

Metavariables Resuming Host Immune Features and Nodal Involvement Are Associated with Oncological Outcomes in Oral Cavity Squamous Cell Carcinoma

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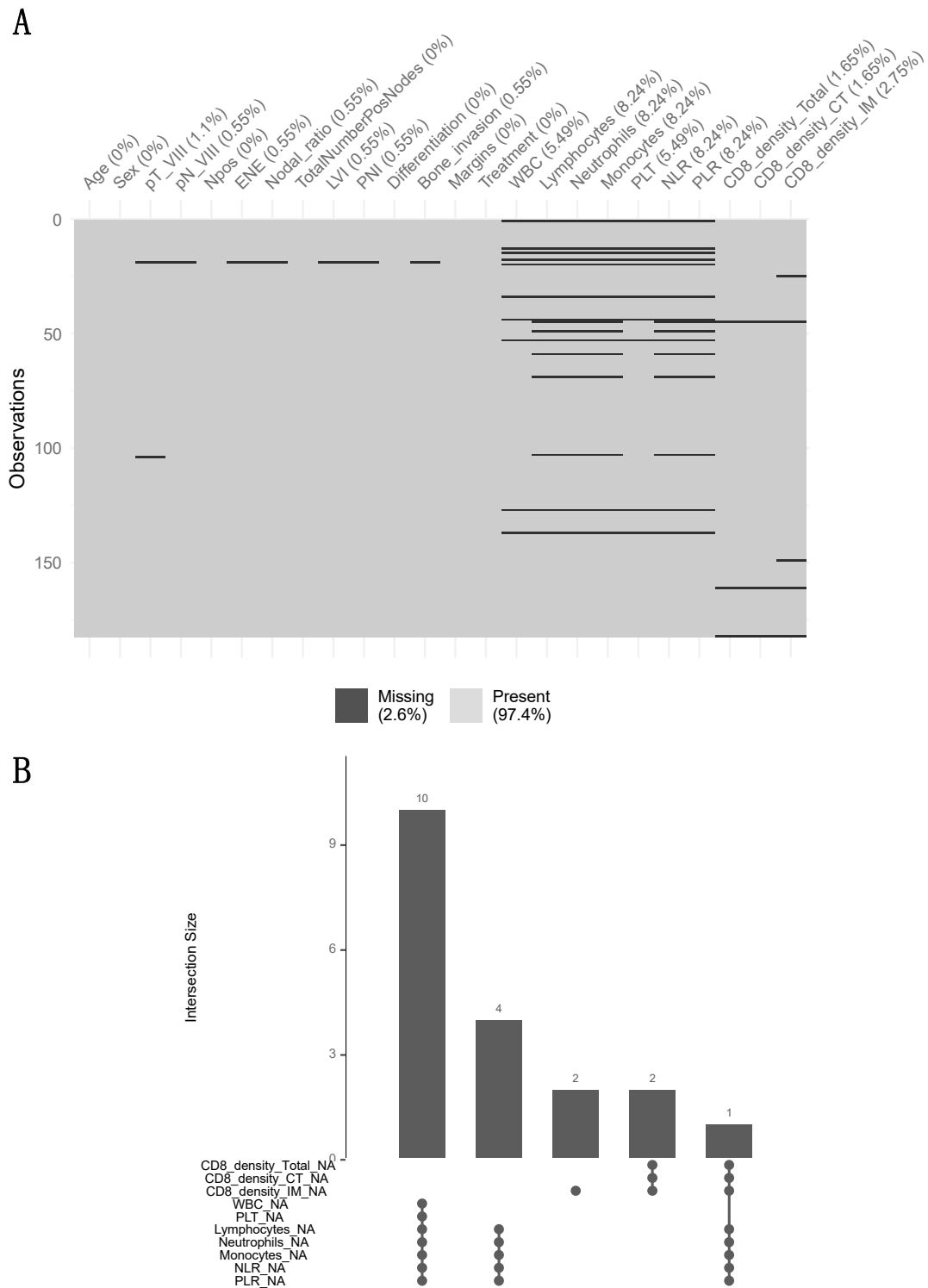
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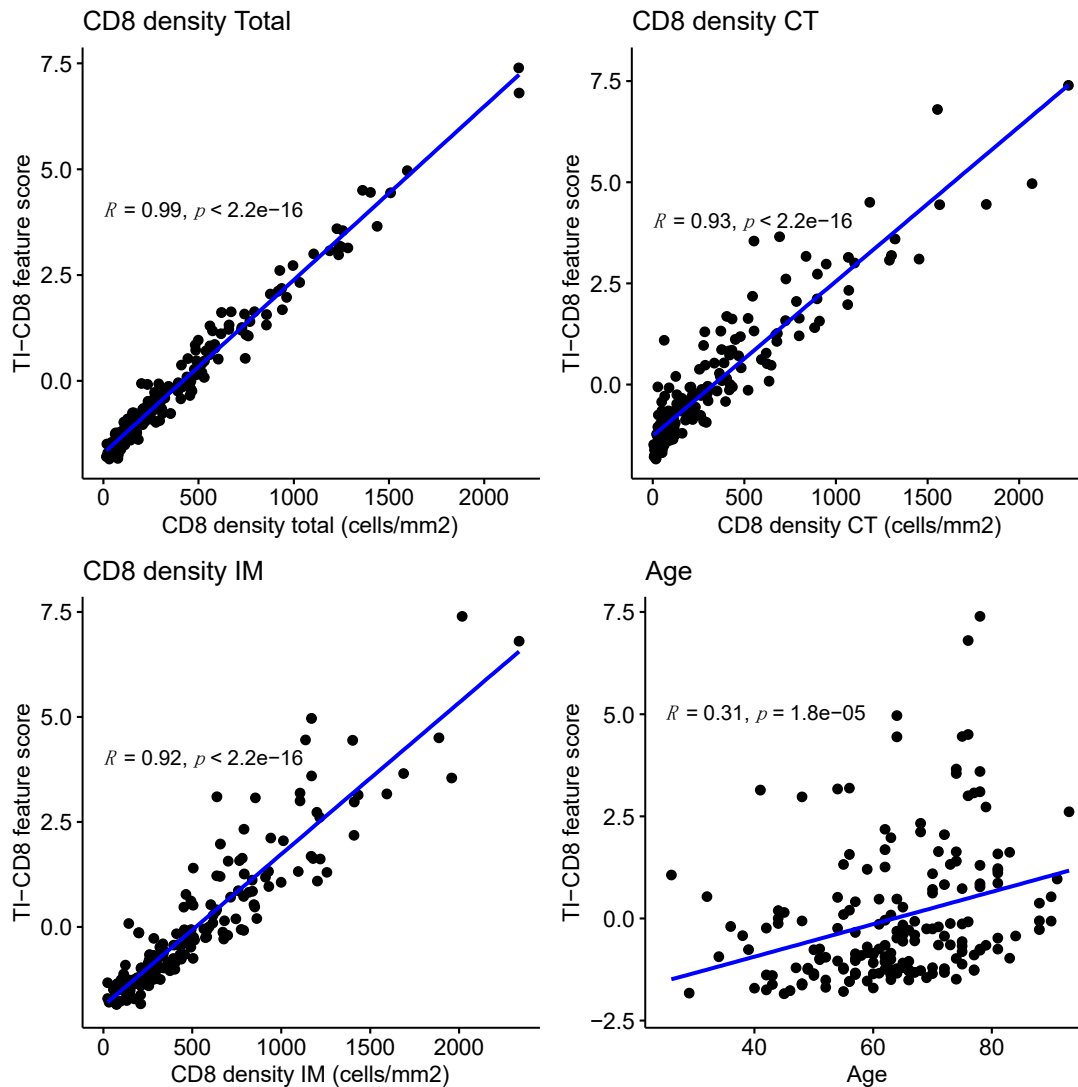
Supplementary Material

