

**Table 1. Relapse-free survival in stage I-III colorectal cancer and associations of clinicopathological features with GMS in patients from the validation cohort (N=862).**

Clinicopathological characteristics	Disease-free survival					Relapse-free survival					GMS category				Pearson $\chi^2$
	N (%) <sup>a</sup>	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P	0 (n=300) N (%) <sup>a</sup>	1 (n=424) N (%)	2 (n=138) N (%)			
Age															
≤64	245 (28)									80 (27)	111 (26)	54 (39)			<b>0.04</b>
65-74	276 (32)								98 (33)	138 (33)	40 (29)				
≥75	341 (40)	1.66 (1.48-1.86)	<b>&lt;0.001</b>	1.71 (1.51-1.95)	<b>&lt;0.001</b>	1.10 (0.95-1.28)	0.20	–	–	122 (41)	175 (41)	44 (32)			
Gender															
Female	419 (49)									151 (50)	207 (49)	61 (44)			0.27
Male	443 (51)	1.12 (0.95-1.33)	0.18	–	–	1.15 (0.91-1.47)	0.24	–	–	149 (50)	217 (51)	77 (56)			
Presentation															
Elective	686 (80)									260 (87)	319 (75)	107 (78)			<b>0.002</b>
Emergency	175 (20)	1.55 (1.27-1.89)	<b>&lt;0.001</b>	–	0.17	1.94 (1.49-2.53)	<b>&lt;0.001</b>	–	0.10	39 (13)	105 (25)	31 (22)			
TNM															
I-II (low risk)	499 (58)									201 (67)	244 (58)	54 (39)			<b>&lt;0.001</b>
II-III (high risk)	363 (42)	1.58 (1.33-1.87)	<b>&lt;0.001<sup>b</sup></b>	–	–	3.02 (2.36-3.87)	<b>&lt;0.001<sup>b</sup></b>	–	–	99 (33)	180 (42)	84 (61)			
T-stage															
T1	42 (5)									28 (9)	13 (3)	1 (1)			<b>&lt;0.001</b>
T2	113 (13)									65 (22)	39 (9)	9 (7)			
T3	488 (57)									150 (50)	260 (61)	78 (56)			
T4a	179 (20)									43 (14)	93 (22)	43 (31)			
T4b	40 (5)	1.30 (1.15-1.46)	<b>&lt;0.001</b>	1.25 (1.08-1.44)	<b>0.003</b>	1.81 (1.51-2.16)	<b>&lt;0.001</b>	1.46 (1.17-1.82)	<b>0.001</b>	14 (5)	19 (5)	7 (6)			
N-stage															
N0	556 (65)									217 (73)	272 (64)	67 (49)			<b>&lt;0.001</b>
N1	218 (25)									66 (22)	105 (25)	47 (34)			
N2	84 (10)	1.38 (1.22-1.55)	<b>&lt;0.001</b>	1.31 (1.14-1.51)	<b>&lt;0.001</b>	1.96 (1.68-2.30)	<b>&lt;0.001</b>	1.58 (1.32-1.90)	<b>&lt;0.001</b>	16 (5)	45 (11)	23 (17)			
Site															
Colon	650 (75)									206 (69)	345 (81)	99 (72)			0.08
Rectum	212 (25)	0.93 (0.76-1.13)	0.44	–	–	0.96 (0.73-1.27)	0.78			94 (31)	79 (19)	39 (28)			
Differentiation															
Well/mod	775 (90)									271 (90)	379 (89)	125 (91)			0.95
Poor	87 (10)	1.36 (1.04-1.79)	<b>0.03</b>	–	0.46	1.61 (1.13-2.30)	<b>0.01</b>	–	0.87	29 (10)	45 (11)	13 (9)			
Venous invasion															
Absent	589 (68)									226 (75)	290 (69)	73 (53)			<b>&lt;0.001</b>
Present	273 (32)	1.38 (1.15-1.65)	<b>&lt;0.001</b>	–	0.18	1.86 (1.46-2.37)	<b>&lt;0.001</b>	1.34 (1.01-1.76)	<b>0.04</b>	74 (25)	134 (31)	65 (47)			
Tumour budding															
Absent	618 (72)									219 (73)	304 (72)	95 (69)			0.39
Present	244 (28)	1.04 (0.86-1.25)	0.70	–	–	1.33 (1.03-1.71)	<b>0.03</b>	–	0.15	81 (27)	120 (28)	43 (31)			
KRAS status (n=212)															
Wild-type	111 (52)									36 (55)	53 (50)	22 (55)			0.86
Mutant	101 (48)	1.16 (0.84-1.59)	0.37	–	–	1.08 (0.72-1.61)	0.71	–	–	29 (45)	54 (50)	18 (45)			
BRAF status (n=212)															
Wild-type	182 (86)									54 (83)	91 (85)	37 (93)			0.21
Mutant	30 (14)	1.03 (0.66-1.59)	0.90	–	–	0.91 (0.51-1.64)	0.76	–	–	11 (17)	16 (15)	3 (7)			
MMR															
Proficient	686 (82)									230 (78)	342 (83)	114 (84)			0.10
Deficient	155 (18)	0.99 (0.80-1.23)	0.94	–	–	0.80 (0.57-1.11)	0.18	–	–	64 (22)	69 (17)	22 (16)			
mGPS															
0	386 (55)									152 (59)	175 (52)	59 (54)			0.19
1	201 (29)									68 (27)	102 (30)	31 (28)			
2	115 (16)	1.59 (1.40-1.79)	<b>&lt;0.001</b>	1.52 (1.34-1.73)	<b>&lt;0.001</b>	1.69 (1.43-1.99)	<b>&lt;0.001</b>	1.59 (1.34-1.90)	<b>&lt;0.001</b>	37 (14)	59 (18)	19 (17)			

