

Supplementary Tables S1-S19

Table S1 Characteristics of patients with clear cell renal cell carcinoma

Characteristic	Total (n=310)	3:2 ratio		1:1 ratio	
		training cohort (n=186)	validation cohort (n=124)	training cohort (n=155)	validation cohort (n=155)
Age					
<60	185 (59.7%)	116 (62.4%)	69 (55.6%)	89 (57.4%)	96 (61.9%)
≥60	125 (40.3%)	70 (37.6%)	55 (44.4%)	66 (42.6%)	59 (38.1%)
Gender					
Male	223 (71.9%)	131 (70.4%)	92 (74.2%)	106 (68.4%)	117 (75.5%)
Female	87 (28.1%)	55 (29.6%)	32 (25.8%)	49 (31.6%)	38 (24.5%)
WHO/ISUP					
Grading					
I-II	244 (78.7%)	143 (76.9%)	101 (81.5%)	122 (78.7%)	122 (78.7%)
III-IV	66 (21.3%)	43 (23.1%)	23 (18.5%)	33 (21.3%)	33 (21.3%)
TNM stage					
I-II	270 (87.1%)	159 (85.5%)	111 (89.5%)	138 (89.0%)	132 (85.2%)
III	40 (12.9%)	27 (14.5%)	13 (10.5%)	17 (11.0%)	23 (14.8%)
SSIGN					
0-4	286 (92.3%)	171 (91.9%)	115 (92.7%)	144 (92.9%)	142 (91.6%)
≥5	24 (7.7%)	15 (8.1%)	9 (7.3%)	11 (7.1%)	13 (8.4%)

Table S2 The correlation between UBR5 expression and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the validation cohort (n=124) (3:2 ratio)

Characteristic	UBR5*		Sum (124)	P** value
	Low expression (n=47)	High expression (n=77)		
Age				0.491
<60	28	41	69	
≥60	19	36	55	
Gender				0.633
Male	36	56	92	
Female	11	21	32	
WHO/ISUP Grading				0.012
I-II	33	68	101	
III-IV	14	9	23	
TNM stage				0.002*
I-II	37	74	111	
III	10	3	13	
SSIGN				0.011*
0-4	40	75	115	
≥5	7	2	9	

*: UBR5^{low} expression: H-scores of UBR5 < 130 ; UBR5^{high} expression: H-scores of UBR5 ≥ 130.

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures

Table S3 The correlation between UBR5 expression and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the training cohort (n=155) (1:1 ratio)

Characteristic	UBR5*		Sum (155)	P** value
	Low expression (n=40)	High expression (n=115)		
Age				0.715
<60	22	67	89	
≥60	18	48	66	
Gender				0.593
Male	26	80	106	
Female	14	35	49	
WHO/ISUP Grading				0.044
I-II	27	95	122	
III-IV	13	20	33	
TNM stage				0.044*
I-II	32	106	138	
III	8	9	17	
SSIGN				0.035*
0-4	34	110	144	
≥5	6	5	11	

*: UBR5^{low} expression: H-scores of UBR5 < 100 ; UBR5^{high} expression: H-scores of UBR5 ≥ 100.

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures

Table S4 The correlation between UBR5 expression and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the validation cohort (n=155) (1:1 ratio)

Characteristic	UBR5*		Sum (155)	P** value
	Low expression (n=40)	High expression (n=115)		
Age				0.502
<60	23	73	96	
≥60	17	42	59	
Gender				0.441
Male	32	85	117	
Female	8	30	38	
WHO/ISUP Grading				0.044
I-II	27	95	122	
III-IV	13	20	33	
TNM stage				0.002
I-II	28	104	132	
III	12	11	23	
SSIGN				0.024*
0-4	33	109	142	
≥5	7	6	13	

*: UBR5^{low} expression: H-scores of UBR5 < 100; UBR5^{high} expression: H-scores of UBR5 ≥ 100.

