

Supplementary Materials

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Fig. E3. The VIF plot and Eigenvalues plot of 11 variables used in multivariate analysis.

Fig. E4. The stratified model-based trees classified patients into different treatment effects subgroups based on the prognostic score derived from nomogram (Figure 3A) by controlling the max depth of the tree. Here, a max depth of three was found to be ideal. Patients with a prognostic score ≤ 102 exhibited more survival benefit when comparing the two treatment modalities.

Fig. E5. General dominance of independent predictors for receiving definitive radiotherapy in low-risk cohort.

Table E1. Comparison of Treatment-Specific Factors According to Treatment Modality.

Characteristic	Total (N=460)	PCT plus DRT (N=244)	PCT alone (N=216)	P value
First-line PCT regimen				<0.001
FP	167 (36.3)	74 (30.3)	93 (43.1)	
TP	114 (24.8)	62 (25.4)	52 (24.1)	
GP	36 (7.8)	13 (5.3)	23 (10.6)	
TPF	143 (31.1)	95 (38.9)	48 (22.2)	
Cycle of first-line PCT				0.124
<6	167 (36.3)	97 (39.8)	70 (32.4)	
≥6	293 (63.7)	147 (60.2)	146 (67.6)	
RT technique				-
CRT	39 (8.5)	39 (16.0)	-	
IMRT	205 (44.6)	205 (84.0)	-	
RT dose (continuous)				-
Mean (Gy)	69.1	69.1	-	
Median (Gy)	70	70	-	
Range (Gy)	44-74	44-74	-	
Interquartile Range	68-70	68-70	-	
RT dose (group)				-
<60Gy	2 (0.4)	2 (0.8)	-	
60-69.9Gy	71 (15.4)	71 (29.1)	-	
≥70Gy	171 (37.2)	171 (70.1)	-	
Concurrent chemotherapy				-
No	122 (26.5)	122 (50.0)	-	
Cisplatin	90 (19.6)	90 (36.9)	-	
Other platinum drugs	15 (3.3)	15 (6.1)	-	
Non-platinum drugs	17 (3.7)	17 (7.0)	-	
Cycle of concurrent chemotherapy				-
0	122 (26.5)	122 (50.0)	-	
1	15 (3.3)	15 (6.1)	-	
2	82 (17.8)	82 (33.6)	-	
3	15 (3.3)	15 (6.1)	-	
≥4	10 (2.2)	10 (4.1)	-	
Other concurrent treatment				-
No	229 (49.8)	229 (93.9)	-	
Nimotuzumab	8 (1.7)	8 (3.3)	-	
Cetuximab	5 (1.1)	5 (2.0)	-	
Bevacizumab	1 (0.2)	1 (0.4)	-	
CIK therapy	1 (0.2)	1 (0.4)	-	
Local treatment				<0.001
No	376 (81.7)	173 (70.9)	203 (94.0)	
Local RT	62 (13.5)	56 (23.0)	6 (2.8)	
Local ablation	15 (3.3)	11 (4.5)	4 (1.9)	
Surgery	3 (0.7)	2 (0.8)	1 (0.5)	
Ablation plus local RT	2 (0.4)	2 (0.8)	0 (0)	
Ablation plus surgery	2 (0.4)	0 (0)	2 (0.9)	
Salvage treatment				0.001
No	285 (62.0)	171 (70.1)	114 (52.8)	
Second-line	84 (18.3)	34 (13.9)	50 (23.1)	
Third-line	41 (8.9)	14 (5.7)	27 (12.5)	
More than third-line	50 (10.9)	25 (10.2)	25 (11.6)	

Abbreviation: PCT, palliative chemotherapy; DRT, definitive radiotherapy; FP, 5-fluorouracil and platinum; TP, taxane and platinum; GP, gemcitabine and platinum; TPF, taxane, platinum and 5-fluorouracil; CRT, conventional radiotherapy; IMRT, intensity-modulated radiotherapy; CIK, cytokines induced killer.