GMS										
0	300 (35)									-
1	424 (49)									-
2	138 (16)	1.24 (1.09-1.40)	<b>0.001</b>	1.24 (1.07-1.43)	<b>0.004</b>	1.76 (1.48-2.08)	<b>&lt;0.001</b>	1.53 (1.26-1.86)	<b>&lt;0.001</b>	-

<sup>a</sup>percentages rounded to nearest whole number and may not total 100%

<sup>b</sup>not included in multivariate model as T-stage and N-stage included separately

**Table 2. Survival for GMS according to low- and high- risk disease and location of cancer in the validation cohort (N=862).**

Group GMS category	Disease-free Survival					Relapse-free Survival				
	N	5-year DFS (%; SE)	Events (N=541)	HR (95% CI)	P	5-year RFS (%; SE)	Events (N=271)	HR (95% CI)	P	
Full cohort				<i>Trend</i>	<i>0.003</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	300	71 (3)	168	1.0 (reference)		83 (2)	61	1.0 (reference)		
1	424	58 (2)	281	1.30 (1.08-1.58)	<b>0.007</b>	70 (2)	141	1.82 (1.35-2.46)	<b>&lt;0.001</b>	
2	138	46 (4)	92	1.50 (1.16-1.93)	<b>0.002</b>	51 (4)	69	3.09 (2.19-4.36)	<b>&lt;0.001</b>	
TNM I-II (low-risk)				<i>Trend</i>	<i>0.89</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	201	73 (3)	113	1.0 (reference)		88 (2)	29	1.0 (reference)		
1	244	70 (3)	148	1.06 (0.83-1.35)	0.65	84 (2)	49	1.42 (0.90-2.25)	0.13	
2	54	57 (7)	29	1.06 (0.70-1.59)	0.79	63 (7)	21	3.24 (1.85-5.68)	<b>&lt;0.001</b>	
TNM II-III (high-risk)				<i>Trend</i>	<i>0.003</i>			<i>Trend</i>	<i>0.001</i>	
0	99	66 (5)	55	1.0 (reference)		72 (5)	32	1.0 (reference)		
1	180	43 (4)	133	1.67 (1.22-2.29)	<b>0.001</b>	51 (4)	92	1.95 (1.30-2.92)	<b>0.001</b>	
2	84	38 (5)	63	1.72 (1.19-2.47)	<b>0.003</b>	43 (6)	48	2.18 (1.39-3.41)	<b>0.001</b>	
Colon cancer				<i>Trend</i>	<i>0.004</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	206	72 (3)	113	1.0 (reference)		84 (3)	41	1.0 (reference)		
1	345	58 (3)	233	1.38 (1.10-1.73)	<b>0.005</b>	69 (3)	115	1.88 (1.32-2.68)	<b>0.001</b>	
2	99	45 (5)	67	1.57 (1.16-2.12)	<b>0.004</b>	51 (5)	49	3.15 (2.08-4.77)	<b>&lt;0.001</b>	
Rectal Cancer				<i>Trend</i>	<i>0.46</i>			<i>Trend</i>	<i>0.003</i>	
0	94	68 (5)	55	1.0 (reference)		80 (4)	20	1.0 (reference)		
1	79	62 (5)	48	1.07 (0.73-1.58)	0.72	72 (5)	26	1.66 (0.92-2.97)	0.09	
2	39	46 (8)	25	1.35 (0.84-2.17)	0.21	51 (8)	20	2.95 (1.58-5.48)	<b>0.001</b>	

Abbreviation: DFS, Disease-free survival; RFS, Relapse-free survival

**Table 3. Disease-free survival in the TransSCOT cohort and associations of clinicopathological features with GMS (N=2912).**