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures

Table S5 The correlation between UBR5 expression and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the combined cohort (n=310)

Characteristic	UBR5*		Sum (310)	P** value
	Low expression (n=133)	High expression (n=177)		
Age				0.883
<60	80	105	185	
≥60	53	72	125	
Gender				0.735
Male	97	126	223	
Female	36	51	87	
WHO/ISUP Grading				<0.001
I-II	92	152	244	
III-IV	41	25	66	
TNM stage				<0.001
I-II	105	165	270	
III	28	12	40	
SSIGN				0.001
0-4	115	171	286	
≥5	18	6	24	

*: UBR5^{low} expression: H-scores of UBR5 < 130 ; UBR5^{high} expression: H-scores of UBR5 ≥ 130.

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures

Table S6 The correlation between expressions of UBR5, CD163 and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the validation cohort (n=124) (3:2 ratio)

Characteristic	UBR5/CD163 expression*				Sum (124)	P** value
	UBR5 ^{high} CD163 ^{low} (n=55)	UBR5 ^{high} CD163 ^{high} (n=22)	UBR5 ^{low} CD163 ^{low} (n=10)	UBR5 ^{low} CD163 ^{high} (n=37)		
Age						0.788
<60	29	12	7	21	69	
≥60	26	10	3	16	55	
Gender						0.320
Male	37	19	7	29	92	
Female	18	3	3	8	32	
WHO/ISU						0.001*
P Grading						
I-II	48	20	3	30	101	
III-IV	7	2	7	7	23	
TNM stage						0.020*
I-II	53	21	7	30	111	
III	2	1	3	7	13	
SSIGN						0.008*
0-4	55	20	8	32	115	
≥5	0	2	2	5	9	

*: UBR5^{low} expression: H-scores of UBR5 < 130; UBR5^{high} expression: H-scores of UBR5 ≥ 130; CD163^{low} expression: Density of CD163 < 15 cells/mm²; CD163^{high} expression: Density of CD163 ≥ 15 cells/mm².

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures and ANOVA for continuous measures

Table S7 The correlation between expressions of UBR5, CD163 and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the training cohort (n=155) (1:1 ratio)

Characteristic	UBR5/CD163 expression*				Sum (155)	P** value
	UBR5 ^{high} CD163 ^{low} (n=73)	UBR5 ^{high} CD163 ^{high} (n=42)	UBR5 ^{low} CD163 ^{low} (n=10)	UBR5 ^{low} CD163 ^{high} (n=30)		
Age						0.640
<60	44	23	7	15	89	
≥60	29	19	3	15	66	
Gender						0.389
Male	48	32	5	21	106	
Female	25	10	5	9	49	
WHO/ISU P Grading						<0.001
I-II	61	34	2	25	122	
III-IV	12	8	8	5	33	
TNM stage						0.035*
I-II	70	36	9	23	138	
III	3	6	1	7	17	
SSIGN						0.031*
0-4	72	38	9	25	144	
≥5	1	4	1	5	11	

*: UBR5^{low} expression: H-scores of UBR5<100; UBR5^{high} expression: H-scores of UBR5≥100; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm²;

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures and ANOVA for continuous measures

Table S8 The correlation between expressions of UBR5, CD163 and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the validation cohort (n=155) (1:1 ratio)

Characteristic	UBR5/CD163 expression*				Sum (155)	P** value
	UBR5 ^{high} CD163 ^{low} (n=70)	UBR5 ^{high} CD163 ^{high} (n=45)	UBR5 ^{low} CD163 ^{low} (n=17)	UBR5 ^{low} CD163 ^{high} (n=23)		
Age						0.449
<60	45	28	12	11	96	
≥60	25	17	5	12	59	
Gender						0.063
Male	46	39	13	19	117	
Female	24	6	4	4	38	
WHO/ISU						0.010*
P Grading						
I-II	60	35	15	12	122	
III-IV	10	10	2	11	33	
TNM stage						0.001*
I-II	67	37	10	18	132	
III	3	8	7	5	23	
SSIGN						0.017*
0-4	68	41	16	17	142	
≥5	2	4	1	6	13	

*: UBR5^{low} expression: H-scores of UBR5<100; UBR5^{high} expression: H-scores of UBR5≥100; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm².

