Supplemental Data

eTable1. Prognostic factors in cox proportional hazard model(Overall survival)

	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	p	HR	95%CI	P
Group			<0.001			<0.001
Initial pCRC	1			1		
Second pCRC	1.384	1.358-1.410		1.102	1.081-1.123	
Gender			<0.001			<0.001
Male	1			1		
Female	0.962	0.954-0.970		0.845	0.838-0.852	
Age at diagnosis			<0.001			<0.001
<50	1			1		
50-59	1.034	1.014-1.054		1.158	1.136-1.180	
60-69	1.352	1.328-1.376		1.590	1.561-1.618	
70-79	1.972	1.939-2.006		2.468	2.426-2.512	
80-89	2.984	2.932-3.036		3.913	3.841-3.986	
≥90	4.393	4.281-4.508		5.770	5.617-5.928	
Race			<0.001			<0.001
White	1			1		
Black	1.100	1.085-1.115		1.224	1.207-1.241	
Other†	0.802	0.789-0.815		0.847	0.834-0.861	
Unknown	0.257	0.218-0.302		0.345	0.293-0.406	
Primary Site			<0.001			<0.001
Right colon	1			1		
Left colon	0.856	0.848-0.865		0.997	0.987-1.007	
Rectum	0.862	0.853-0.871		1.041	1.029-1.054	
Histology			<0.001			<0.001
AC	1			1		
MC	1.206	1.191-1.223		1.017	1.004-1.031	
SRCC	2.197	2.120-2.276		1.313	1.266-1.361	
Other	2.004	1.924-2.087		1.051	1.009-1.096	
Grade‡			<0.001			<0.001
Grade I	1			1		
Grade II	1.230	1.209-1.251		1.040	1.022-1.057	
Grade III	1.898	1.864-1.934		1.225	1.202-1.249	
Grade IV	2.070	1.996-2.148		1.340	1.291-1.391	
Unknown	1.807	1.767-1.847		1.093	1.068-1.119	
pT			<0.001			<0.001
Tis	0.469	0.449-0.489		0.589	0.563-0.615	
T1	0.521	0.512-0.530		0.650	0.638-0.662	
T2	0.656	0.647-0.666		0.748	0.737-0.759	
T3	1			1		

T4a	1.539	1.515-1.563		1.383	1.361-1.405	
T4b	2.127	2.092-2.163		1.934	1.901-1.967	
Unknown	5.368	5.306-5.431		2.293	2.253-2.334	
pN			<0.001			<0.001
N0	1			1		
N1a	1.411	1.391-1.431		1.384	1.364-1.405	
N1b	1.782	1.759-1.806		1.677	1.654-1.700	
N2a	2.384	2.350-2.418		2.152	2.119-2.185	
N2b	3.498	3.449-3.548		3.006	2.959-3.054	
Unknown	8.621	8.493-8.750		2.118	2.060-2.177	
pM			<0.001			<0.001
M0	1			1		
M1	3.593	3.560-3.627		1.868	1.842-1.894	
Surgery			<0.001			<0.001
None/Unknown	1			1		
Performed	0.159	0.157-0.162		0.537	0.522-0.552	
Radiotherapy sequence			<0.001			<0.001
None/Unknown	1			1		
Before surgery	0.625	0.611-0.639		1.063	1.037-1.090	
After surgery	0.903	0.888-0.919		1.061	1.041-1.082	
Chemotherapy			<0.001			<0.001
None/Unknown	1			1		
Performed	1.045	1.036-1.054		0.769	0.761-0.777	

Abbreviation: AC Adenocarcinoma, MC Mucinous adenocarcinoma, SRCC Signet ring cell carcinoma