Table E2. Comparison of Patient Characteristics within Training and Validation Cohorts.				
Variable	Total (N=460)	Training Cohort (N= 296)	Validation Cohort (N=164)	P
Age (year)				0.662
<45	204 (44.3)	134 (45.3)	70 (42.7)	
≥45	256 (55.7)	162 (54.7)	94 (57.3)	
Sex				1.000
Female	69 (15.0)	44 (14.9)	25 (15.2)	
Male	391 (85.0)	252 (85.1)	139 (84.8)	
Residence				0.014
Rural	199 (43.3)	115 (38.9)	84 (51.2)	
Urban	261 (56.7)	181 (61.1)	80 (48.8)	
Employment				0.181
Unemployed	87 (18.9)	59 (19.9)	28 (17.1)	
Employed	329 (71.5)	204 (68.9)	125 (76.2)	
Retired	44 (9.57)	33 (11.1)	11 (6.71)	
Marital status				0.762
Unmarried	12 (2.61)	7 (2.36)	5 (3.05)	
Married	448 (97.4)	289 (97.6)	159 (97.0)	
Education				0.095
Low	74 (16.1)	45 (15.2)	29 (17.7)	
Medium	248 (53.9)	152 (51.4)	96 (58.5)	
High	138 (30.0)	99 (33.4)	39 (23.8)	
Insurance status				<0.001
Uninsured	244 (53.0)	136 (45.9)	108 (65.9)	
Insured	216 (47.0)	160 (54.1)	56 (34.1)	
KPS				<0.001
≥80	141 (30.7)	122 (41.2)	19 (11.6)	
<80	319 (69.3)	174 (58.8)	145 (88.4)	
Comorbidity				0.566
No	322 (70.0)	204 (68.9)	118 (72.0)	
Yes	138 (30.0)	92 (31.1)	46 (28.0)	
Smoking				0.538
No	276 (60.0)	174 (58.8)	102 (62.2)	
Yes	184 (40.0)	122 (41.2)	62 (37.8)	
Drinking				0.721
No	414 (90.0)	268 (90.5)	146 (89.0)	
Yes	46 (10.0)	28 (9.46)	18 (11.0)	
BMI (kg/m2)				0.606
<18.5	104 (22.6)	67 (22.6)	37 (22.6)	
18.5-24	258 (56.1)	170 (57.4)	88 (53.7)	
>24	98 (21.3)	59 (19.9)	39 (23.8)	
Histology				0.645
II	18 (3.91)	13 (4.39)	5 (3.05)	
III	442 (96.1)	283 (95.6)	159 (97.0)	
Tumor category				0.105
T1	26 (5.65)	15 (5.07)	11 (6.71)	
T2	58 (12.6)	44 (14.9)	14 (8.54)	
T3	231 (50.2)	152 (51.4)	79 (48.2)	
T4	145 (31.5)	85 (28.7)	60 (36.6)	
Node category				0.005
N0	13 (2.83)	9 (3.04)	4 (2.44)	
N1	74 (16.1)	53 (17.9)	21 (12.8)	
N2	191 (41.5)	135 (45.6)	56 (34.1)	
N3	182 (39.6)	99 (33.4)	83 (50.6)	
Liver metastases				0.403
No	307 (66.7)	193 (65.2)	114 (69.5)	
Yes	153 (33.3)	103 (34.8)	50 (30.5)	
Bone metastases				0.799
No	155 (33.7)	98 (33.1)	57 (34.8)	
Yes	305 (66.3)	198 (66.9)	107 (65.2)	

Lung metastases				0.655
No	327 (71.1)	213 (72.0)	114 (69.5)	
Yes	133 (28.9)	83 (28.0)	50 (30.5)	
No. of metastatic sites				0.180
Single	303 (65.9)	202 (68.2)	101 (61.6)	
Multiple	157 (34.1)	94 (31.8)	63 (38.4)	
No. of metastatic lesions				0.827
Single	97 (21.1)	61 (20.6)	36 (22.0)	
Multiple	363 (78.9)	235 (79.4)	128 (78.0)	
ALP (U/L)				0.116
<110	341 (74.1)	227 (76.7)	114 (69.5)	
≥110	119 (25.9)	69 (23.3)	50 (30.5)	
CRP (g/mL)				0.019
<3	255 (55.4)	158 (53.4)	97 (59.1)	
≥3	194 (42.2)	127 (42.9)	67 (40.9)	
Missing	11 (2.39)	11 (3.72)	0 (0.00)	
LDH (U/L)				0.734
<245	295 (64.1)	192 (64.9)	103 (62.8)	
≥245	165 (35.9)	104 (35.1)	61 (37.2)	
Pretreatment EBV DNA				<0.001
Undetectable	67 (14.6)	44 (14.9)	23 (14.0)	
Detectable	356 (77.4)	217 (73.3)	139 (84.8)	
Missing	37 (8.04)	35 (11.8)	2 (1.22)	
First-line PCT y regimen				0.012
PF	167 (36.3)	92 (31.1)	75 (45.7)	
GP	36 (7.83)	23 (7.77)	13 (7.93)	
TP	114 (24.8)	83 (28.0)	31 (18.9)	
TPF	143 (31.1)	98 (33.1)	45 (27.4)	
Cycle of first-line PCT				0.104
<6	167 (36.3)	116 (39.2)	51 (31.1)	
≥6	293 (63.7)	180 (60.8)	113 (68.9)	
DRT				0.379
No	216 (47.0)	144 (48.2)	72 (43.9)	
Yes	244 (53.0)	152 (51.8)	92 (56.1)	
Local treatment				0.307
No	380 (82.6)	249 (84.1)	131 (79.9)	
Yes	80 (17.4)	47 (15.9)	33 (20.1)	
Salvage treatment				1.000
No	285 (62.0)	183 (61.8)	102 (62.2)	
Yes	175 (38.0)	113 (38.2)	62 (37.8)	
Posttreatment EBV DNA				<0.001
Undetectable	240 (52.2)	150 (50.7)	90 (54.9)	
Detectable	143 (31.1)	81 (27.4)	62 (37.8)	
Missing	77 (16.7)	65 (22.0)	12 (7.32)	
Response of primary tumor				0.014
CR	57 (12.4)	26 (8.78)	31 (18.9)	
PR	376 (81.7)	253 (85.5)	123 (75.0)	
SD	18 (3.91)	12 (4.05)	6 (3.66)	
PD	9 (1.96)	5 (1.69)	4 (2.44)	
Response of metastasis				0.296
CR	46 (10.0)	27 (9.12)	19 (11.6)	
PR	250 (54.3)	170 (57.4)	80 (48.8)	
SD	106 (23.0)	66 (22.3)	40 (24.4)	
PD	58 (12.6)	33 (11.1)	25 (15.2)	