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures and ANOVA for continuous measures

Table S9 The correlation between expressions of UBR5, CD163 and clinicopathologic characteristics of patients with clear cell renal cell carcinoma in the combined cohort (n=310)

Characteristic	UBR5/CD163 expression*				Sum (310)	P** value
	UBR5 ^{high} CD163 ^{low} (n=120)	UBR5 ^{high} CD163 ^{high} (n=57)	UBR5 ^{low} CD163 ^{low} (n=50)	UBR5 ^{low} CD163 ^{high} (n=83)		
Age						0.307
<60	73	32	35	45	185	
≥60	47	25	15	38	125	
Gender						0.043
Male	78	48	34	63	223	
Female	42	9	16	20	87	
WHO/ISU P Grading						0.002
I-II	106	46	32	60	244	
III-IV	14	11	18	23	66	
TNM stage						<0.001
I-II	117	48	39	66	270	
III	3	9	11	17	40	
SSIGN						<0.001
0-4	118	53	47	68	286	
≥5	2	4	3	15	24	

*: UBR5^{low} expression: H-scores of UBR5<130; UBR5^{high} expression: H-scores of UBR5≥130; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm².

** : Statistical significance was calculated by chi-square test or fisher's exact test for categorical/binary measures and ANOVA for continuous measur

Table S10 Univariate and multivariate cox regression analysis of UBR5, CD163 and clinicopathologic characteristics with overall survival and progression-free survival in the training cohort (n=186) (3:2 ratio)

Characteristics	Overall survival				Progression free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.844 (0.748-4.541)	0.184	1.316 (0.487-3.552)	0.588	1.38 (0.715-2.663)	0.337	0.895 (0.431-1.859)	0.766
Gender (Male vs Female)	1.165 (0.443-3.068)	0.757	1.484 (0.52-4.236)	0.461	0.809 (0.38-1.72)	0.581	0.692 (0.308-1.556)	0.374
WHO/ISUP Grading (1-2 vs 3-4)	2.783 (1.115-6.947)	0.028	2.473 (0.869-7.042)	0.09	2.348 (1.2-4.597)	0.013	1.852 (0.887-3.866)	0.101
TNM stage (1-2 vs 3)	6.923 (2.773-17.287)	<0.001	2.808 (1.014-7.779)	0.047	5.556 (2.855-10.811)	<0.001	2.348 (1.162-4.744)	0.017
SSIGN (1-4 vs ≥5)	9.308 (3.726-23.251)	<0.001	3.277 (1.07-10.035)	0.038	16.027 (7.444-34.507)	<0.001	9.749 (3.673-25.871)	<0.001
UBR5 expression (Low vs High)*	0.108 (0.031-0.374)	<0.001	0.192 (0.052-0.703)	0.013	0.14 (0.061-0.323)	<0.001	0.198 (0.083-0.473)	<0.001
CD163 expression (Low vs High)*	8.689 (2.516-30.013)	0.001	4.43 (1.171-16.763)	0.028	4.956 (2.324-10.572)	<0.001	3.031 (1.348-6.816)	0.007

*: UBR5^{low} expression: H-scores of UBR5<130; UBR5^{high} expression: H-scores of UBR5≥130; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm²;

Table S11 Univariate and multivariate cox regression analysis of UBR5, CD163 and clinicopathologic characteristics with overall survival and progression-free survival in the validation cohort (n= 124) (3:2 ratio)

Characteristics	Overall survival				Progression free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	0.844 (0.306-2.328)	0.743	0.984 (0.309-3.133)	0.978	0.959 (0.473-1.944)	0.908	1.169 (0.555-2.462)	0.682
Gender (Male vs Female)	0.646 (0.184-2.269)	0.496	1.077 (0.249-4.658)	0.92	0.657 (0.27-1.595)	0.353	0.911 (0.346-2.397)	0.85
WHO/ISUP Grading (1-2 vs 3-4)	2.882 (1.045-7.945)	0.041	2.01 (0.548-7.366)	0.292	2.754 (1.325-5.726)	0.007	1.515 (0.618-3.715)	0.364
TNM stage (1-2 vs 3)	9.018 (3.324-24.468)	<0.001	3.448 (1.061-11.203)	0.04	7.442 (3.446-16.072)	<0.001	3.278 (1.324-8.116)	0.01
SSIGN (1-4 vs ≥5)	16.012 (5.573-46.005)	<0.001	9.122 (2.314-35.962)	0.002	14.949 (5.764-38.769)	<0.001	7.44 (2.489-22.241)	<0.001
UBR5 expression (Low vs High)*	0.116 (0.033-0.409)	0.001	0.215 (0.053-0.878)	0.032	0.149 (0.067-0.333)	<0.001	0.331 (0.134-0.813)	0.016
CD163 expression (Low vs High)*	5.746 (1.633-20.215)	0.006	5.232 (1.26-21.724)	0.023	2.999 (1.418-6.34)	0.004	2.531 (1.049-6.107)	0.039