Supplementary Figures

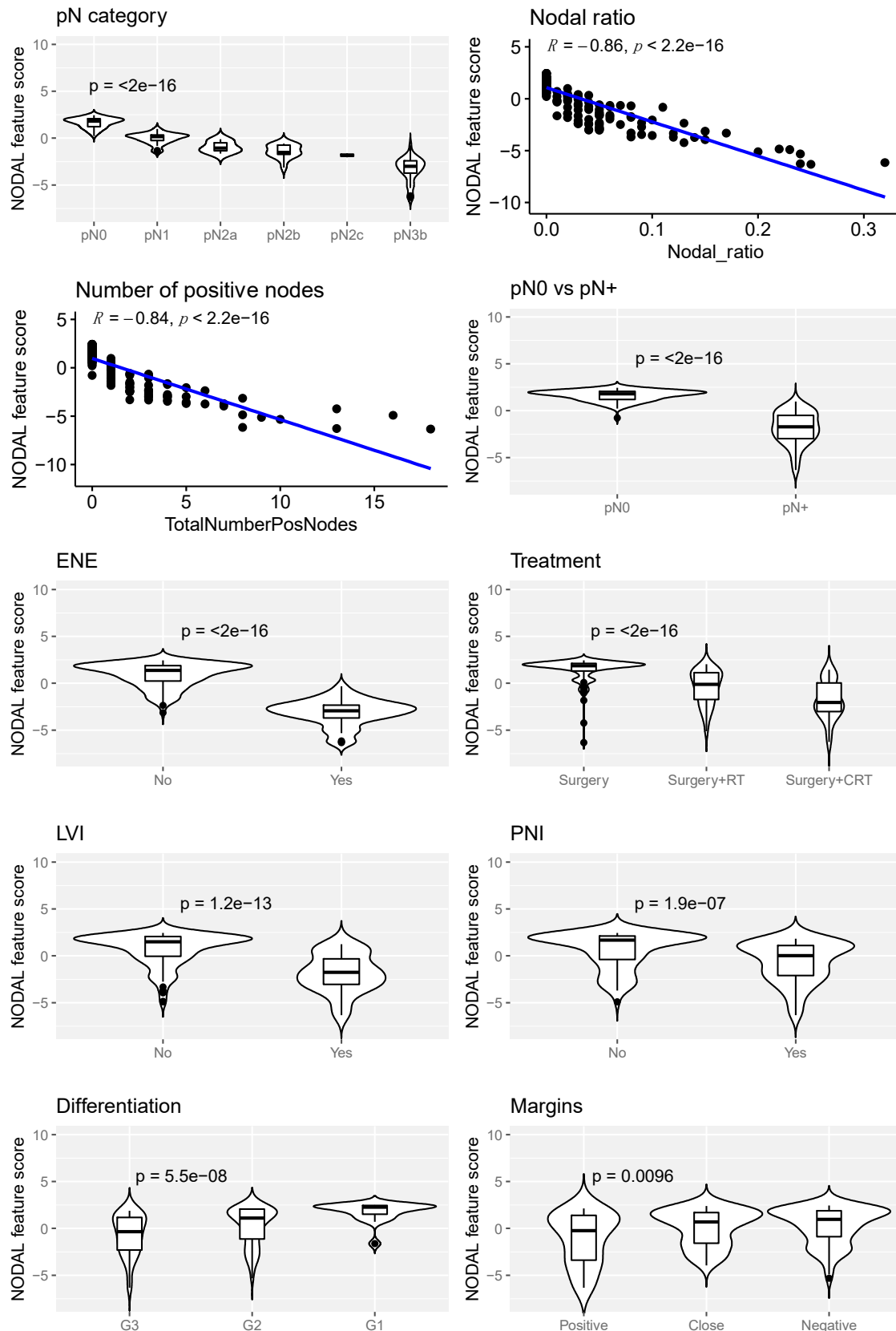
Supplementary Figure S1: Heatmap showing the missingness data in the whole cohort (**A**); intersection plot of missing data (**B**).



