 (0.2–0.91)	0,0281		8.9 (-6.7-24.4)	0,2630
IS 3-4	17 (17.7)	NR	90.9 (75.4-100)	75.8 (50.6-100)	0.22 (0.06–0.78)	0,0197		23.1 (5.5-40.7)	0,0101

* Wald P Value stratified by participating center. ** Restricted Mean Survival Time (RMST) P value. IS: Immunoscore; ISb Immunoscore biopsy like.

Table S2: Multivariable analysis Immunoscore vs clinical parameters for TTR and OS

	TTR Model (45/110)*			OS Model (40/110)*		
	Hazard Ratio (95% CI)	P-value ¹	C-Index (95% CI)	Hazard Ratio (95% CI)	P-value ¹	C-Index (95% CI)
Multivariable Cox Model stratified by center			0,71 (0.62-0.79)			0,7 (0.6-0.79)
Immunoscore (3 groups)						
IS 1-2 vs IS 0	0.62 (0.29-1.33)	0,2214		0.35 (0.16-0.8)	0,0121	
IS 3-4 vs IS 0	0.14 (0.03-0.67)	0,0134		0.17 (0.04-0.66)	0,011	
Unclassified vs IS 0	0.35 (0.12-1.05)	0,0602		0.37 (0.12-1.17)	0,0908	
Gender						
Female vs Male	1.23 (0.59-2.56)	0,5828		0.75 (0.32-1.77)	0,5087	
Professional toxic exposure						
Yes vs No	0.25 (0.04-1.45)	0,1204		0.75 (0.19-2.93)	0,6754	
Unkown vs No	0.71 (0.22-2.31)	0,5637		0.88 (0.26-3.02)	0,8451	
Histologic variant						
Variant vs UC	0.67 (0.26-1.71)	0,4009		1.11 (0.44-2.78)	0,8244	
Unkown vs UC	0 (0-Inf)	0,9979		-	-	
T-stage						
T3-4 vs T2	2.42 (0.76-7.67)	0,1345		3.26 (0.81-13.21)	0,0976	
Unknown vs T2	5.87 (1.19-28.92)	0,0298		1 (0.18-5.52)	0,9976	
N-stage						
N+ vs N0	2.48 (0.64-9.59)	0,1882		1.31 (0.23-7.46)	0,7588	
Unknown vs N0	1.26 (0.29-5.55)	0,7603		2.11 (0.43-10.39)	0,3577	

* (Events/Total); ¹Stratified covariate Wald p-value; Stratified by center. IS: Immunoscore