*: UBR5^{low} expression: H-scores of UBR5<130; UBR5^{high} expression: H-scores of UBR5≥130; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm².

Table S12 Univariate and multivariate cox regression analysis of UBR5, CD163 and clinicopathologic characteristics with overall survival and progression-free survival in the training cohort (n=155) (1:1 ratio)

Characteristics	Overall survival				Progression free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.355 (0.55-3.338)	0.509	1.081 (0.392-2.984)	0.881	1.099 (0.562-2.147)	0.783	0.924 (0.451-1.895)	0.829
Gender (Male vs Female)	1.452 (0.57-3.699)	0.434	0.767 (0.234-2.516)	0.662	1.151 (0.563-2.353)	0.701	0.754 (0.331-1.719)	0.502
WHO/ISUP Grading (1-2 vs 3-4)	3.172 (1.266-7.946)	0.014	1.74 (0.605-5.006)	0.304	2.248 (1.115-4.533)	0.024	1.166 (0.528-2.575)	0.704
TNM stage (1-2 vs 3)	11.027 (4.426-27.469)	<0.001	6.225 (1.754-22.097)	0.005	8.838 (4.406-17.73)	<0.001	6.212 (2.531-15.245)	<0.001
SSIGN (1-4 vs ≥5)	13.561 (5.225-35.197)	<0.001	3.294 (0.92-11.785)	0.027	16.547 (6.611-41.419)	<0.001	3.864 (1.231-12.129)	0.021
UBR5 expression (Low vs High)*	0.14 (0.055-0.36)	<0.001	0.221 (0.071-0.686)	0.009	0.206 (0.105-0.404)	<0.001	0.303 (0.138-0.668)	0.003
CD163 expression (Low vs High)*	7.245 (2.109-24.897)	0.002	3.322 (0.88-12.542)	0.037	3.595 (1.725-7.494)	0.001	2.104 (0.959-4.613)	0.043

*: UBR5^{low} expression: H-scores of UBR5<100; UBR5^{high} expression: H-scores of UBR5≥100; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm².

Table S13 Univariate and multivariate cox regression analysis of UBR5, CD163 and clinicopathologic characteristics with overall survival and progression-free survival in the validation cohort (n=155) (1:1 ratio)

Characteristics	Overall survival				Progression free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.255 (0.467-3.372)	0.653	1.091 (0.383-3.109)	0.87	1.185 (0.598-2.346)	0.627	0.867 (0.414-1.814)	0.705
Gender (Male vs Female)	0.364 (0.082-1.609)	0.182	0.969 (0.19-4.932)	0.97	0.423 (0.163-1.096)	0.077	0.598 (0.216-1.658)	0.323
WHO/ISUP Grading (1-2 vs 3-4)	2.363 (0.857-6.513)	0.046	2.393 (0.763-7.505)	0.135	2.519 (1.26-5.036)	0.009	2.025 (0.973-4.216)	0.059
TNM stage (1-2 vs 3)	5.596 (2.055-15.236)	0.001	2.905 (1.038-8.13)	0.042	4.128 (2.029-8.401)	<0.001	1.976 (0.92-4.243)	0.031
SSIGN (1-4 vs ≥5)	9.983 (3.701-26.927)	<0.001	5.346 (1.739-16.434)	0.003	16.046 (7.163-35.945)	<0.001	13.498 (5.21-34.971)	<0.001
UBR5 expression (Low vs High)*	0.135 (0.048-0.379)	<0.001	0.22 (0.075-0.643)	0.006	0.251 (0.127-0.497)	<0.001	0.405 (0.191-0.856)	0.018
CD163 expression (Low vs High)*	7.466 (2.09-26.671)	0.002	4.416 (1.191-16.378)	0.026	4.875 (2.252-10.553)	<0.001	4.287 (1.902-9.665)	<0.001