Clinicopathological characteristics	Disease-free survival					GMS category			
	N (%) <sup>a</sup>	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P	0 (n=383) N (%) <sup>a</sup>	1 (n=1867) N (%)	2 (n=663) N (%)	Pearson X <sup>2</sup>
Gender									
Female	1135 (39)					156 (41)	716 (38)	263 (40)	0.63
Male	1778 (61)	0.96 (0.83-1.11)	0.60	-	-	227 (59)	1151 (62)	400 (60)	
T-stage									
T1	78 (3)					19 (5)	55 (3)	4 (1)	<0.001
T2	250 (9)					59 (15)	160 (9)	31 (5)	
T3	1696 (58)					227 (60)	1131 (61)	338 (51)	
T4	889 (30)	1.70 (1.51-1.91)	<0.001	1.74 (1.53-1.98)	<0.001	78 (20)	521 (28)	290 (43)	
N-stage									
N0	556 (19)					79 (21)	362 (19)	115 (17)	0.002
N1	1663 (57)					224 (58)	1086 (58)	353 (53)	
N2	694 (24)	1.75 (1.57-1.96)	<0.001	1.73 (1.48-2.03)	<0.001	80 (21)	419 (22)	195 (29)	
Site									
Colon	2402 (82)					310 (81)	1522 (81)	570 (86)	0.021
Rectum	511 (18)	0.69 (0.56-0.85)	<0.001	-	0.12	73 (19)	345 (19)	93 (14)	
Risk Group									
T1-3/N1 (lower-risk)	1284 (55)					202 (66)	861 (57)	221 (40)	<0.001
T4 and/or N2 (higher-risk)	1073 (45)	2.45 (2.08-2.88)	<0.001	-	0.13	102 (34)	644 (43)	327 (60)	
Adjuvant therapy									
FOLFOX	846 (29)					120 (31)	526 (28)	200 (30)	0.36
CAPOX	2067 (71)	1.08 (0.92-1.27)	0.32	-	-	263 (69)	1341 (72)	463 (70)	
Treatment time									
3 months	1469 (50)					194 (51)	956 (51)	319 (48)	0.39
6 months	1444 (50)	1.01 (0.88-1.16)	0.85	-	-	180 (49)	911 (49)	344 (52)	
GMS									
0	300 (35)					-	-	-	-
1	424 (49)					-	-	-	
2	138 (16)	1.48 (1.32-1.68)	<0.001	1.28 (1.12-1.47)	<0.001	-	-	-	

<sup>a</sup>percentages rounded to nearest whole number and may not total 100%



0	386 (55)								
1	201 (29)								
2	115 (16)	1.58 (1.40-1.78)	<0.001	1.51 (1.33-1.71)	<0.001	1.75 (1.47-2.08)	<0.001	1.61 (1.35-1.93)	<0.001
GMS									
0	300 (35)								
1	424 (49)								
2	138 (16)	1.23 (1.09-1.39)	0.001	1.21 (1.05-1.39)	0.009	1.88 (1.56-2.25)	<0.001	1.63 (1.32-2.00)	<0.001

<sup>a</sup>percentages rounded to nearest whole number and may not total 100%

<sup>b</sup>not included in multivariate model as T-stage and N-stage included separately

**Supplementary Table S2. Overall and Cancer-Specific Survival for GMS according to low- and high-risk disease and location of cancer in the validation cohort (N=862).**

Group GMS category	Overall Survival					Cancer-specific Survival				
	N	5-year OS (%; SE)	Events (N=554)	HR (95% CI)	P	5-year CSS (%; SE)	Events (N=235)	HR (95% CI)	P	
Full cohort				<i>Trend</i>	<i>0.003</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	300	69 (3)	176	1.0 (reference)		87 (2)	48	1.0 (reference)		
1	424	58 (2)	282	1.27 (1.05-1.53)	<b>0.015</b>	72 (2)	123	2.00 (1.43-2.79)	<b>&lt;0.001</b>	
2	138	48 (4)	96	1.50 (1.17-1.93)	<b>0.001</b>	55 (4)	64	3.55 (2.44-5.16)	<b>&lt;0.001</b>	
TNM I-II (low-risk)				<i>Trend</i>	<i>0.79</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	201	71 (3)	115	1.0 (reference)		93 (2)	20	1.0 (reference)		
1	244	68 (3)	152	1.08 (0.85-1.38)	0.52	86 (2)	42	1.74 (1.02-2.97)	<b>0.04</b>	
2	54	61 (7)	31	1.09 (0.73-1.63)	0.66	66 (7)	19	3.94 (2.10-7.39)	<b>&lt;0.001</b>	
TNM II-III (high-risk)				<i>Trend</i>	<i>0.008</i>			<i>Trend</i>	<i>0.001</i>	
0	99	64 (5)	61	1.0 (reference)		74 (5)	28	1.0 (reference)		
1	180	43 (4)	130	1.50 (1.10-2.03)	<b>0.01</b>	54 (4)	81	1.91 (1.24-2.93)	<b>0.003</b>	
2	84	40 (5)	65	1.67 (1.18-2.38)	<b>0.004</b>	47 (6)	45	2.34 (1.46-3.76)	<b>&lt;0.001</b>	
Colon cancer				<i>Trend</i>	<i>0.02</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	206	72 (3)	120	1.0 (reference)		87 (2)	33	1.0 (reference)		
1	345	57 (3)	232	1.29 (1.04-1.61)	<b>0.02</b>	72 (3)	97	1.94 (1.30-2.87)	<b>0.001</b>	
2	99	49 (5)	70	1.49 (1.11-2.00)	<b>0.008</b>	57 (5)	44	3.36 (2.14-5.27)	<b>&lt;0.001</b>	
Rectal Cancer				<i>Trend</i>	<i>0.21</i>			<i>Trend</i>	<i>&lt;0.001</i>	
0	94	62 (5)	56	1.0 (reference)		86 (4)	15	1.0 (reference)		
1	79	59 (6)	50	1.13 (0.77-1.65)	0.54	71 (5)	26	2.23 (1.18-4.20)	<b>0.014</b>	
2	39	46 (8)	26	1.51 (0.95-2.41)	0.08	50 (8)	20	4.07 (2.08-7.96)	<b>0.001</b>	