Abbreviation: KPS, Karnofsky Performance Score; BMI, body mass index; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; EBV DNA, Epstein–Barr virus DNA; FP, 5-fluorouracil and platinum; TP, taxane and platinum; GP, gemcitabine and platinum; TPF, taxane, platinum and 5-fluorouracil; PCT, palliative chemotherapy; DRT, definitive radiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Table E3. Univariable Association of the Patient Characteristics with Overall Survival in the Training Cohorts.

Variable	HR	95% CI	P
Age (year): ≥ 45 v < 45	1.231	0.923-1.642	0.158
Sex: male v female	1.275	0.849-1.917	0.242
Residence: urban v rural	0.808	0.605-1.079	0.149
Employment			
employed v unemployed	0.772	0.549-1.085	0.136
retired v unemployed	0.757	0.451-1.272	0.293
Marital status: married v unmarried	2.999	0.744-12.086	0.122
Education			
medium v low	1.193	0.791-1.800	0.400
high v low	0.925	0.592-1.445	0.732
Insurance: insured v uninsured	0.839	0.632-1.114	0.225
Kamofsky score: ≥ 80 v < 80	1.352	1.017-1.796	0.038
Comorbidity: yes v no	1.053	0.777-1.427	0.740
Smoking: yes v no	1.209	0.909-1.608	0.192
Drinking: yes v no	0.911	0.560-1.482	0.708
BMI (kg/m ²)			
18.5-24 v < 18.5	1.320	0.925-1.884	0.127
> 24 v < 18.5	0.902	0.572-1.421	0.656
Histology: III v II	1.943	0.799-4.725	0.143
T stage:			
T3 v T1-2	0.975	0.669-1.421	0.895
T4 v T1-2	1.106	0.736-1.664	0.627
N stage			
N2 v N0-1	1.056	0.719-1.553	0.780
N3 v N0-1	1.577	1.056-2.354	0.026
Live metastasis: yes v no	2.623	1.963-3.506	< 0.001
Bone metastasis: yes v no	0.920	0.682-1.241	0.585
Lung metastasis: yes v no	0.966	0.702-1.328	0.831
No. of metastatic sites:			
multiple v single	2.552	1.902-3.421	< 0.001
No. of metastatic lesions:			
multiple v single	1.921	1.312-2.810	< 0.001
ALP (U/L): ≥ 110 v < 110	1.597	1.158-2.202	0.004
CRP (g/mL): ≥ 3 v < 3	1.619	1.202-2.181	0.002
LDH (U/L): ≥ 245 v < 245	2.144	1.602-2.869	< 0.001
Pretreatment EBV DNA:			
detectable v undetectable	1.412	0.929-2.147	0.106
First-line PCT regimen:			
GP v FP	1.570	0.916-2.690	0.101
TP v FP	0.893	0.615-1.297	0.553
TPF v FP	0.821	0.578-1.166	0.271
Cycle of first-line PCT: ≥ 6 v < 6	1.065	0.794-1.429	0.675
Posttreatment EBV DNA:			
detectable v undetectable	4.235	3.024-5.929	< 0.001
Response of primary tumor:			
PR v CR	1.002	0.615-1.631	0.995
SD/PD v CR	1.927	0.943-3.936	0.072
Response of metastasis:			
PR v CR	2.142	1.083-4.234	0.029
SD v CR	3.497	1.717-7.121	0.001
PD v CR	11.644	5.461-24.826	< 0.001

Abbreviation: BMI, body mass index; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; EBV DNA, Epstein-Barr virus DNA; FP, 5-fluorouracil and platinum; TP, taxane and platinum; GP, gemcitabine and platinum; TPF, taxane, platinum and 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Table E4. Determinants for Patients Receiving DRT in the Primary, Low-risk, and High-risk Cohorts.