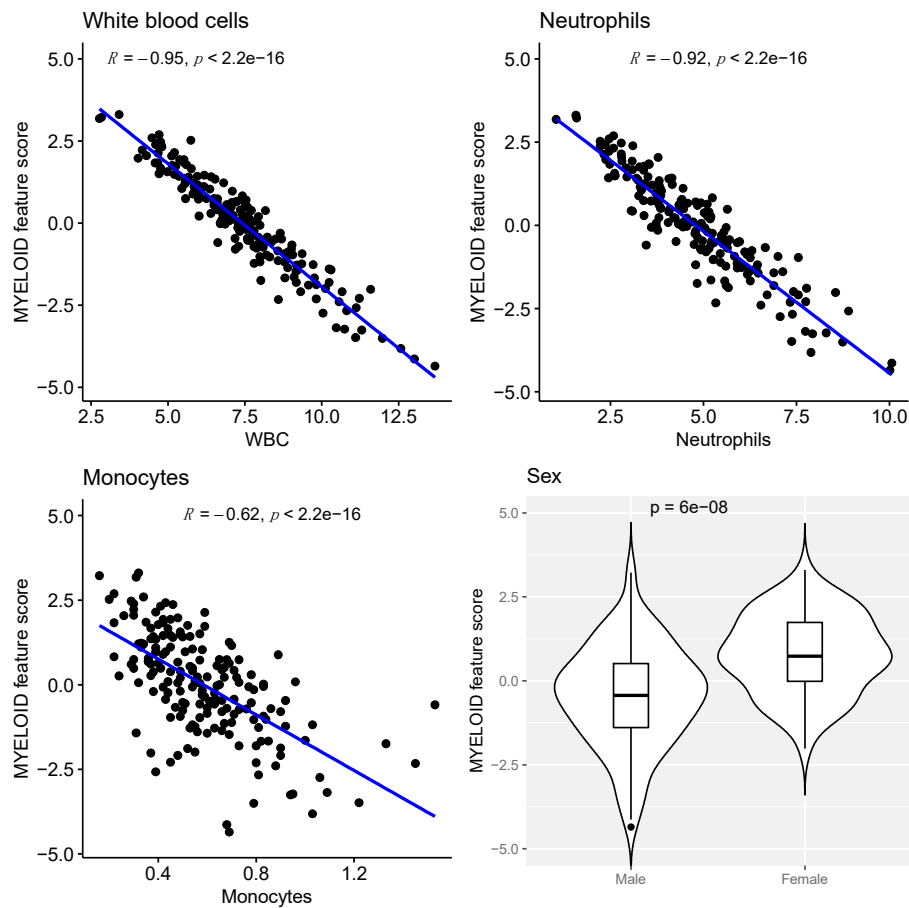
Supplementary Figure S2: Scatter plots showing the relationship between TI-CD8^{MV} and the variables from which it is defined. P values are estimated by Spearman correlation test.



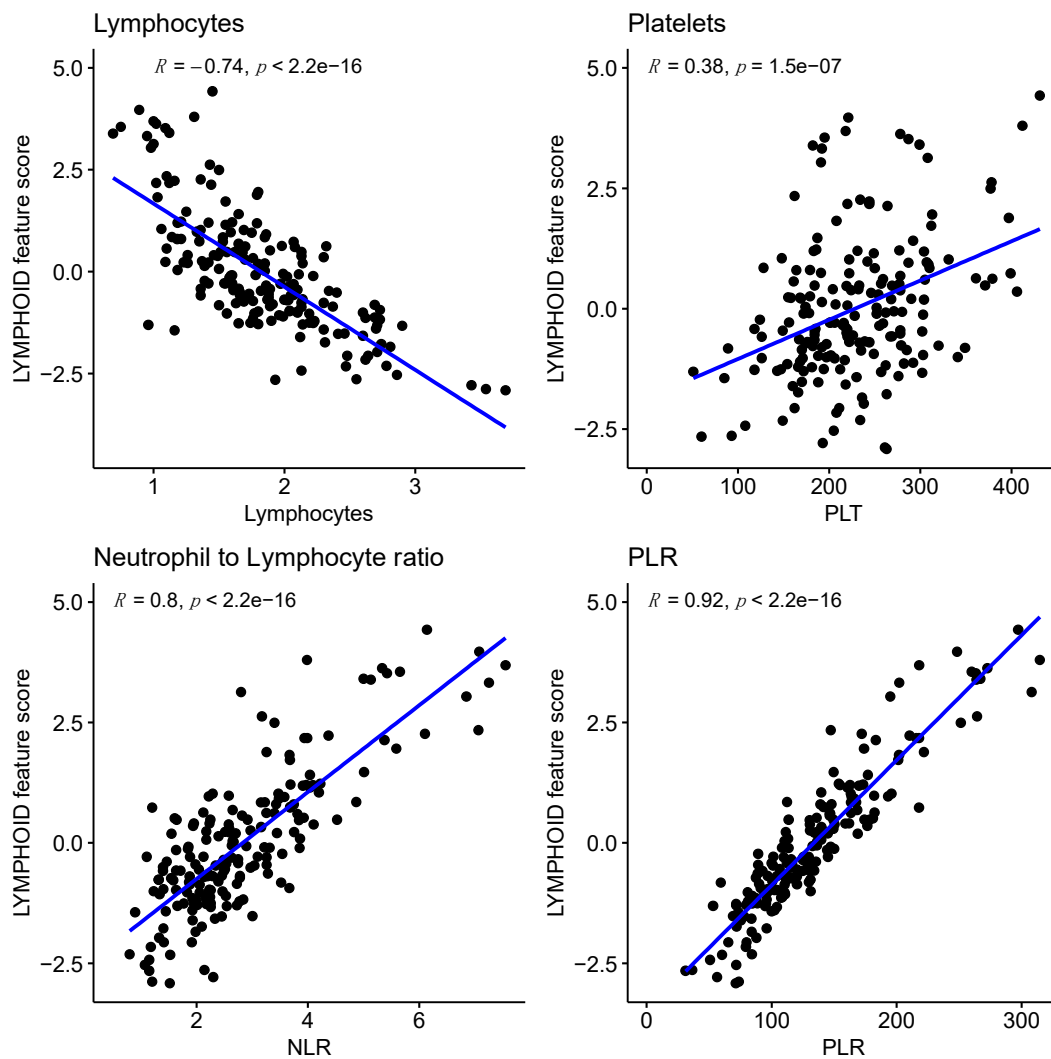
Supplementary Figure S3: Box plots and scatter plots showing the relationship between the NODAL^{MV} and the variables from which it is defined. P values are estimated by Kruskal-Wallis test, Wilcoxon sign-rank test or Spearman correlation test.



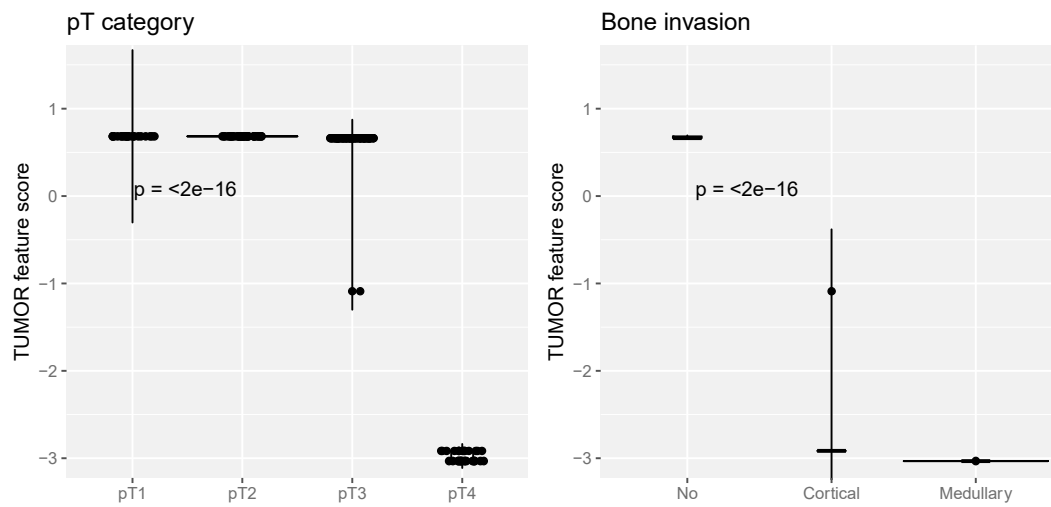
Supplementary Figure S4: Scatter plots and box plots showing the relationship between the MYELOID^{MV} and the variables from which it is defined. P values are estimated by the Spearman correlation test or Wilcoxon sign-rank test.