Abbreviation: OS, Overall survival; CSS, Cancer-specific survival

**Supplementary Table S3. GMS and recurrence location (n=833).**

Recurrence location	N	GMS						Pearson $\chi^2$
		0 (n=293)		1 (n=424)		2 (n=138)		
		N (%) <sup>a</sup>		N (%)		N (%)		
None	630	250 (85)		304 (74)		76 (59)	<b>&lt;0.001</b>	
Local	35	8 (3)		10 (2)		17 (13)		
Distant	168	35 (12)		97 (24)		36 (28)		

<sup>a</sup>total percentage may not equal 100 as rounded to nearest whole number



**Supplementary Table S4. Univariate RFS for immune cell densities per tumour location and associations between GMS and CD3, CD8 and composite CD3/CD8 score (N=208).**

Group GMS category	Relapse-free Survival					GMS						
	N	5-year RFS (%; SE)	Events (N=67)	HR (95% CI)	P	0 (n=74) N (%) <sup>a</sup>		1 (n=96) N (%)		2 (n=38) N (%)		Pearson X <sup>2</sup>
GMS				<i>Trend</i>	<0.001							
0	74	81 (5)	16	0.38 (0.33-0.67)	<b>0.001</b>	-	-	-	-	-	-	
1	96	72 (5)	29	0.27 (0.14-0.51)	<b>&lt;0.001</b>	-	-	-	-	-	-	
2	38	42 (8)	22	1.0 (reference)		-	-	-	-	-	-	
CD3 Invasive margin				<i>Trend</i>	<0.001							
Low	117	59 (5)	49	1.0 (reference)		17	(23)	75	(78)	25	(66)	<b>&lt;0.001</b>
High	91	84 (4)	18	0.38 (0.22-0.65)	<b>&lt;0.001</b>	57	(77)	21	(22)	13	(34)	
CD3 Stroma				<i>Trend</i>	<0.001							
Low	106	57 (5)	48	1.0 (reference)		25	(34)	57	(59)	24	(63)	<b>&lt;0.001</b>
High	102	83 (4)	19	0.33 (0.19-0.56)	<b>&lt;0.001</b>	49	(66)	39	(41)	14	(37)	
CD3 Cancer nests				<i>Trend</i>	<0.001							
Low	139	60 (4)	60	1.0 (reference)		33	(45)	71	(74)	35	(92)	<b>&lt;0.001</b>
High	69	90 (4)	7	0.18 (0.08-0.39)	<b>&lt;0.001</b>	41	(55)	25	(26)	3	(8)	
CD8 Invasive margin				<i>Trend</i>	0.001							
Low	122	62 (5)	49	1.0 (reference)		28	(38)	69	(72)	25	(66)	<b>&lt;0.001</b>
High	86	82 (4)	18	0.43 (0.25-0.74)	<b>0.002</b>	46	(62)	27	(28)	13	(34)	
CD8 Stroma				<i>Trend</i>	0.001							
Low	157	64 (4)	60	1.0 (reference)		45	(61)	82	(85)	30	(79)	<b>0.006</b>
High	51	88 (5)	7	0.30 (0.14-0.66)	<b>0.003</b>	29	(39)	14	(15)	8	(21)	
CD8 Cancer nests				<i>Trend</i>	<0.001							
Low	149	61 (4)	61	1.0 (reference)		42	(57)	72	(75)	35	(92)	<b>&lt;0.001</b>
High	59	93 (4)	6	0.19 (0.08-0.45)	<b>&lt;0.001</b>	32	(43)	24	(25)	3	(8)	
Composite CD3/CD8 score				<i>Trend</i>	<0.001							
0	72	55 (6)	33	1.0 (reference)		10	(14)	48	(50)	14	(37)	<b>&lt;0.001</b>
1	36	55 (9)	16	0.96 (0.53-1.74)	0.88	6	(8)	20	(21)	10	(26)	
2	34	82 (7)	8	0.43 (0.20-0.93)	<b>0.03</b>	17	(23)	11	(12)	6	(16)	
3	38	79 (7)	10	0.43 (0.21-0.88)	<b>0.02</b>	23	(31)	9	(9)	6	(16)	
4	28	NA	0	NA	NA	18	(24)	8	(8)	2	(5)	

Abbreviation: RFS, Relapse-free survival; HR, hazard ratio; CI, confidence interval; NA, not applicable, incalculable as no terminal events in this category

<sup>a</sup>total percentage may not equal 100 as rounded to nearest whole number