Predictors	HR (95% CI)	P value
Primary Cohort		
Insurance status, yes	2.700 (1.738-4.233)	<0.001
Education		
Low	Reference	
Medium	1.767 (0.962-3.301)	0.069
High	2.816 (1.429-5.649)	0.003
Karnofsky Performance Score, ≥ 80	1.928 (1.192-3.141)	0.008
Liver metastasis, yes	0.414 (0.250-0.679)	0.021
Number of metastatic sites, multiple	0.551 (0.329-0.920)	0.023
Number of metastatic lesions, multiple	0.536 (0.291-0.967)	0.041
Pre-treatment EBV DNA	0.519 (0.278-0.949)	0.036
Response of metastasis		
CR	Reference	
PR	0.376 (0.157-0.839)	0.021
SD	0.328 (0.129-0.779)	0.014
PD	0.109 (0.037-0.296)	<0.001
Low-risk Cohort		
Insurance status, yes	3.094 (1.854-5.236)	<0.001
Education		
Low	Reference	
Medium	1.890 (0.905-4.001)	0.092
High	3.008 (1.429-5.649)	0.008
T category		
T1-2	Reference	
T3	1.511 (0.755-3.027)	0.242
T4	2.341 (1.109-4.993)	0.026
Liver metastasis, yes	0.235 (0.120-0.446)	<0.001
Response of metastasis		
CR	Reference	
PR	0.349 (0.142-0.792)	0.016
SD	0.234 (0.084-0.609)	0.004
PD	0.025 (0.001-0.207)	0.003
High-risk Cohort		
Alkaline phosphatase, ≥ 110	0.240 (0.072-0.675)	0.011

Abbreviation: DRT, definitive radiotherapy; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; EBV DNA, Epstein–Barr virus DNA; CR, complete response; PR, partial response; SD, stable disease; PD, disease progression.