Supplementary Figure S5: Scatter plots showing the relationship between the LYMPHOID^{MV} and the variables from which it is defined. P values are estimated by Spearman correlation test.



Supplementary Figure S6: Box plots showing the relationship between the TUMOR^{MV} and the variables from which it is defined. P values are estimated by Kruskal-Wallis test.



Supplementary Tables

Supplementary Table S1: R values of the Spearman's correlation analysis between continuous variables analyzed. Legend: ****, $p < 0.0001$; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

	Age	Nodal Ratio	N° Positive Nodes	WBC	Lymphocytes	Neutrophils	Monocytes	PLT	NLR	PLR	TOTCD8 density	CTCD8 density
Age												
Nodal Ratio	-0.03											
N° Positive Nodes	-0.04	0.98****										
WBC	-0.19*	-0.01	0.01									
Lymphocytes	-0.16*	-0.04	-0.01	0.41****								
Neutrophils	-0.17*	0.00	0.02	0.94****	0.15*							
Monocytes	0.02	0.01	0.05	0.51****	0.20**	0.37****						
PLT	-0.09	-0.06	-0.04	0.30****	0.26***	0.26***	0.16*					
NLR	-0.03	0.03	0.03	0.48****	-0.52****	0.71****	0.16*	0.03				
PLR	0.05	-0.04	-0.05	-0.07	-0.57****	0.12	-0.03	0.57****	0.49****			
TOTCD8 density	0.22**	0.11	0.11	-0.02	0.06	-0.04	-0.10	0.02	-0.07	-0.04		
CTCD8 density	0.21**	0.20**	0.20**	-0.02	0.05	-0.04	-0.11	0.03	-0.04	-0.03	0.92****	
IMCD8 density	0.24**	0.01	0.01	-0.06	-0.01	-0.08	-0.10	-0.04	-0.06	-0.02	0.92****	0.78****

Supplementary Table S2: Association analysis between peripheral or intratumoral biomarkers measures and Sex. P values estimated by Wilcoxon test.

	Male (N=115)	Female (N=67)	P-value
WBC (10⁹/L)			
Mean (SD)	7.75 (2.05)	6.84 (1.60)	0.002
Median [Min, Max]	7.65 [2.77, 13.7]	6.91 [3.41, 11.6]	
Lymphocytes (10⁹/L)			
Mean (SD)	1.82 (0.587)	1.81 (0.438)	0.881
Median [Min, Max]	1.80 [0.690, 3.69]	1.76 [1.00, 2.78]	
Neutrophils (10⁹/L)			
Mean (SD)	5.07 (1.70)	4.31 (1.42)	0.002
Median [Min, Max]	4.97 [1.04, 10.1]	4.15 [1.57, 8.55]	
Monocytes (10⁹/L)			
Mean (SD)	0.613 (0.234)	0.535 (0.219)	0.018
Median [Min, Max]	0.580 [0.160, 1.45]	0.490 [0.200, 1.53]	
PLT (10⁹/L)			
Mean (SD)	219 (68.0)	243 (67.4)	0.015
Median [Min, Max]	215 [51.0, 431]	242 [60.0, 412]	
NLR (10⁹/L)			
Mean (SD)	3.02 (1.40)	2.50 (1.07)	0.015
Median [Min, Max]	2.65 [0.897, 7.25]	2.26 [0.799, 7.55]	
PLR (10⁹/L)			
Mean (SD)	130 (56.1)	140 (46.0)	0.057
Median [Min, Max]	113 [36.5, 308]	132 [31.1, 315]	
^{TOT}CD8 density (/mm²)			
Mean (SD)	385 (352)	473 (477)	0.237
Median [Min, Max]	244 [16.4, 1440]	290 [42.2, 2180]	
^{CT}CD8 density (/mm²)			
Mean (SD)	297 (338)	395 (500)	0.316
Median [Min, Max]	132 [5.13, 1820]	213 [9.96, 2270]	
^{IM}CD8 density (/mm²)			
Mean (SD)	500 (417)	554 (448)	0.288
Median [Min, Max]	361 [23.6, 1960]	437 [79.6, 2340]	

Supplementary Table S3: Association analysis between peripheral or intratumoral biomarkers measures and pT category. P values estimated by Kruskal-Wallis test.

	pT1 (N=23)	pT2 (N=41)	pT3 (N=85)	pT4 (N=33)	P-value
WBC (10⁹/L)					
Mean (SD)	7.83 (2.52)	7.11 (1.54)	7.46 (1.98)	7.38 (1.85)	0.701
Median [Min, Max]	7.59 [3.41, 12.6]	6.99 [4.30, 11.1]	7.47 [2.77, 13.7]	7.17 [4.67, 13.0]	
Lymphocytes (10⁹/L)					
Mean (SD)	2.01 (0.681)	1.73 (0.480)	1.83 (0.562)	1.76 (0.382)	0.245
Median [Min, Max]	2.02 [0.690, 3.43]	1.65 [0.980, 2.70]	1.79 [0.750, 3.69]	1.69 [1.03, 2.71]	
Neutrophils (10⁹/L)					
Mean (SD)	5.06 (1.98)	4.55 (1.29)	4.82 (1.69)	4.83 (1.70)	0.745
Median [Min, Max]	5.11 [1.57, 8.74]	4.75 [2.22, 7.77]	4.72 [1.04, 10.0]	4.46 [2.48, 10.1]	
Monocytes (10⁹/L)					
Mean (SD)	0.579 (0.200)	0.603 (0.272)	0.584 (0.209)	0.568 (0.257)	0.88
Median [Min, Max]	0.510 [0.220, 1.03]	0.520 [0.290, 1.45]	0.590 [0.160, 1.33]	0.540 [0.220, 1.53]	
PLT (10⁹/L)					
Mean (SD)	230 (56.7)	224 (68.7)	220 (62.9)	253 (84.9)	0.243
Median [Min, Max]	217 [108, 349]	208 [60.0, 399]	220 [51.0, 431]	233 [89.0, 412]	
NLR (10⁹/L)					
Mean (SD)	2.77 (1.51)	2.88 (1.38)	2.83 (1.31)	2.81 (1.10)	0.927
Median [Min, Max]	2.34 [1.11, 7.08]	2.51 [1.15, 7.06]	2.59 [0.799, 7.55]	2.65 [1.23, 5.59]	
PLR (10⁹/L)					
Mean (SD)	130 (61.2)	139 (54.5)	128 (49.2)	145 (52.5)	0.181
Median [Min, Max]	116 [50.7, 264]	130 [31.1, 308]	120 [36.5, 297]	138 [59.3, 315]	
^{TOT}CD8 density (/mm²)					
Mean (SD)	341 (353)	496 (449)	411 (383)	392 (427)	0.315
Median [Min, Max]	207 [61.8, 1250]	339 [22.2, 2180]	281 [16.4, 1600]	290 [31.0, 2180]	
^{CT}CD8 density (/mm²)					
Mean (SD)	199 (275)	367 (410)	347 (419)	349 (443)	0.104
Median [Min, Max]	72.2 [9.09, 947]	215 [21.9, 1570]	173 [5.13, 2070]	208 [17.5, 2270]	
^{IM}CD8 density (/mm²)					
Mean (SD)	442 (419)	637 (470)	494 (386)	496 (477)	0.117
Median [Min, Max]	288 [96.9, 1590]	489 [23.6, 2340]	396 [23.6, 1960]	393 [56.3, 2020]	