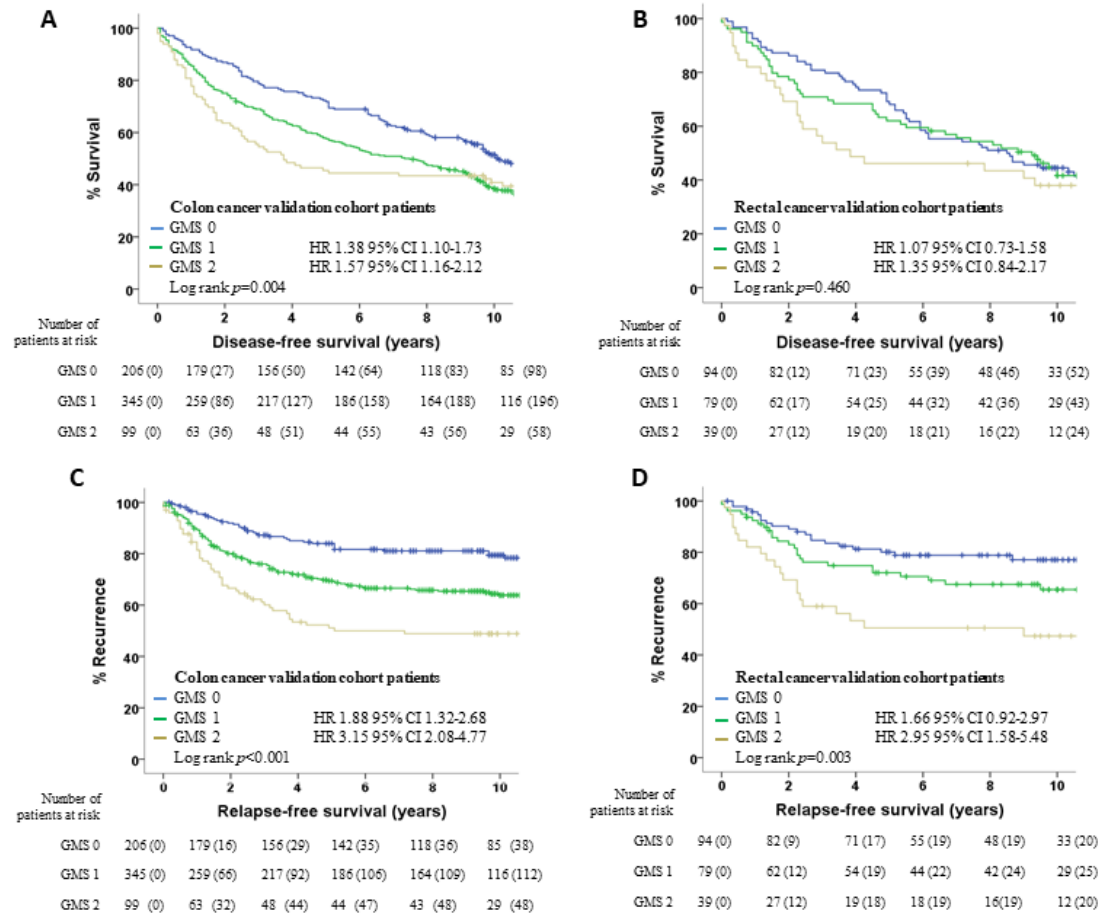
**Supplementary Table S5. Interactions between GMS and chemotherapy Type or duration (N=2912).**

	GMS category			<i>Interaction P</i>
	<b>0 (N)</b>	<b>1 (N)</b>	<b>2 (N)</b>	
<b>Full Cohort (n=2912)</b>				
Chemotherapy Type	383	1867	663	<b>0.013</b>
FOLFOX	120	526	200	
CAPOX	263	1341	463	
Chemotherapy Duration	383	1867	663	0.64
<b>Lower Risk Stage III Patients (T1-3/N1; n=1284)</b>				
Chemotherapy Type				<b>0.005</b>
Chemotherapy Duration	202	861	221	0.82
<b>Higher Risk Stage III Patients (T4 and/or N2; n=1073)</b>				
Chemotherapy Type				0.61
Chemotherapy Duration	102	643	327	0.84