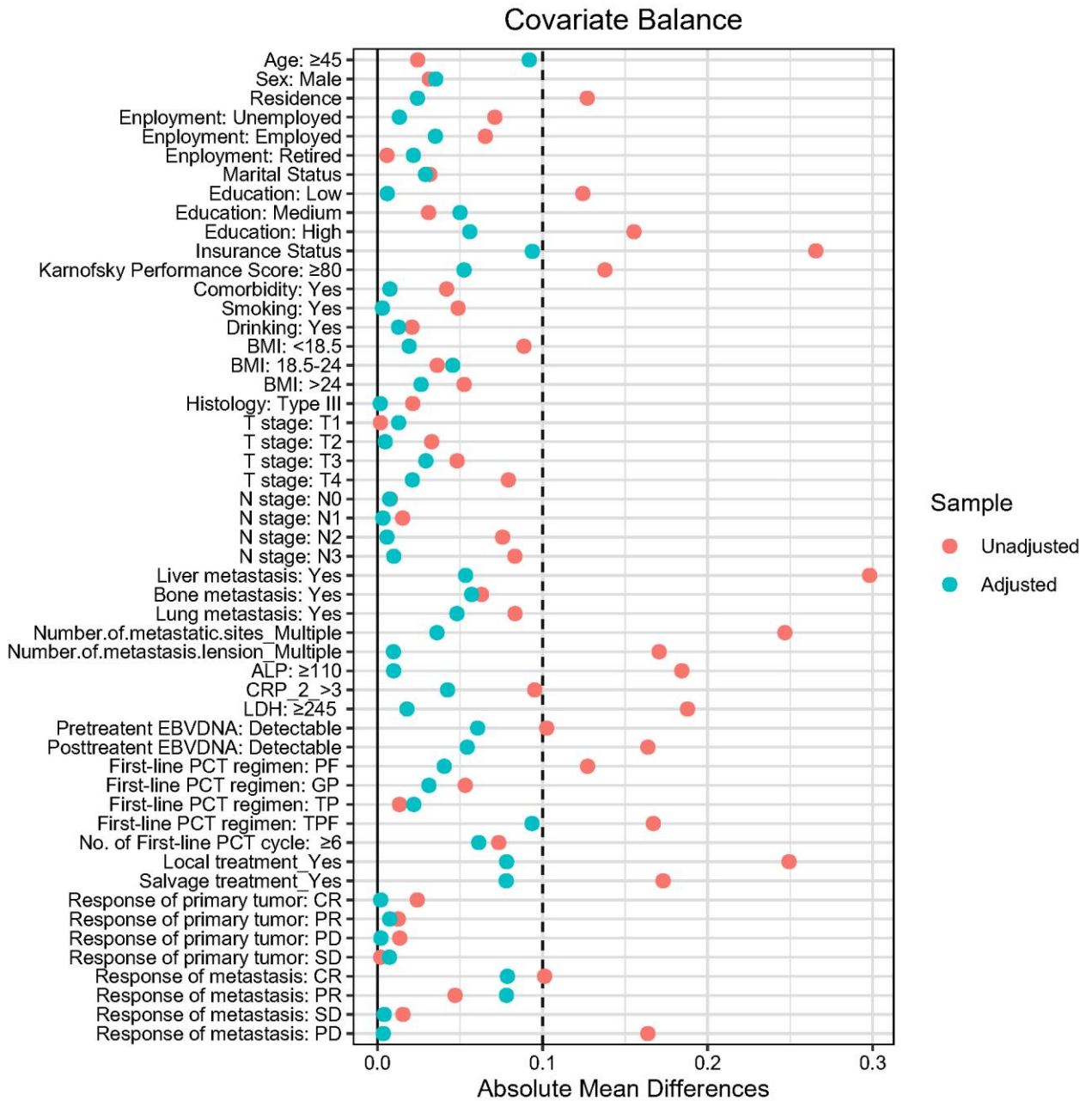
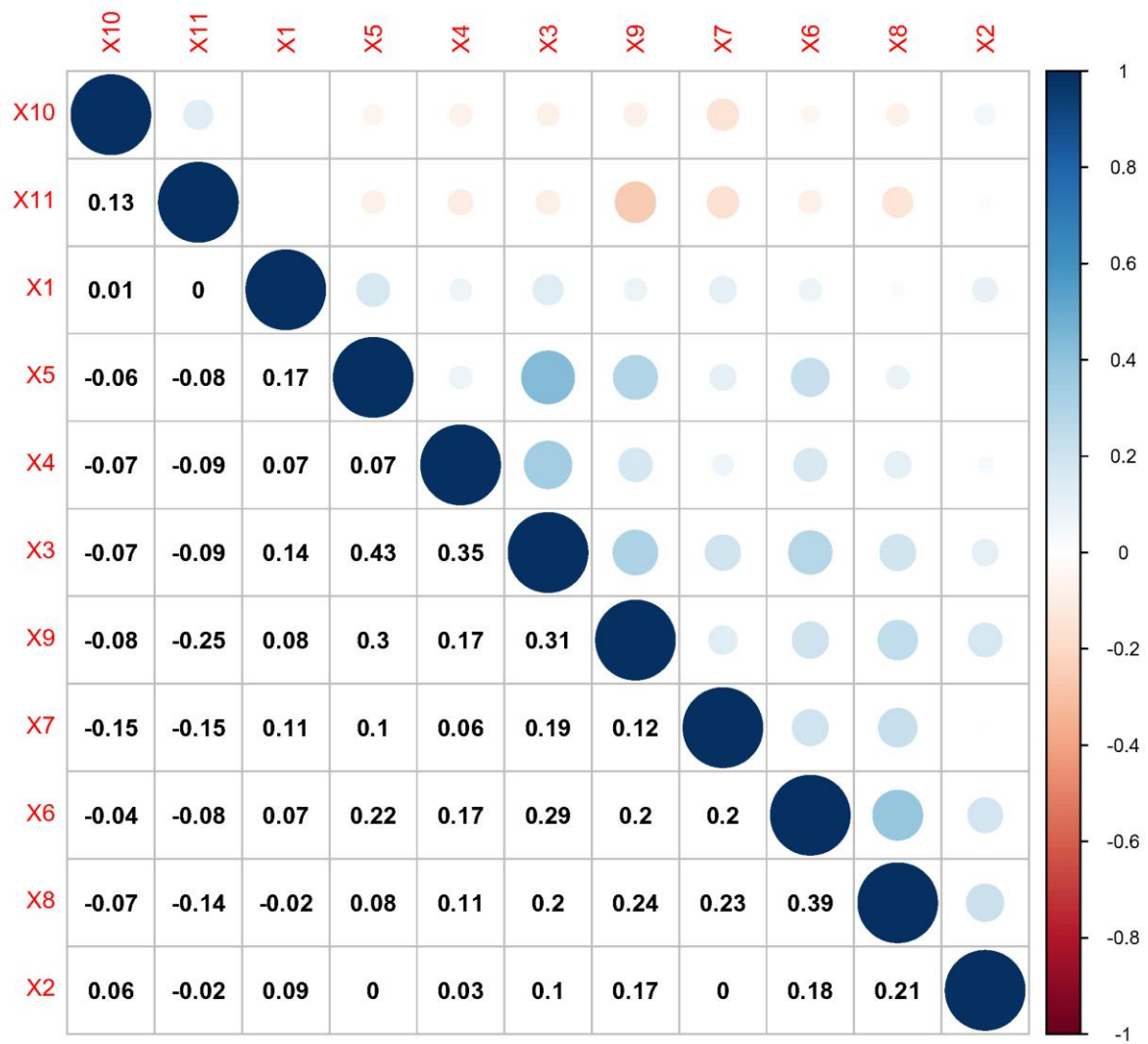