† other=American Indian/AK Native, Asian/Pacific Islander, according to SEER

‡ grade I = well differentiated; grade II = moderately differentiated; grade III = poorly differentiated; grade IV = undifferentiated; anaplastic
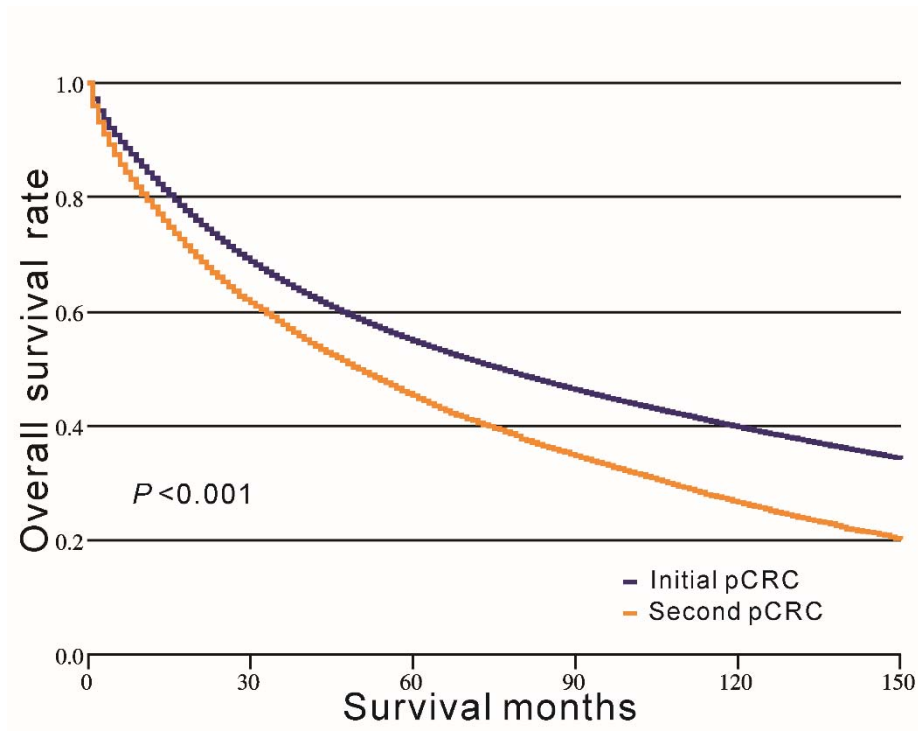
eFigure 1 Kaplan-Meier comparison of overall survival among patients with initial pCRC and second pCRC.

Figure 2 Kaplan-Meier comparison of overall survival among patients with initial pCRC and second pCRC stratified by primary site.