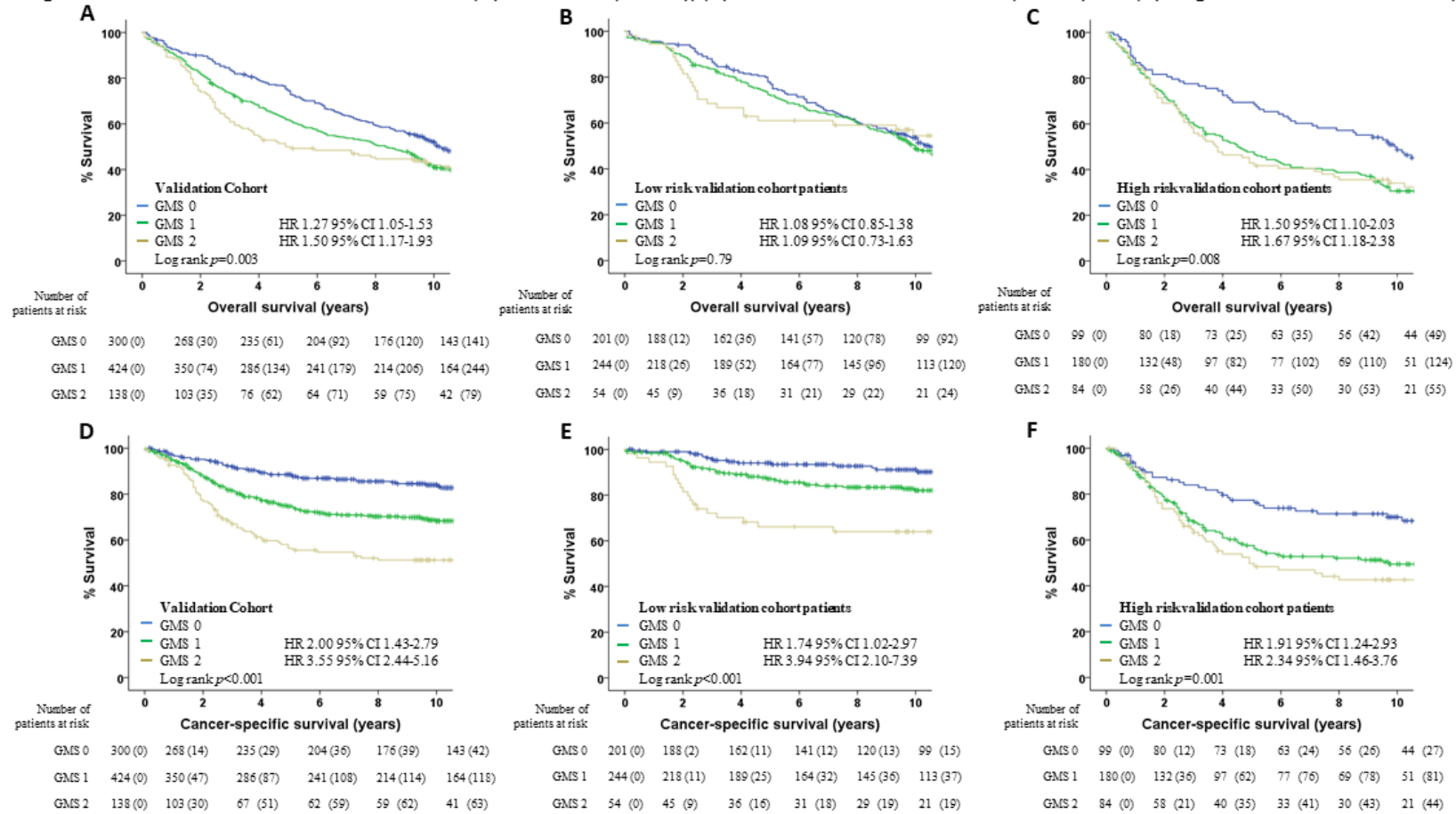
**Supplementary Table S6. Association between chemotherapy type and duration in GMS 0 subgroup (N=383).**

	Chemotherapy type		Pearson $X^2$
	FOLFOX N (%)	CAPOX N (%)	
<b>GMS 0 (n=383)</b>			
Chemotherapy duration			<i>0.11</i>
<b>3-months</b>	68 (57)	52 (48)	
<b>6-months</b>	52 (43)	137 (52)	

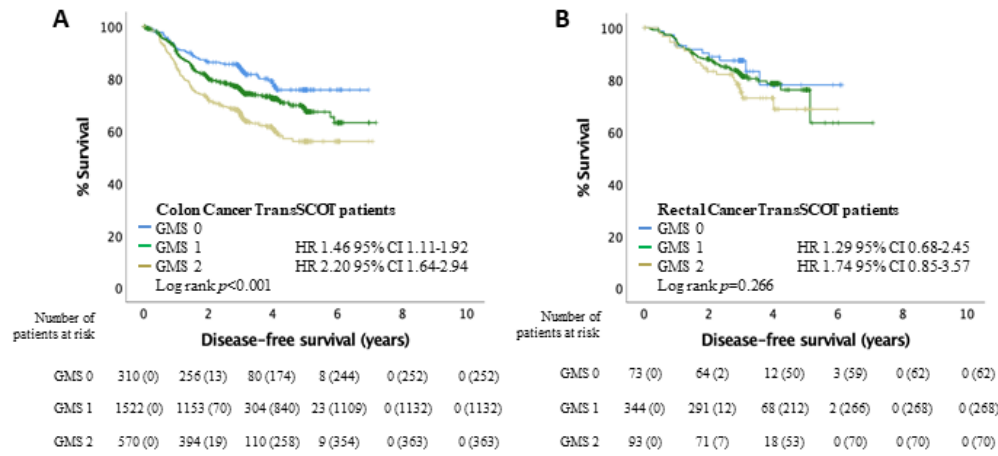
**Figure S1. GMS can stratify RFS in colon and rectal cancer patients and DFS in colon cancer patients within the validation cohort.** (A, B) Kaplan Meier curves showing associations between GMS and DFS in patients with (A) colon ( $n=650$ ) or (B) rectal cancer ( $n=212$ ). (C, D) Kaplan Meier curves showing associations between GMS and RFS in patients with (C) colon ( $n=650$ ) or (D) rectal cancer ( $n=212$ ).