Supplementary Table S4: Association analysis between peripheral or intratumoral biomarkers measures and pN category. P values estimated by Kruskal-Wallis test.

	pN0 (N=96)	pN1 (N=24)	pN2a (N=6)	pN2b (N=16)	pN2c (N=2)	pN3b (N=38)	P- value
WBC (10⁹/L)							
Mean (SD)	7.56 (2.02)	6.88 (1.77)	6.30 (1.82)	6.70 (1.60)	9.70 (2.27)	7.73 (1.83)	0.099
Median [Min, Max]	7.39 [3.41, 13.0]	6.90 [2.77, 10.7]	6.78 [2.84, 7.88]	7.30 [4.16, 9.82]	9.70 [8.09, 11.3]	7.80 [4.03, 13.7]	
Lymphocytes (10⁹/L)							
Mean (SD)	1.84 (0.556)	1.85 (0.402)	1.54 (0.667)	1.60 (0.464)	2.06 (0.0283)	1.87 (0.566)	0.299
Median [Min, Max]	1.79 [0.750, 3.54]	1.88 [1.12, 2.70]	1.50 [0.890, 2.74]	1.61 [0.690, 2.37]	2.06 [2.04, 2.08]	1.79 [1.02, 3.69]	
Neutrophils (10⁹/L)							
Mean (SD)	4.91 (1.74)	4.23 (1.40)	4.07 (1.54)	4.37 (1.28)	6.44 (2.11)	5.05 (1.57)	0.173
Median [Min, Max]	4.81 [1.57, 10.1]	4.29 [1.04, 7.55]	4.20 [1.59, 6.30]	4.59 [2.22, 7.33]	6.44 [4.94, 7.93]	5.22 [2.32, 10.0]	
Monocytes (10⁹/L)							
Mean (SD)	0.590 (0.263)	0.606 (0.204)	0.532 (0.193)	0.483 (0.193)	0.835 (0.148)	0.595 (0.165)	0.14
Median [Min, Max]	0.535 [0.200, 1.53]	0.610 [0.220, 1.03]	0.605 [0.160, 0.670]	0.450 [0.220, 0.920]	0.835 [0.730, 0.940]	0.580 [0.300, 1.06]	
PLT (10⁹/L)							
Mean (SD)	231 (66.2)	227 (72.7)	211 (114)	232 (92.2)	304 (1.41)	218 (52.5)	0.53
Median [Min, Max]	222 [89.0, 431]	219 [85.0, 379]	227 [51.0, 378]	198 [60.0, 412]	304 [303, 305]	220 [118, 312]	
NLR (10⁹/L)							
Mean (SD)	2.90 (1.41)	2.28 (0.715)	3.07 (2.08)	2.94 (1.11)	2.61 (1.70)	2.94 (1.23)	0.391
Median [Min, Max]	2.53 [0.799, 7.55]	2.19 [0.897, 3.94]	2.55 [1.41, 7.08]	2.73 [1.15, 5.13]	2.61 [1.41, 3.81]	2.67 [1.07, 7.06]	
PLR (10⁹/L)							
Mean (SD)	134 (48.6)	125 (37.6)	147 (90.7)	159 (79.0)	122 (35.4)	126 (50.2)	0.621
Median [Min, Max]	130 [50.7, 297]	126 [36.5, 218]	123 [53.1, 264]	148 [31.1, 315]	122 [96.6, 147]	112 [65.3, 273]	
^{TOT}CD8 density (/mm²)							
Mean (SD)	393 (400)	481 (506)	375 (374)	507 (424)	383 (102)	412 (353)	0.881
Median [Min, Max]	253 [16.4, 2180]	289 [71.7, 2180]	262 [70.1, 1100]	374 [49.7, 1360]	383 [310, 455]	331 [22.2, 1440]	
^{CT}CD8 density (/mm²)							
Mean (SD)	291 (394)	406 (539)	314 (402)	428 (402)	211 (72.9)	363 (358)	0.335
Median [Min, Max]	120 [5.13, 2070]	149 [27.7, 2270]	162 [40.0, 1100]	329 [20.7, 1300]	211 [159, 262]	289 [18.3, 1820]	
^{IM}CD8 density (/mm²)							
Mean (SD)	525 (433)	511 (460)	467 (342)	645 (506)	434 (52.2)	473 (396)	0.904
Median [Min, Max]	350 [31.9, 2340]	350 [99.0, 2020]	407 [122, 1110]	482 [56.3, 1890]	434 [397, 471]	346 [23.6, 1690]	

Supplementary Table S5: Association analysis between peripheral or intratumoral biomarkers measures and Extranodal extension (ENE). P values estimated by Wilcoxon test.