(A) Patients with right-sided colon cancer (initial pCRC vs. second pCRC); (B) Patients with left-sided colon cancer (initial pCRC vs. second pCRC); (C) Patients with rectum cancer (initial pCRC vs. second pCRC).
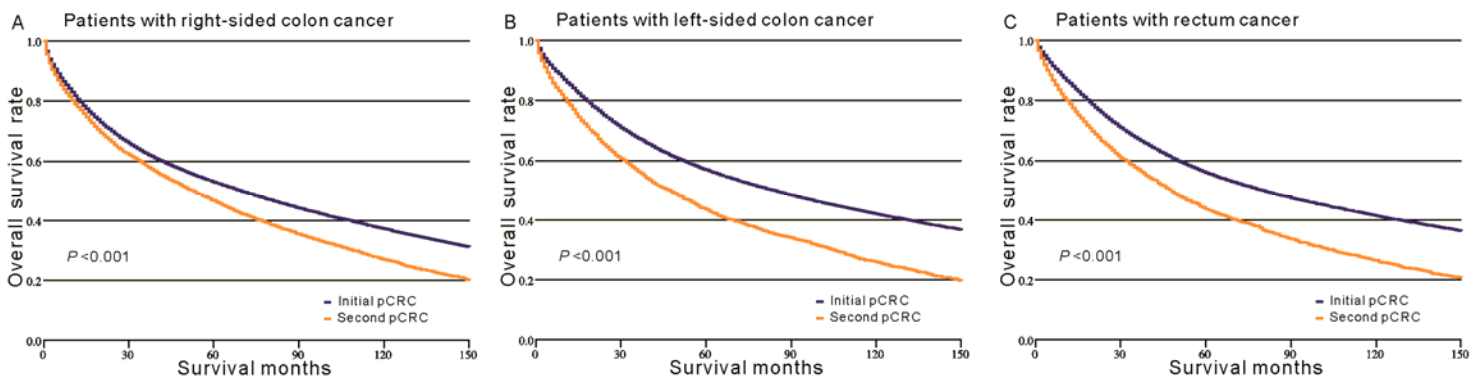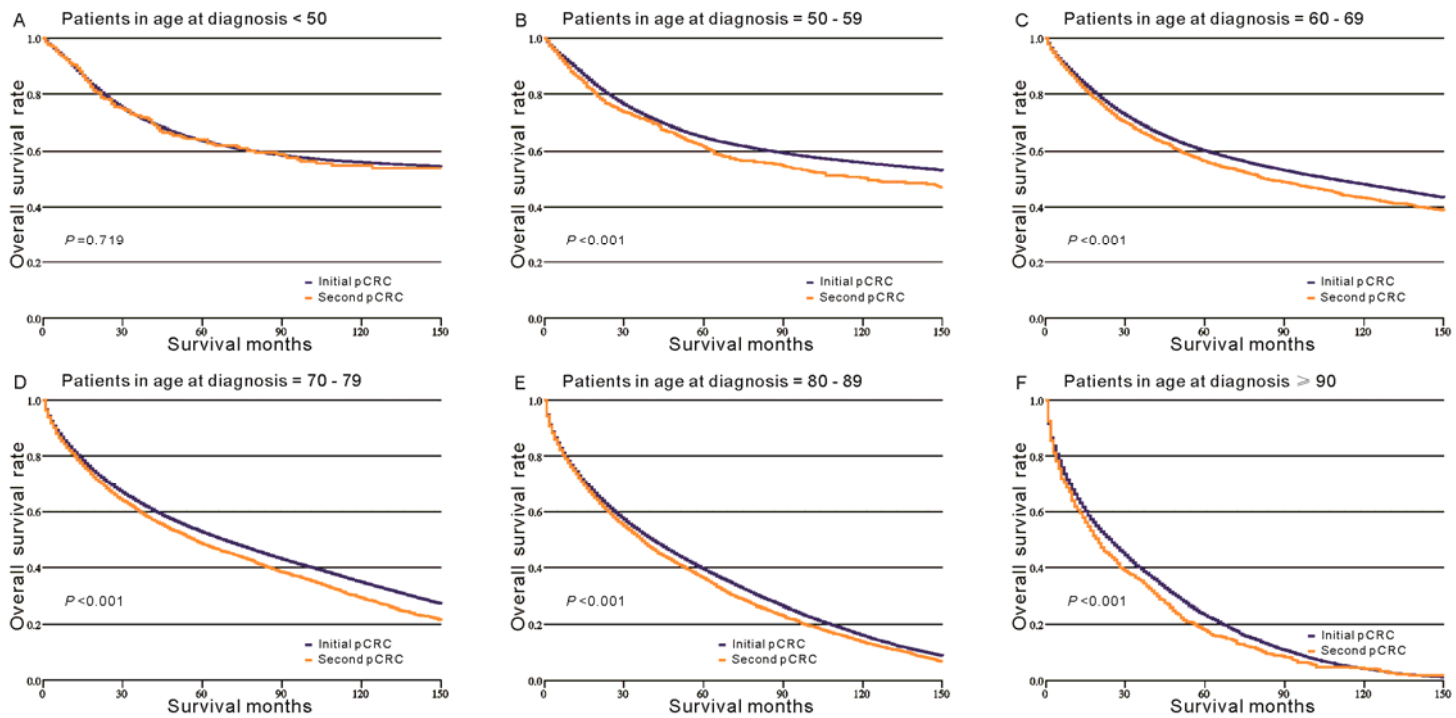
Figure 3 Kaplan-Meier comparison of overall survival among patients with initial pCRC and second pCRC stratified by age at diagnosis.