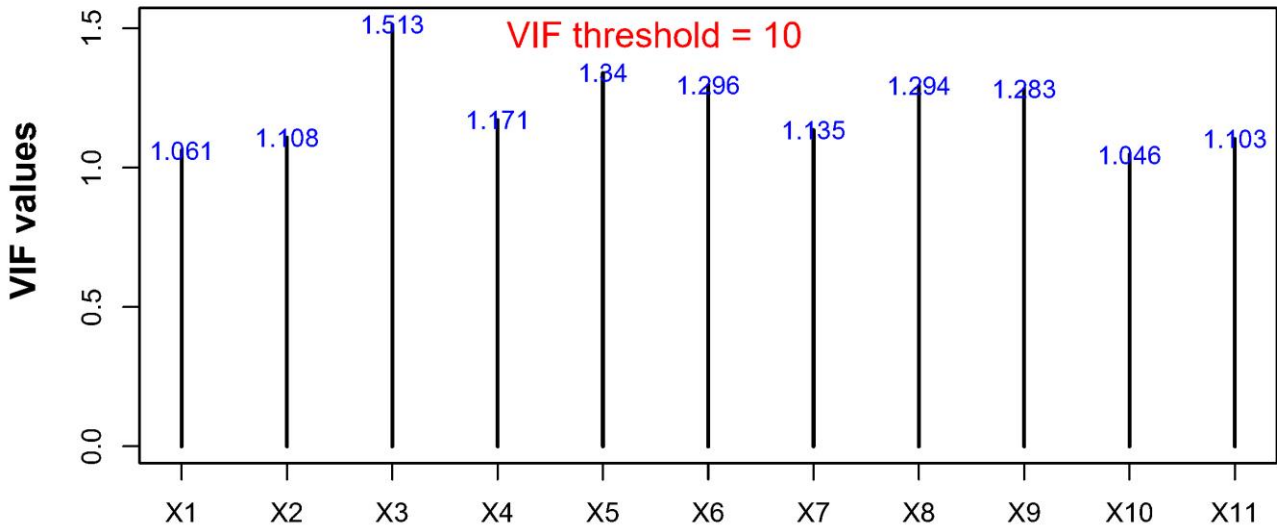
Fig. E1. Balance between treatment groups evaluated by standardized mean difference (SMD) before and after inverse probability of treatment weighting (IPTW) adjustment. A SMD less than 0.1 indicates excellent balance.



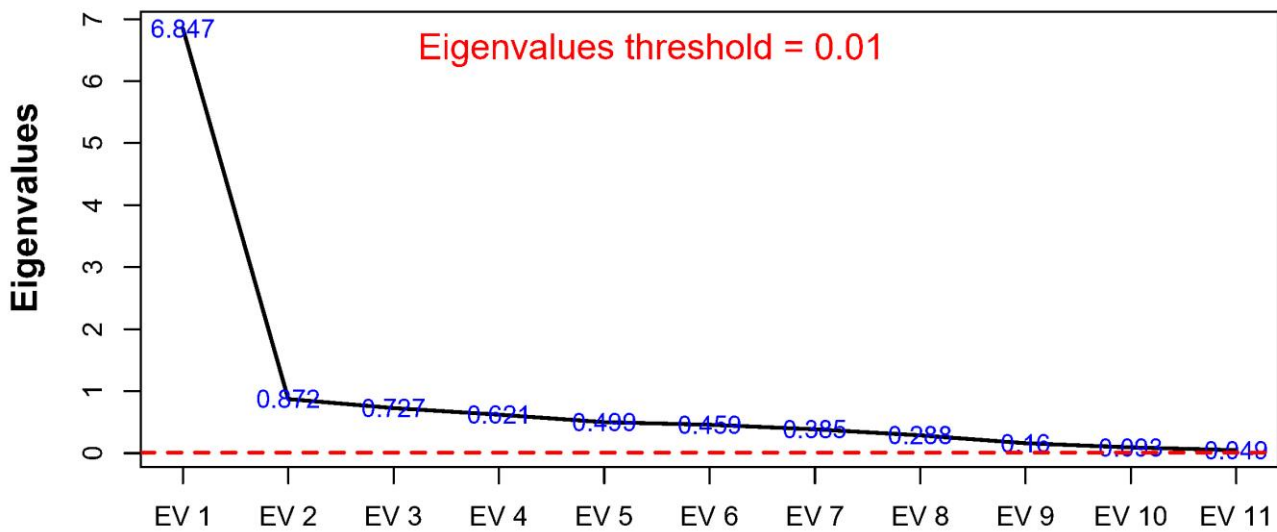
X1: KPS **X2:** N category **X3:** Number of metastatic sites
X4: Number of metastasis lension **X5:** Liver metastasis
X6: LDH **X7:** ALP **X8:** CRP **X9:** Posttreatment EBV DNA
X10: Response of primary tumor **X11:** Response of metastasis