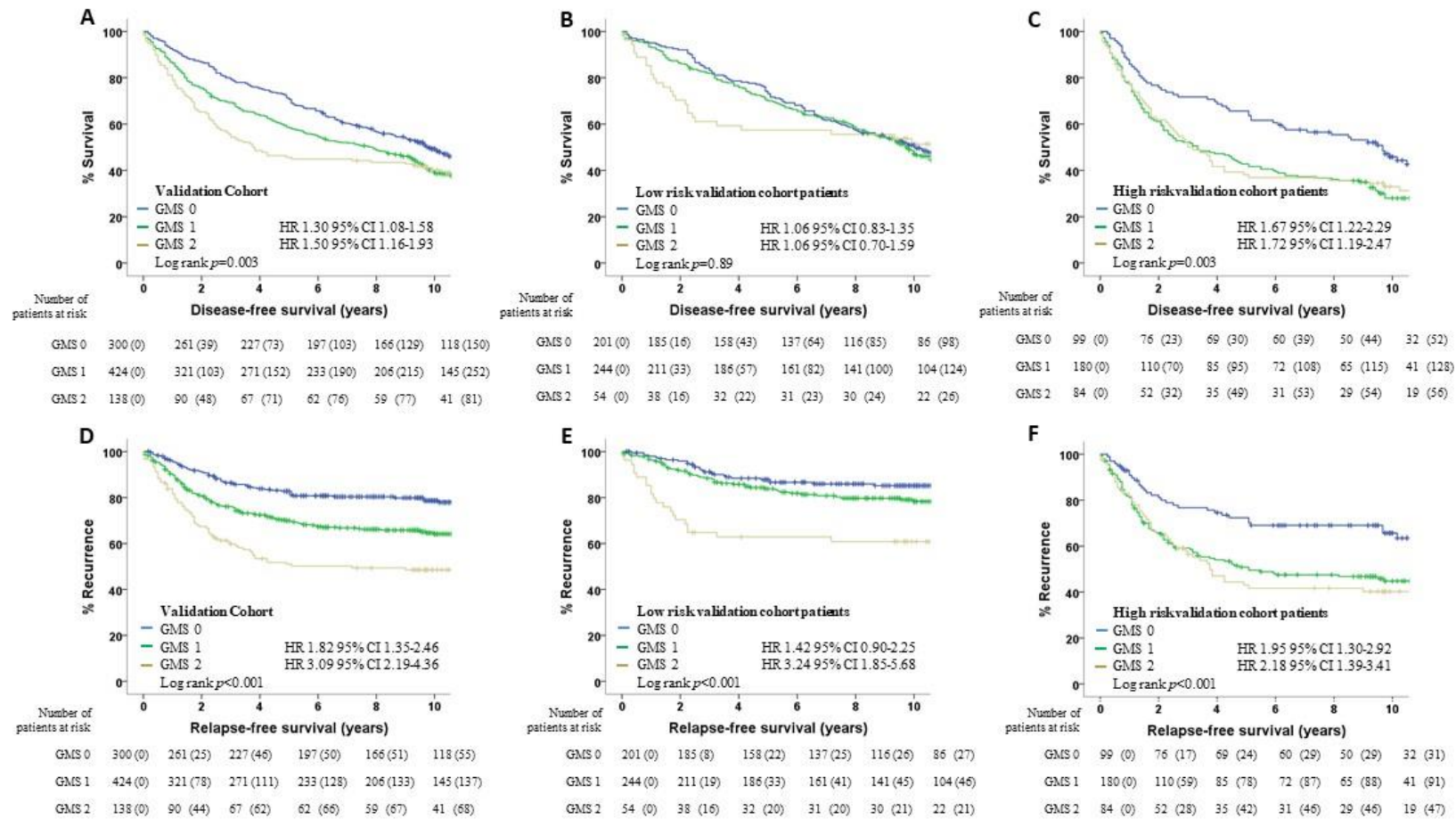
**Figure S2. GMS can stratify overall and cancer-specific survival according to disease risk in the validation cohort.** (A-C) Kaplan Meier curve showing associations between GMS and OS in the (A) full cohort (n=862), (B) “low-risk” colorectal cancer (n=499) and (C) “high-risk” colorectal cancer (n=363). (D-E) Kaplan Meier curve showing associations between GMS and CSS in the (A) full cohort (n=862), (B) “low-risk” colorectal cancer (n=499) and (C) “high-risk” colorectal cancer (n=363).