(A) Patients in age at diagnosis > 50 (initial pCRC vs. second pCRC); (B) Patients in age at diagnosis = 50 - 59 (initial pCRC vs. second pCRC); (C) Patients in age at diagnosis = 60 - 69 (initial pCRC vs. second pCRC); (D) Patients in age at diagnosis = 70 - 79 (initial pCRC vs. second pCRC); (E) Patients in age at diagnosis = 80 - 89 (initial pCRC vs. second pCRC); (F) Patients in age at diagnosis ⩾ 90 (initial pCRC vs. second pCRC).
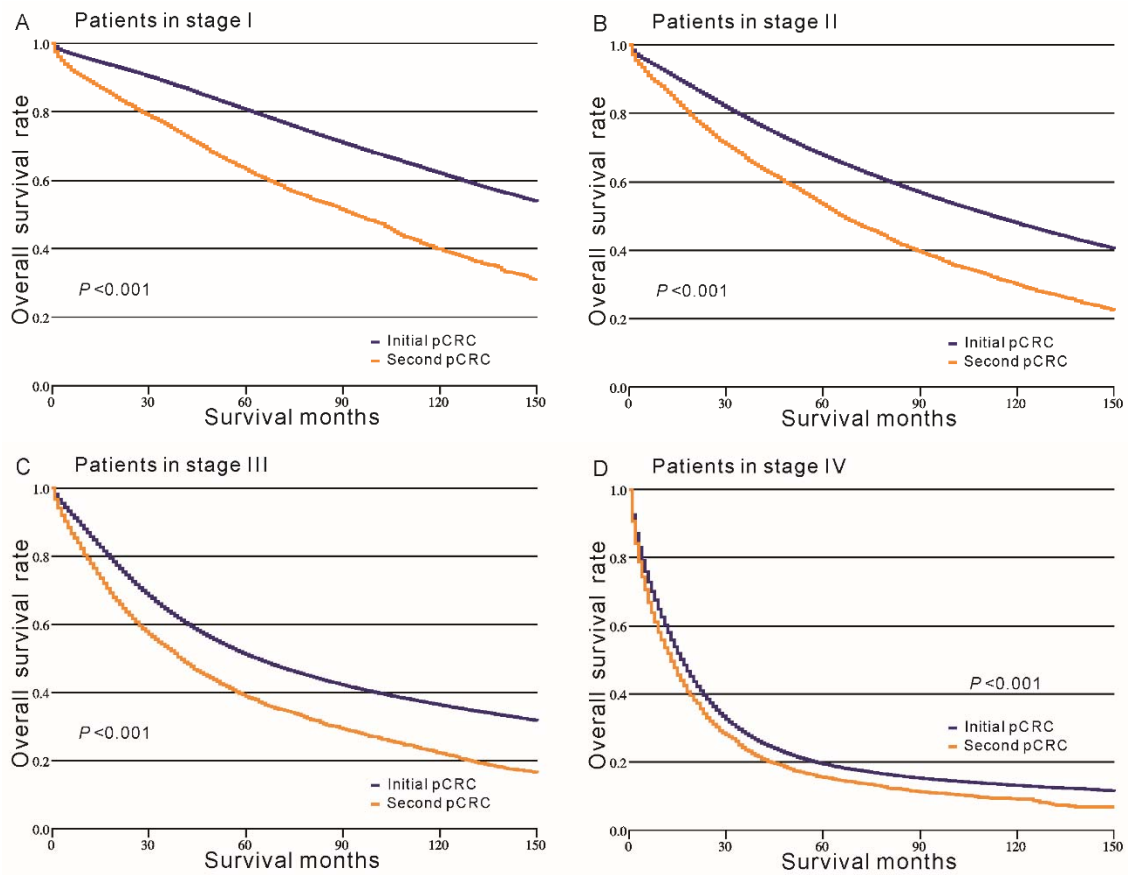
Figure 4 Kaplan-Meier comparison of overall survival among patients with initial pCRC and second pCRC stratified by pTNM stage.

(A) Patients in stage I (initial pCRC vs. second pCRC); (B) Patients in stage II (initial pCRC vs. second pCRC); (C) Patients in stage III (initial pCRC vs. second pCRC); (D) Patients in stage IV (initial pCRC vs. second pCRC).