Fig. E2. The pair-wise correlations among 11 variables used in multivariate analysis.

VIF Plot



Eigenvalues Plot



X1: KPS **X2:** N category **X3:** Number of metastatic site
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X10: Response of primary tumor **X11:** Response of metastasis

Fig. E3. The VIF plot and Eigenvalues plot of 11 variables used in multivariate analysis

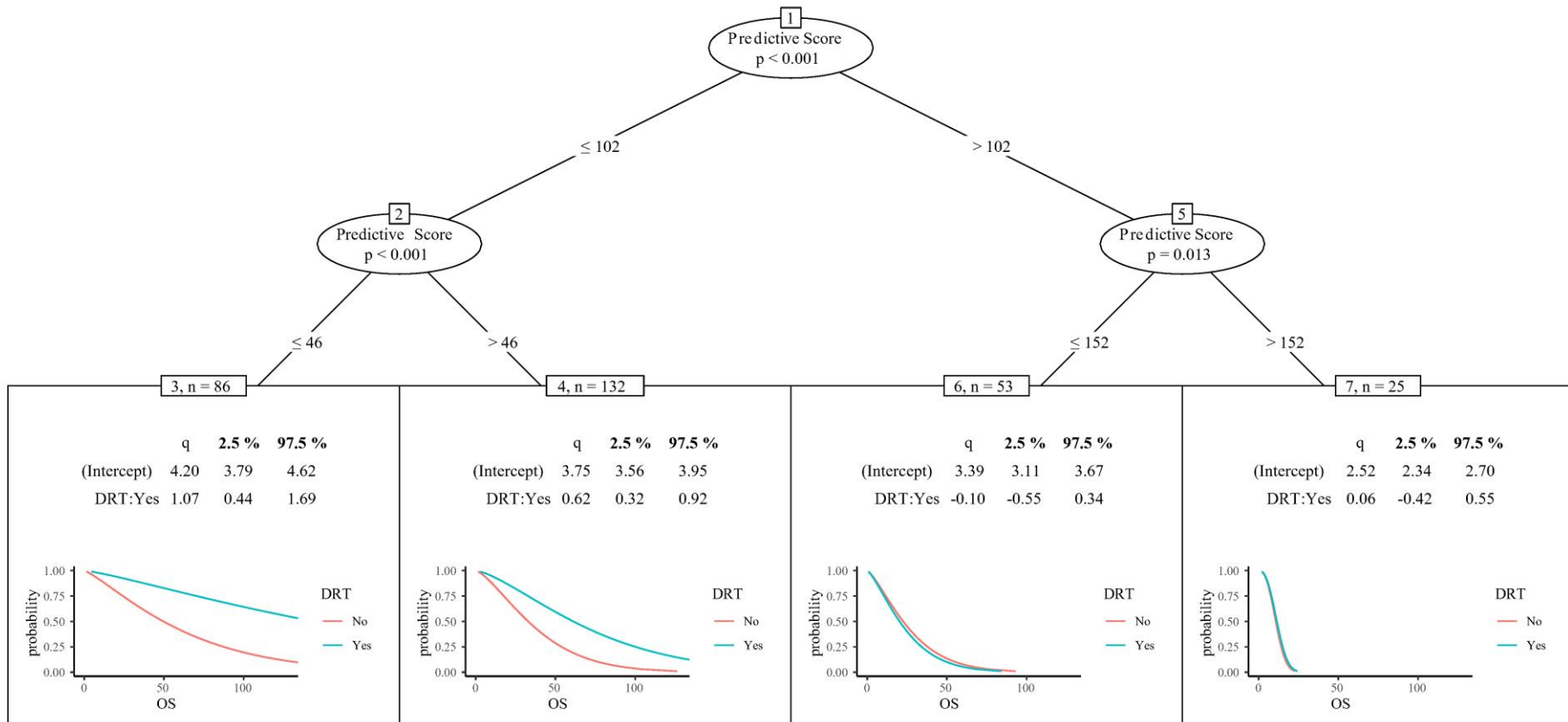


Fig. E4. The stratified model-based trees classified patients into different treatment effects subgroups based on the prognostic score derived from nomogram (Figure 3A) by controlling the max depth of the tree. Here, a max depth of three was found to be ideal. Patients with a prognostic score ≤ 102 exhibited more survival benefit when comparing the two treatment modalities.