*: UBR5^{low} expression: H-scores of UBR5<100; UBR5^{high} expression: H-scores of UBR5≥100; CD163^{low} expression: Density of CD163<15 cells/mm²; CD163^{high} expression: Density of CD163≥15 cells/mm².

Table S14 Univariate cox regression analysis of UBR5, EZH2, CXCR4 and clinicopathologic characteristics with overall survival and progression-free survival in the combined cohort (n=310)

Characteristics	Univariate			
	Overall survival		Progression free survival	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.326 (0.682-2.577)	0.405	1.143 (0.708-1.842)	0.585
Gender (Male vs Female)	0.902 (0.422-1.923)	0.789	0.772 (0.375-1.350)	0.363
WHO/ISUP Grading (1-2 vs 3-4)	2.786 (1.412-5.495)	0.003	2.381 (1.456-3.906)	0.001
TNM stage (1-2 vs 3)	7.634 (3.891-14.925)	0.003	5.747 (3.497-9.434)	<0.001
SSIGN (1-4 vs ≥5)	11.628 (5.882-22.727)	<0.001	15.152 (8.403-27.027)	<0.001
UBR5 expression (Low vs High)*	0.114 (0.047-0.277)	<0.001	0.146 (0.082-0.260)	<0.001
EZH2 expression (Low vs High)**	3.175 (1.318-7.634)	0.010	2.398 (1.353-4.255)	0.003
CXCR4 expression (Low vs High)***	7.299 (2.558-20.833)	<0.001	6.410 (3.175-12.987)	<0.001

*: UBR5^{low} expression: H-scores of UBR5<130; UBR5^{high} expression: H-scores of UBR5≥130.

** : EZH2^{low} expression: H-scores of EZH2<160; EZH2^{high} expression: H-scores of EZH2≥160.

***: CXCR4^{low} expression: H-scores of CXCR4<160; CXCR4^{high} expression: H-scores of CXCR4≥160.

Table S15 Multivariate cox regression analysis of UBR5 and clinicopathologic characteristics with overall survival and progression-free survival in the combined cohort (n=310)

Characteristics	Overall survival		Progression free survival	
	Multivariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.076 (0.542-2.138)	0.834	1.028 (0.629-1.678)	0.913
Gender (Male vs Female)	1.118 (0.513-2.435)	0.780	0.823 (0.469-1.445)	0.497
WHO/ISUP Grading (1-2 vs 3-4)	1.960 (0.960-4.002)	0.065	1.397 (0.826-2.358)	0.212
TNM stage (1-2 vs 3)	2.955 (1.416-6.170)	0.004	2.457 (1.404-4.292)	0.002
SSIGN (1-4 vs ≥5)	6.550 (3.113-13.785)	<0.001	8.475 (4.386-16.393)	<0.001
UBR5 expression (Low vs High)*	0.189 (0.076-0.471)	<0.001	0.215 (0.117-0.394)	<0.001

*: UBR5^{low} expression: H-scores of UBR5<130; UBR5^{high} expression: H-scores of UBR5≥130.

Table S16 C-index analysis of the prognostic accuracy of UBR5, CD163 and other variables for overall survival and progression-free survival in the training and validation cohorts (1:1 ratio)