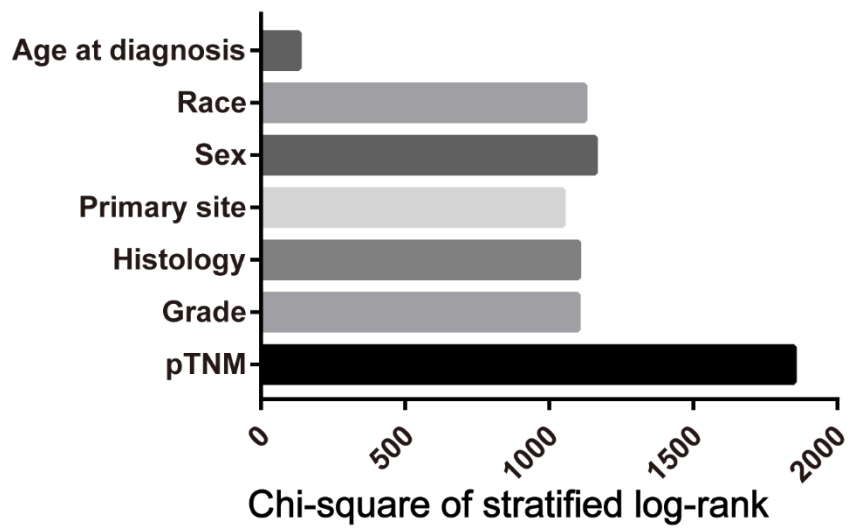**Figure 5 Chi-square of OS log rank after stratified by pTNM stage, grade, histology, primary site, sex, race and age at diagnosis.** The Chi-square for Age at diagnosis was lowest.

Groups for surgical patients with rectum cancer(cases)   Hazard ratio(95% CI)   P value for interaction

None vs Postoperative radiotherapy for patients in stage I
Initial primary(16311/708)   1.080(0.992,1.171)
Second primary(926/60)   0.883(0.662,1.178)   0.414

None vs Preoperative radiotherapy for patients in stage I
Initial primary(16311/3239)   0.977(0.826,1.157)
Second primary(926/94)   0.607(0.326,1.128)   0.647

None vs Postoperative radiotherapy for patients in stage II
Initial primary(10777/4892)   1.032(1.001,1.065)
Second primary(668/123)   0.944(0.815,1.092)   0.210

None vs Preoperative radiotherapy for patients in stage II
Initial primary(10777/8980)   0.948(0.877,1.024)
Second primary(668/300)   0.729(0.532,0.997)   0.176

None vs Postoperative radiotherapy for patients in stage III
Initial primary(12933/9425)   0.976(0.957,0.996)
Second primary(529/172)   0.990(0.880,1.113)   0.750

None vs Preoperative radiotherapy for patients in stage III
Initial primary(12933/6170)   1.056(1.003,1.111)
Second primary(529/148)   0.890(0.665,1.191)   0.170

None vs Chemotherapy for patients in stage I
Initial primary(16415/3843)   0.995(0.895,1.106)
Second primary(931/149)   1.489(0.970,2.287)   0.225

None vs Chemotherapy for patients in stage II
Initial primary(10225/14424)   0.721(0.685,0.759)
Second primary(612/479)   0.738(0.590,0.923)   0.436

None vs Chemotherapy for patients in stage III
Initial primary(8161/20367)   0.720(0.693,0.748)
                                                              0.653(0.539,0.792)   0.550