	ENE No (N=140)	ENE Yes (N=42)	P-value
WBC (10⁹/L)			
Mean (SD)	7.35 (1.97)	7.62 (1.86)	0.221
Median [Min, Max]	7.27 [2.77, 13.0]	7.69 [2.84, 13.7]	
Lymphocytes (10⁹/L)			
Mean (SD)	1.81 (0.519)	1.84 (0.592)	0.879
Median [Min, Max]	1.79 [0.690, 3.54]	1.75 [0.890, 3.69]	
Neutrophils (10⁹/L)			
Mean (SD)	4.73 (1.67)	4.99 (1.57)	0.181
Median [Min, Max]	4.46 [1.04, 10.1]	5.10 [1.59, 10.0]	
Monocytes (10⁹/L)			
Mean (SD)	0.583 (0.247)	0.589 (0.170)	0.369
Median [Min, Max]	0.540 [0.200, 1.53]	0.580 [0.160, 1.06]	
PLT (10⁹/L)			
Mean (SD)	233 (70.9)	212 (58.0)	0.178
Median [Min, Max]	221 [60.0, 431]	220 [51.0, 312]	
NLR (10⁹/L)			
Mean (SD)	2.78 (1.29)	2.98 (1.36)	0.345
Median [Min, Max]	2.51 [0.799, 7.55]	2.67 [1.07, 7.08]	
PLR (10⁹/L)			
Mean (SD)	137 (52.4)	125 (53.0)	0.076
Median [Min, Max]	131 [31.1, 315]	111 [53.1, 273]	
^{TOT}CD8 density (/mm²)			
Mean (SD)	424 (421)	397 (340)	0.869
Median [Min, Max]	279 [16.4, 2180]	295 [22.2, 1440]	
^{CT}CD8 density (/mm²)			
Mean (SD)	329 (424)	345 (347)	0.225
Median [Min, Max]	156 [5.13, 2270]	271 [18.3, 1820]	
^{IM}CD8 density (/mm²)			
Mean (SD)	536 (442)	465 (379)	0.391
Median [Min, Max]	384 [31.9, 2340]	403 [23.6, 1690]	

Supplementary Table S6: Association analysis between peripheral or intratumoral biomarkers measures and grading. P values estimated by Kruskal-Wallis test.

	G3 (N=77)	G2 (N=87)	G1 (N=18)	P-value
WBC (10⁹/L)				
Mean (SD)	7.54 (2.09)	7.34 (1.84)	7.23 (1.84)	0.738
Median [Min, Max]	7.58 [2.77, 13.7]	7.19 [4.03, 12.0]	7.27 [3.41, 11.1]	
Lymphocytes (10⁹/L)				
Mean (SD)	1.82 (0.556)	1.81 (0.543)	1.85 (0.423)	0.901
Median [Min, Max]	1.80 [0.750, 3.69]	1.72 [0.690, 3.54]	1.83 [1.23, 2.71]	
Neutrophils (10⁹/L)				
Mean (SD)	4.90 (1.74)	4.74 (1.55)	4.55 (1.74)	0.557
Median [Min, Max]	4.92 [1.04, 10.1]	4.46 [2.22, 8.74]	4.09 [1.57, 8.90]	
Monocytes (10⁹/L)				
Mean (SD)	0.578 (0.208)	0.577 (0.229)	0.651 (0.322)	0.779
Median [Min, Max]	0.570 [0.160, 1.03]	0.540 [0.200, 1.45]	0.530 [0.320, 1.53]	
PLT (10⁹/L)				
Mean (SD)	231 (73.6)	223 (62.0)	241 (77.5)	0.481
Median [Min, Max]	233 [51.0, 397]	218 [89.0, 412]	220 [126, 431]	
NLR (10⁹/L)				
Mean (SD)	2.91 (1.37)	2.82 (1.23)	2.53 (1.40)	0.3
Median [Min, Max]	2.54 [0.897, 7.08]	2.60 [0.799, 7.55]	2.14 [1.11, 6.14]	
PLR (10⁹/L)				
Mean (SD)	136 (57.1)	132 (47.3)	135 (59.7)	0.966
Median [Min, Max]	126 [31.1, 308]	130 [36.5, 315]	123 [60.3, 297]	
TOTCD8 density (/mm²)				
Mean (SD)	404 (370)	435 (456)	395 (249)	0.613
Median [Min, Max]	294 [18.6, 2180]	231 [16.4, 2180]	351 [42.2, 996]	
CTCD8 density (/mm²)				
Mean (SD)	322 (392)	358 (446)	261 (243)	0.917
Median [Min, Max]	191 [5.13, 2270]	152 [8.38, 2070]	235 [22.0, 899]	
IMCD8 density (/mm²)				
Mean (SD)	516 (402)	513 (463)	573 (379)	0.477
Median [Min, Max]	420 [23.6, 2020]	305 [23.6, 2340]	481 [95.8, 1260]	

Supplementary Table S7: Association analysis between peripheral or intratumoral biomarkers measures and bone invasion. P values estimated by Kruskal-Wallis test.

	No bone invasion (N=148)	Cortical invasion (N=16)	Medullary invasion (N=18)	P-value
WBC (10⁹/L)				
Mean (SD)	7.41 (1.97)	7.08 (2.13)	7.76 (1.56)	0.378
Median [Min, Max]	7.43 [2.77, 13.7]	6.51 [4.67, 13.0]	7.62 [4.71, 10.7]	
Lymphocytes (10⁹/L)				
Mean (SD)	1.83 (0.562)	1.81 (0.492)	1.76 (0.316)	0.92
Median [Min, Max]	1.79 [0.690, 3.69]	1.71 [1.03, 2.71]	1.72 [1.31, 2.32]	
Neutrophils (10⁹/L)				
Mean (SD)	4.77 (1.64)	4.55 (1.89)	5.15 (1.48)	0.341
Median [Min, Max]	4.78 [1.04, 10.0]	3.81 [2.48, 10.1]	5.16 [2.58, 7.74]	
Monocytes (10⁹/L)				
Mean (SD)	0.589 (0.226)	0.544 (0.309)	0.588 (0.196)	0.41
Median [Min, Max]	0.565 [0.160, 1.45]	0.520 [0.240, 1.53]	0.550 [0.220, 1.09]	
PLT (10⁹/L)				
Mean (SD)	223 (63.6)	228 (67.7)	273 (92.7)	0.056
Median [Min, Max]	220 [51.0, 431]	219 [126, 341]	278 [89.0, 412]	
NLR (10⁹/L)				
Mean (SD)	2.84 (1.36)	2.57 (1.11)	3.00 (1.05)	0.46
Median [Min, Max]	2.53 [0.799, 7.55]	2.31 [1.23, 5.59]	3.15 [1.32, 5.38]	
PLR (10⁹/L)				
Mean (SD)	132 (52.6)	128 (42.1)	157 (58.5)	0.084
Median [Min, Max]	125 [31.1, 308]	118 [80.8, 202]	156 [59.3, 315]	
TOTCD8 density (/mm²)				
Mean (SD)	425 (399)	271 (224)	485 (529)	0.344
Median [Min, Max]	279 [16.4, 2180]	170 [31.0, 724]	396 [42.2, 2180]	
CTCD8 density (/mm²)				
Mean (SD)	331 (400)	224 (234)	445 (548)	0.56
Median [Min, Max]	170 [5.13, 2070]	108 [17.5, 799]	344 [22.0, 2270]	
IMCD8 density (/mm²)				
Mean (SD)	527 (420)	416 (299)	555 (585)	0.613
Median [Min, Max]	396 [23.6, 2340]	340 [59.8, 912]	402 [56.3, 2020]	

Supplementary Table S8: Association analysis between peripheral or intratumoral biomarkers measures and perineural invasion (PNI). P values estimated by Wilcoxon test.