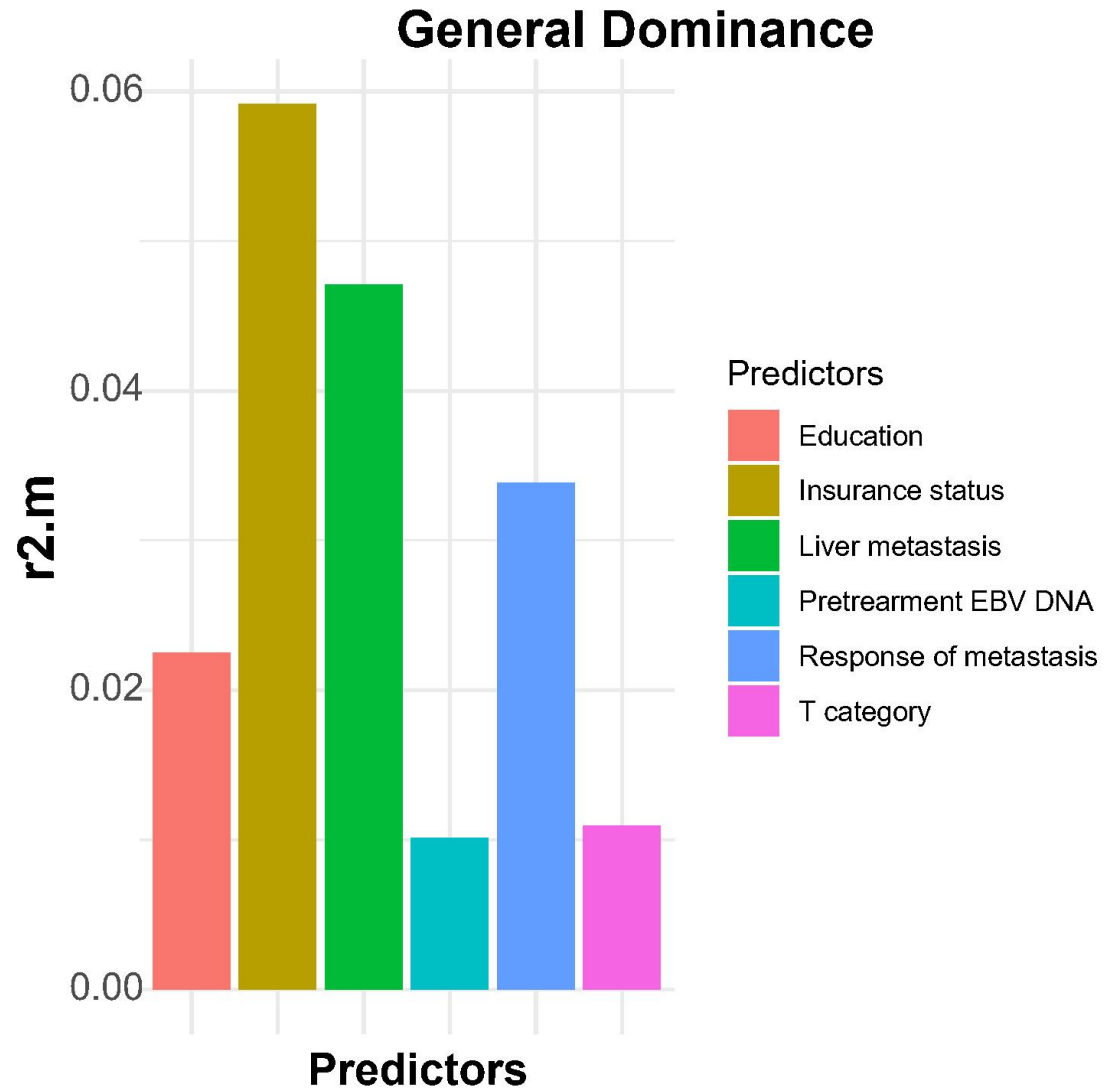


Fig. E5. General dominance of independent predictors for receiving definitive radiotherapy in low-risk cohort.