0.5   1   1.5   2   3

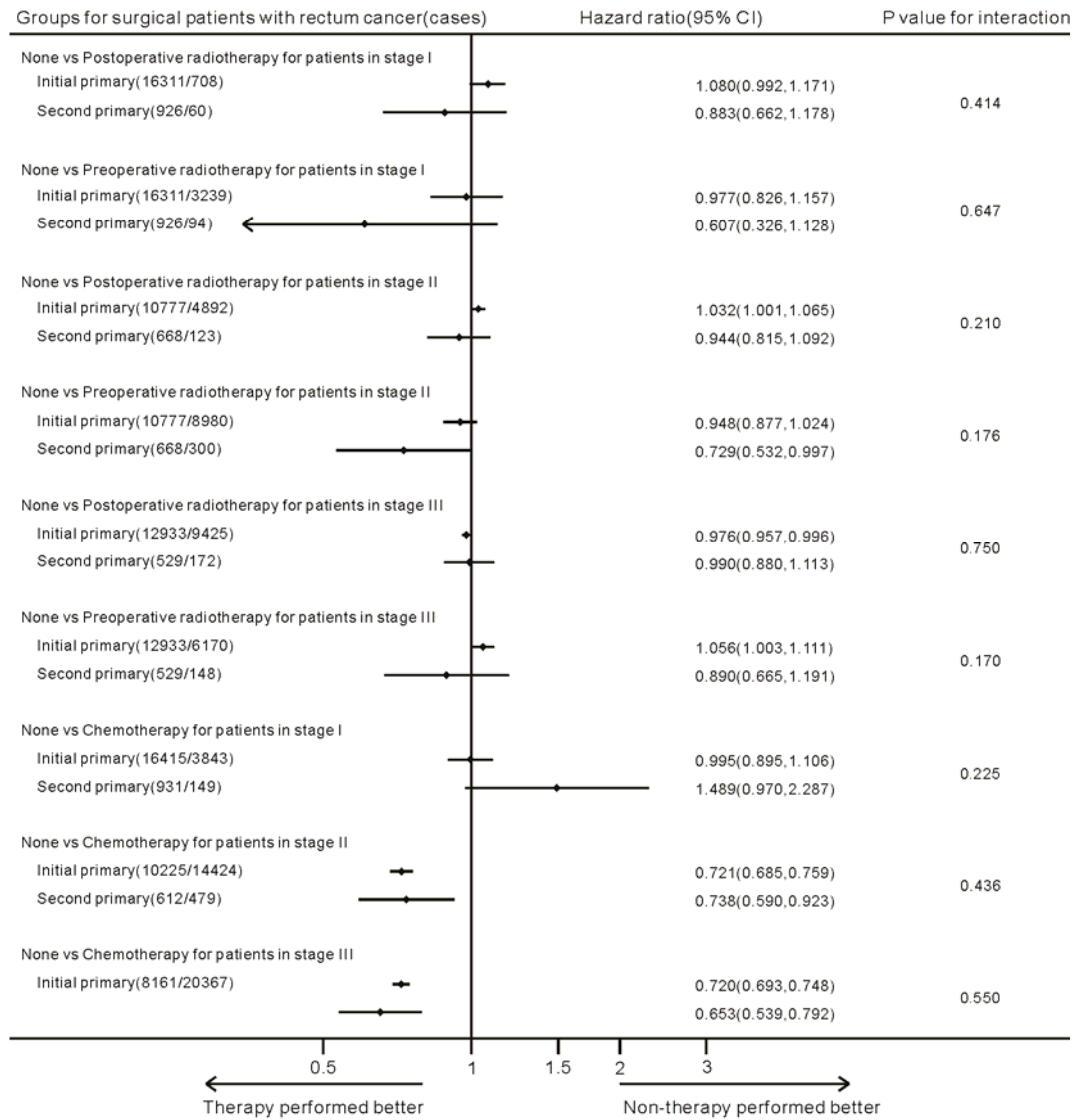Therapy performed better   Non-therapy performed better

Figure 6 Forest plot of Hazard ratios (HR) and 95% CI in OS different subgroups (Cox proportional hazards model analysis) and interaction comparison between patients with initial and second primary surgical rectum cancer.