	No (N=92)	Yes (N=90)	P-value
WBC (10⁹/L)			
Mean (SD)	7.23 (1.98)	7.60 (1.89)	0.277
Median [Min, Max]	7.22 [2.77, 12.6]	7.50 [4.16, 13.7]	
Lymphocytes (10⁹/L)			
Mean (SD)	1.81 (0.541)	1.82 (0.533)	0.831
Median [Min, Max]	1.79 [0.690, 3.43]	1.76 [0.890, 3.69]	
Neutrophils (10⁹/L)			
Mean (SD)	4.61 (1.62)	4.98 (1.66)	0.208
Median [Min, Max]	4.46 [1.04, 8.74]	4.84 [2.22, 10.1]	
Monocytes (10⁹/L)			
Mean (SD)	0.589 (0.251)	0.580 (0.210)	0.891
Median [Min, Max]	0.545 [0.160, 1.53]	0.560 [0.220, 1.33]	
PLT (10⁹/L)			
Mean (SD)	226 (68.2)	230 (69.2)	0.586
Median [Min, Max]	218 [51.0, 399]	231 [60.0, 431]	
NLR (10⁹/L)			
Mean (SD)	2.72 (1.26)	2.94 (1.35)	0.26
Median [Min, Max]	2.48 [0.799, 7.25]	2.62 [1.07, 7.55]	
PLR (10⁹/L)			
Mean (SD)	133 (53.1)	134 (52.5)	0.698
Median [Min, Max]	127 [50.7, 308]	130 [31.1, 315]	
^{TOT}CD8 density (/mm²)			
Mean (SD)	405 (396)	430 (412)	0.586
Median [Min, Max]	250 [18.6, 2180]	300 [16.4, 2180]	
^{CT}CD8 density (/mm²)			
Mean (SD)	297 (344)	370 (461)	0.185
Median [Min, Max]	127 [5.13, 1550]	193 [8.38, 2270]	
^{IM}CD8 density (/mm²)			
Mean (SD)	531 (448)	508 (410)	0.958
Median [Min, Max]	398 [23.6, 2340]	377 [23.6, 2020]	

Supplementary Table S9: Association analysis between peripheral or intratumoral biomarkers measures and lymphovascular invasion (LVI). P values estimated by Wilcoxon test.

	LVI No (N=130)	LVI Yes (N=52)	P-value
WBC (10⁹/L)			
Mean (SD)	7.44 (2.00)	7.34 (1.79)	0.945
Median [Min, Max]	7.31 [2.77, 13.0]	7.58 [4.03, 13.7]	
Lymphocytes (10⁹/L)			
Mean (SD)	1.84 (0.555)	1.75 (0.483)	0.407
Median [Min, Max]	1.80 [0.690, 3.69]	1.76 [1.00, 2.86]	
Neutrophils (10⁹/L)			
Mean (SD)	4.77 (1.68)	4.83 (1.57)	0.704
Median [Min, Max]	4.58 [1.04, 10.1]	4.94 [2.32, 10.0]	
Monocytes (10⁹/L)			
Mean (SD)	0.597 (0.248)	0.554 (0.181)	0.476
Median [Min, Max]	0.555 [0.160, 1.53]	0.545 [0.220, 1.06]	
PLT (10⁹/L)			
Mean (SD)	228 (72.0)	229 (59.7)	0.765
Median [Min, Max]	220 [51.0, 431]	221 [118, 406]	
NLR (10⁹/L)			
Mean (SD)	2.79 (1.33)	2.93 (1.25)	0.3
Median [Min, Max]	2.48 [0.799, 7.25]	2.66 [1.07, 7.55]	
PLR (10⁹/L)			
Mean (SD)	132 (52.1)	139 (54.3)	0.5
Median [Min, Max]	125 [31.1, 315]	132 [60.3, 308]	
^{TOT}CD8 density (/mm²)			
Mean (SD)	453 (433)	330 (301)	0.104
Median [Min, Max]	298 [18.6, 2180]	237 [16.4, 1440]	
^{CT}CD8 density (/mm²)			
Mean (SD)	363 (446)	259 (273)	0.523
Median [Min, Max]	176 [5.13, 2270]	164 [8.38, 1450]	
^{IM}CD8 density (/mm²)			
Mean (SD)	568 (460)	399 (308)	0.032
Median [Min, Max]	438 [23.6, 2340]	317 [31.9, 1690]	

Supplementary Table S10: Details of the loadings for each variable and level composing the 5 metavariables (^{MV}).