C-index (95% CI)	Overall survival		Progression-free survival	
	Training cohort (n=155)	Validation cohort (n=155)	Training cohort (n=155)	Validation cohort (n=155)
TNM stage	0.72 (0.686~0.754)	0.623 (0.574~0.671)	0.672 (0.648~0.695)	0.608 (0.576~0.641)
SSIGN	0.655 (0.628~0.681)	0.711 (0.675~0.746)	0.631 (0.614~0.647)	0.691 (0.67~0.711)
UBR5	0.742 (0.692~0.792)	0.751 (0.693~0.81)	0.688 (0.652~0.725)	0.664 (0.625~0.704)
CD163	0.696 (0.636~0.755)	0.689 (0.62~0.758)	0.658 (0.614~0.702)	0.668 (0.622~0.715)
UBR5+CD163	0.788 (0.724~0.852)	0.794 (0.719~0.869)	0.755 (0.708~0.803)	0.732 (0.681~0.783)
UBR5+CD163+TNM stage	0.842 (0.777~0.907)	0.812 (0.736~0.889)	0.806 (0.758~0.854)	0.757 (0.706~0.809)
UBR5+CD163+SSIGN	0.847 (0.783~0.911)	0.863 (0.787~0.939)	0.799 (0.751~0.846)	0.805 (0.754~0.856)

Table S17 C-index analysis of the prognostic accuracy of UBR5, CD163, EZH2, CXCR4 and other variables for overall survival and progression-free survival in the combined cohort (n=310)

	C-index (95% CI)	
	Overall survival	Progression-free survival
TNM stage	0.679 (0.65~0.707)	0.642 (0.623~0.662)
SSIGN	0.677 (0.656~0.699)	0.657 (0.644~0.67)
CD163	0.691 (0.646~0.736)	0.663 (0.631~0.695)
UBR5	0.677 (0.656~0.699)	0.676 (0.649~0.702)
EZH2	0.519 (0.475~0.563)	0.502 (0.47~0.533)
CXCR4	0.678 (0.633~0.723)	0.665 (0.633~0.697)
UBR5+CD163	0.81 (0.762~0.859)	0.739 (0.705~0.774)
UBR5+CD163+TNM stage	0.821 (0.772~0.87)	0.774 (0.739~0.809)
UBR5+CD163+SSIGN	0.854 (0.805~0.903)	0.791 (0.756~0.826)

Table S18 Multivariate cox regression analysis of EZH2 and clinicopathologic characteristics with overall survival and progression-free survival in the combined cohort (n=310)

Characteristics	Overall survival		Progression free survival	
	Multivariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.247 (0.616-2.525)	0.540	1.147 (0.704-1.869)	0.582
Gender (Male vs Female)	0.988 (0.456-2.141)	0.976	0.708 (0.402-1.247)	0.232
WHO/ISUP Grading (1-2 vs 3-4)	1.961 (0.945-4.082)	0.071	1.745 (1.029-2.959)	0.039
TNM stage (1-2 vs 3)	4.219 (2.053-8.696)	<0.001	3.205 (1.828-5.618)	<0.001
SSIGN (1-4 vs ≥5)	6.897 (3.333-14.286)	<0.001	9.524 (4.975-18.182)	<0.001
EZH2 expression (Low vs High)*	2.793 (1.131-6.897)	0.026	2.004 (1.117-3.597)	0.020

*: EZH2^{low} expression: H-scores of EZH2<160; EZH2^{high} expression: H-scores of EZH2≥160.

Table S19 Multivariate cox regression analysis of CXCR4 and clinicopathologic characteristics with overall survival and progression-free survival in the combined cohort (n=310)

Characteristics	Overall survival		Progression free survival	
	Multivariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (<60y vs ≥60y)	1.036 (0.522-2.058)	0.918	1.059 (0.652-1.718)	0.817
Gender (Male vs Female)	1.473 (0.664-3.268)	0.341	1.071 (0.603-1.901)	0.816
WHO/ISUP Grading (1-2 vs 3-4)	2.028 (1.015-4.049)	0.045	1.667 (0.999-2.778)	0.050
TNM stage (1-2 vs 3)	3.953 (1.972-7.937)	<0.001	2.725 (1.587-2.778)	<0.001
SSIGN (1-4 vs ≥5)	7.519 (3.610-15.625)	<0.001	11.494 (5.952-22.222)	<0.001
CXCR4 expression (Low vs High)*	5.435 (1.880-15.625)	0.002	5.319 (2.584-10.989)	<0.001

***: CXCR4^{low} expression: H-scores of CXCR4<160; CXCR4^{high} expression: H-scores of CXCR4≥160.**