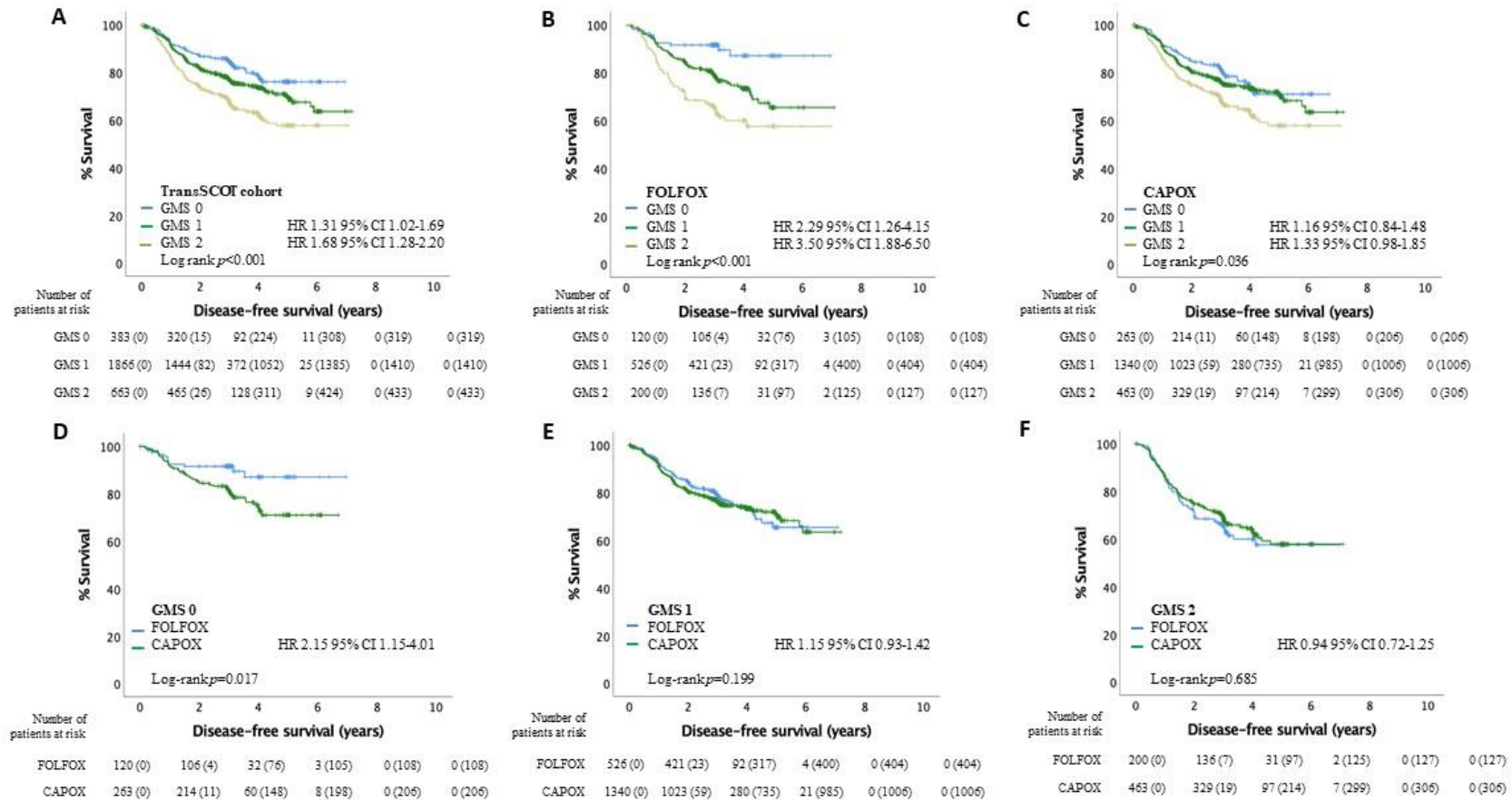
**Figure S3. GMS can stratify patient prognosis for colon cancer patients within the TransSCOT cohort.** (A, B) Kaplan Meier curves showing associations between GMS and DFS in patients with (A) colon ( $n=2402$ ) or (B) rectal cancer ( $n=510$ ).



**Figure 1. GMS can stratify recurrence and survival according to disease risk in the validation cohort.** (A-C) Kaplan Meier curve showing associations between GMS and DFS in the (A) full cohort ( $n=862$ ), (B) “low-risk” colorectal cancer ( $n=499$ ) and (C) “high-risk” colorectal cancer ( $n=363$ ). (D-E) Kaplan Meier curve showing associations between GMS and RFS in the (A) full cohort ( $n=862$ ), (B) “low-risk” colorectal cancer ( $n=499$ ) and (C) “high-risk” colorectal cancer ( $n=363$ ).



**Figure 2. GMS can identify patient response to adjuvant chemotherapy within the TransSCOT cohort.** (A) Kaplan Meier curve showing associations between GMS and DFS in the full cohort (n=2912). (B,C) Kaplan Meier curves showing associations between GMS and DFS in patients receiving (B) FOLFOX (n=846) or (C) CAPOX (n=2066) adjuvant chemotherapy. (D-F) Kaplan Meier curves showing associations between chemotherapy type and DFS in patients with (D) GMS 0 (n=383), (E) GMS 1 (n=1866) or (F) GMS 2 (n=663).





**Figure 3. GMS, prognosis and response to adjuvant chemotherapy in low- and high-risk stage III patients from the TransSCOT cohort (n=2356).** (A,D) Kaplan Meier curves showing associations between GMS and DFS in (A) low-risk (n=1284) and (B) high-risk stage III patients (n=1072). (B,E) Kaplan Meier curves showing associations between GMS and DFS in (B) low-risk (n=374) and (E) high-risk (n=336) stage III patients receiving FOLFOX adjuvant chemotherapy. (C,F) Kaplan Meier curves showing associations between chemotherapy type and DFS in GMS 0 patients within the (C) low-risk (n=202) and (F) high-risk (n=102) stage III groups.