IT-CD8^{MV}		IT-CD8^{MV}	
	squared loading		loading
CD8 density Total	0.973	CD8 density Total	0.9866191
CD8 density CT	0.862	CD8 density CT	0.9286171
CD8 density IM	0.853	CD8 density IM	0.9237935
Age	0.097	Age	0.3117396
NODAL^{MV}		NODAL^{MV}	
	squared loading		loading
pN VIII	0.870	Nodal ratio	0.8597471
Nodal ratio	0.739	Total Number Positive Nodes	0.8376385
Total Number Positive Nodes	0.702	Differentiation=G1	-0.83438891
N0/N+	0.661	pN VIII=pN0	-0.77263130
ENE	0.637	N0/N+=pN0	-0.76093557
Treatment	0.372	Treatment=Surgery	-0.64286893
LVI	0.309	ENE=No	-0.43708058
Differentiation	0.124	LVI=No	-0.35172077
PNI	0.095	PNI=No	-0.30449926
Margins	0.061	Margins=Negative	-0.14653372
MYELOID^{MV}		MYELOID^{MV}	
	squared loading		loading
WBC	0.91	Differentiation=G2	-0.12520442
Neutrophils	0.85	Margins=Close	-0.05056247
Monocytes	0.39	pN VIII=pN1	0.01399685
Sex	0.16	Treatment=Surgery+RT	0.20589926
LYMPHOID^{MV}		LYMPHOID^{MV}	
	squared loading		loading
PLR	0.85	PNI=Yes	0.31126592
NLR	0.63	Differentiation=G3	0.33651668
Lymphocytes	0.55	pN VIII=pN2a	0.44018873
PLT	0.14	Margins=Positive	0.52492533
TUMOR^{MV}		TUMOR^{MV}	
	squared loading		loading
Bone invasion	0.99	pN VIII=pN2b	0.65695459
pT VIII	0.99	pN VIII=pN2c	0.85813671
Gain in cohesion (%)	46.85	N0/N+=pN+	0.86836177
		Treatment=Surgery+CRT	0.87404470
		LVI=Yes	0.87930191
		ENE=Yes	1.4569353
		pN VIII=pN3b	1.5517895
		MYELOID^{MV}	
			loading
		WBC	0.9548163
		Neutrophils	0.9196095
		Monocytes	0.6244274
		Sex=Female	-0.5241825
		Sex=Male	0.3053933
		LYMPHOID^{MV}	
			loading
		PLR	0.9242590
		NLR	0.7958679
		Lymphocytes	-0.7388330
		PLT	0.3775898
		TUMOR^{MV}	
			loading
		pT VIII=pT2	-0.4853636
		pT VIII=pT1	-0.4853636
		Bone invasion=No	-0.4769100
		pT VIII=pT3	-0.4558341
		Bone invasion=Cortical	1.9893744
		pT VIII=pT4	2.1154294
		Bone invasion=Medullary	2.1529270

Supplementary Table S11: Extensive details of multivariable survival Cox proportional hazards models. Legend: d.f., degrees of freedom; Coefficient, regression coefficient; S.E., standard error.

Overall Survival (OS) - Wald statistics				Overall Survival (OS) - Model Details		
Variable	Chi-Square	d.f.	P	Term	Coefficient	S.E.
MYELOID ^{MV}	3.09	1	0.0786	MYELOID ^{MV}	0.1322	0.0752
NODAL ^{MV}	34.00	3	<.0001	NODAL ^{MV}	-0.3837	0.1320
Nonlinear	0.63	2	0.7306	NODAL ^{MV'}	0.2290	0.2896
IT-CD8 ^{MV}	1.06	1	0.3022	NODAL ^{MV''}	-17.252	22.966
TUMOR ^{MV}	1.44	1	0.2303	IT-CD8 ^{MV}	-0.0800	0.0775
LYMPHOID ^{MV}	10.26	3	0.0165	TUMOR ^{MV}	-0.0916	0.0763
Nonlinear	10.25	2	0.0059	LYMPHOID ^{MV}	-0.9900	0.3169
TOTAL NONLINEAR	10.42	4	0.0340	LYMPHOID ^{MV'}	46.362	15.525
TOTAL	41.31	9	<.0001	LYMPHOID ^{MV''}	-132.165	47.542
Disease specific survival (DSS) - Wald statistics				Disease specific survival (DSS) - Model Details		
Variable	Chi-Square	d.f.	P	Term	Coefficient	S.E.
MYELOID ^{MV}	6.26	1	0.0123	MYELOID ^{MV}	0.2389	0.0955
NODAL ^{MV}	40.90	3	<.0001	NODAL ^{MV}	-0.4373	0.1444
Nonlinear	1.01	2	0.6024	NODAL ^{MV'}	0.2302	0.3432
IT-CD8 ^{MV}	0.72	1	0.3956	NODAL ^{MV''}	-26.953	29.459
TUMOR ^{MV}	1.93	1	0.1651	IT-CD8 ^{MV}	-0.0766	0.0902
LYMPHOID ^{MV}	7.74	3	0.0516	TUMOR ^{MV}	-0.1247	0.0898
Nonlinear	7.64	2	0.0220	LYMPHOID ^{MV}	-0.9734	0.3971
TOTAL NONLINEAR	8.34	4	0.0800	LYMPHOID ^{MV'}	52.910	19.297
TOTAL	48.11	9	<.0001	LYMPHOID ^{MV''}	-166.010	60.157
Locoregional recurrence free survival (LRRFS) - Wald statistics				Locoregional recurrence free survival (LRRFS) - Model Details		
Variable	Chi-Square	d.f.	P	Term	Coefficient	S.E.
MYELOID ^{MV}	11.69	3	0.0085	MYELOID ^{MV}	0.8172	0.4655
Nonlinear	2.87	2	0.2384	MYELOID ^{MV'}	-14.469	0.9600
NODAL ^{MV}	20.42	3	0.0001	MYELOID ^{MV''}	70.322	42.615
Nonlinear	5.03	2	0.0809	NODAL ^{MV}	-0.3942	0.1565
IT-CD8 ^{MV}	0.01	1	0.9179	NODAL ^{MV'}	0.5845	0.3373
TUMOR ^{MV}	4.58	1	0.0323	NODAL ^{MV''}	-59.482	27.493
LYMPHOID ^{MV}	0.31	1	0.5758	IT-CD8 ^{MV}	-0.0080	0.0772
TOTAL NONLINEAR	7.24	4	0.1240	TUMOR ^{MV}	-0.1742	0.0814
TOTAL	32.98	9	0.0001	LYMPHOID ^{MV}	0.0536	0.0958
Distant recurrence free survival (DRFS) - Wald statistics				Distant recurrence free survival (DRFS) - Model Details		
Variable	Chi-Square	d.f.	P	Term	Coef	S.E.
MYELOID ^{MV}	2.78	1	0.0957	MYELOID ^{MV}	0.2005	0.1203
NODAL ^{MV}	31.40	3	<.0001	NODAL ^{MV}	-0.6192	0.2106
Nonlinear	0.69	2	0.7080	NODAL ^{MV'}	0.3937	0.5101
IT-CD8 ^{MV}	9.62	3	0.0221	NODAL ^{MV''}	-37.339	44.941
Nonlinear	5.85	2	0.0537	IT-CD8 ^{MV}	-24.305	10.371
TUMOR ^{MV}	0.07	1	0.7944	IT-CD8 ^{MV'}	212.985	127.036
LYMPHOID ^{MV}	11.92	3	0.0077	IT-CD8 ^{MV''}	-370.310	233.995
Nonlinear	11.22	2	0.0037	TUMOR ^{MV}	0.0381	0.1462
TOTAL NONLINEAR	17.74	6	0.0069	LYMPHOID ^{MV}	-17.050	0.4968
TOTAL	41.19	11	<.0001	LYMPHOID ^{MV'}	86.064	26.509
				LYMPHOID ^{MV''}	-257.221	83.674