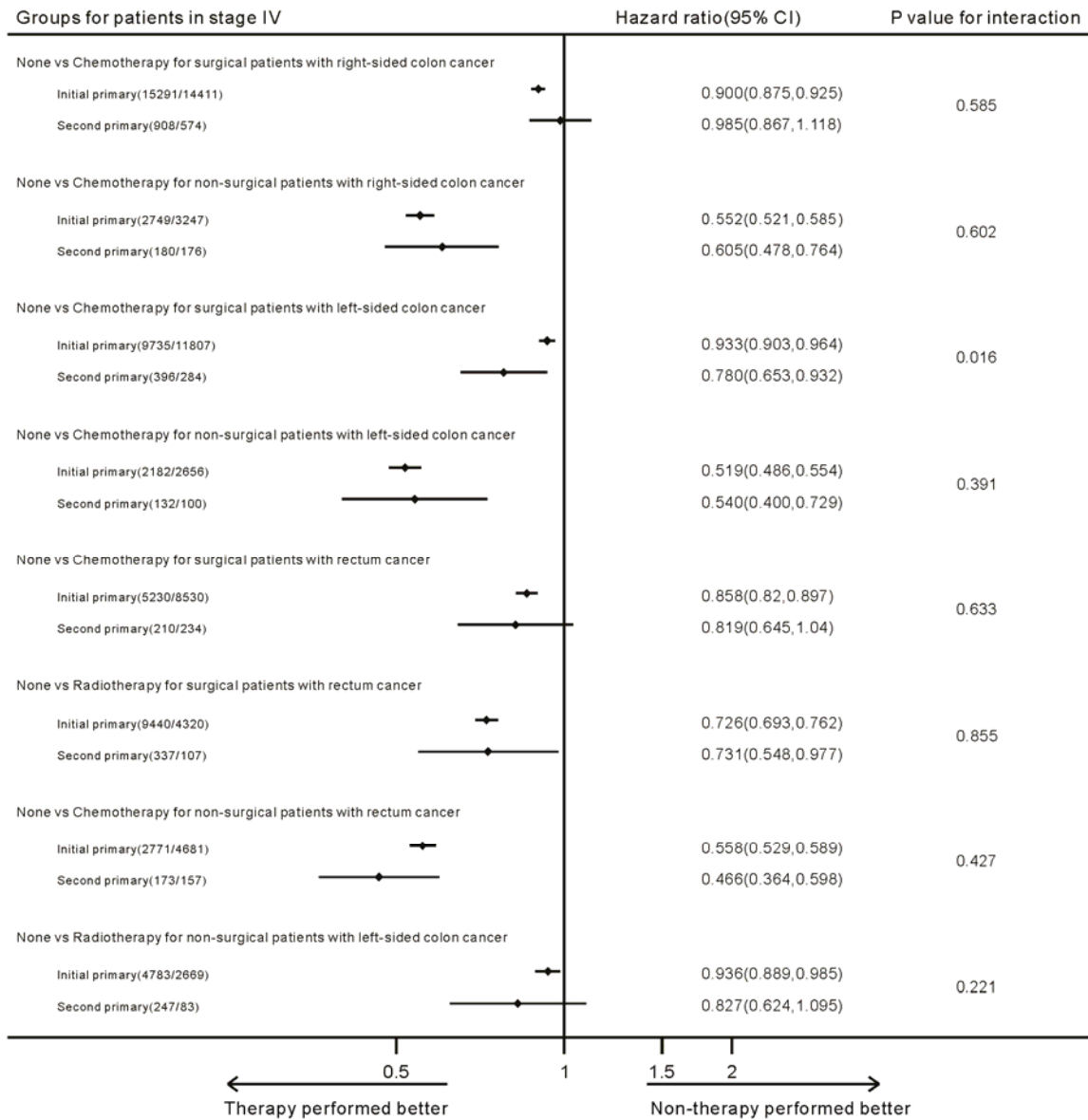| Groups for patients in stage IV	Hazard ratio(95% CI)	P value for interaction
None vs Chemotherapy for surgical patients with right-sided colon cancer		
Initial primary(15291/14411)	0.900(0.875,0.925)	0.585
Second primary(908/574)	0.985(0.867,1.118)	
None vs Chemotherapy for non-surgical patients with right-sided colon cancer		
Initial primary(2749/3247)	0.552(0.521,0.585)	0.602
Second primary(180/176)	0.605(0.478,0.764)	
None vs Chemotherapy for surgical patients with left-sided colon cancer		
Initial primary(9735/11807)	0.933(0.903,0.964)	0.016
Second primary(396/284)	0.780(0.653,0.932)	
None vs Chemotherapy for non-surgical patients with left-sided colon cancer		
Initial primary(2182/2656)	0.519(0.486,0.554)	0.391
Second primary(132/100)	0.540(0.400,0.729)	
None vs Chemotherapy for surgical patients with rectum cancer		
Initial primary(5230/8530)	0.858(0.82,0.897)	0.633
Second primary(210/234)	0.819(0.645,1.04)	
None vs Radiotherapy for surgical patients with rectum cancer		
Initial primary(9440/4320)	0.726(0.693,0.762)	0.855
Second primary(337/107)	0.731(0.548,0.977)	
None vs Chemotherapy for non-surgical patients with rectum cancer		
Initial primary(2771/4681)	0.558(0.529,0.589)	0.427
Second primary(173/157)	0.466(0.364,0.598)	
None vs Radiotherapy for non-surgical patients with left-sided colon cancer		
Initial primary(4783/2669)	0.936(0.889,0.985)	0.221
Second primary(247/83)	0.827(0.624,1.095)	

Figure 7 Forest plot of Hazard ratios (HR) and 95% CI in OS different subgroups (Cox proportional hazards model analysis) and interaction comparison between patients in stage IV with initial and second primary CRC.
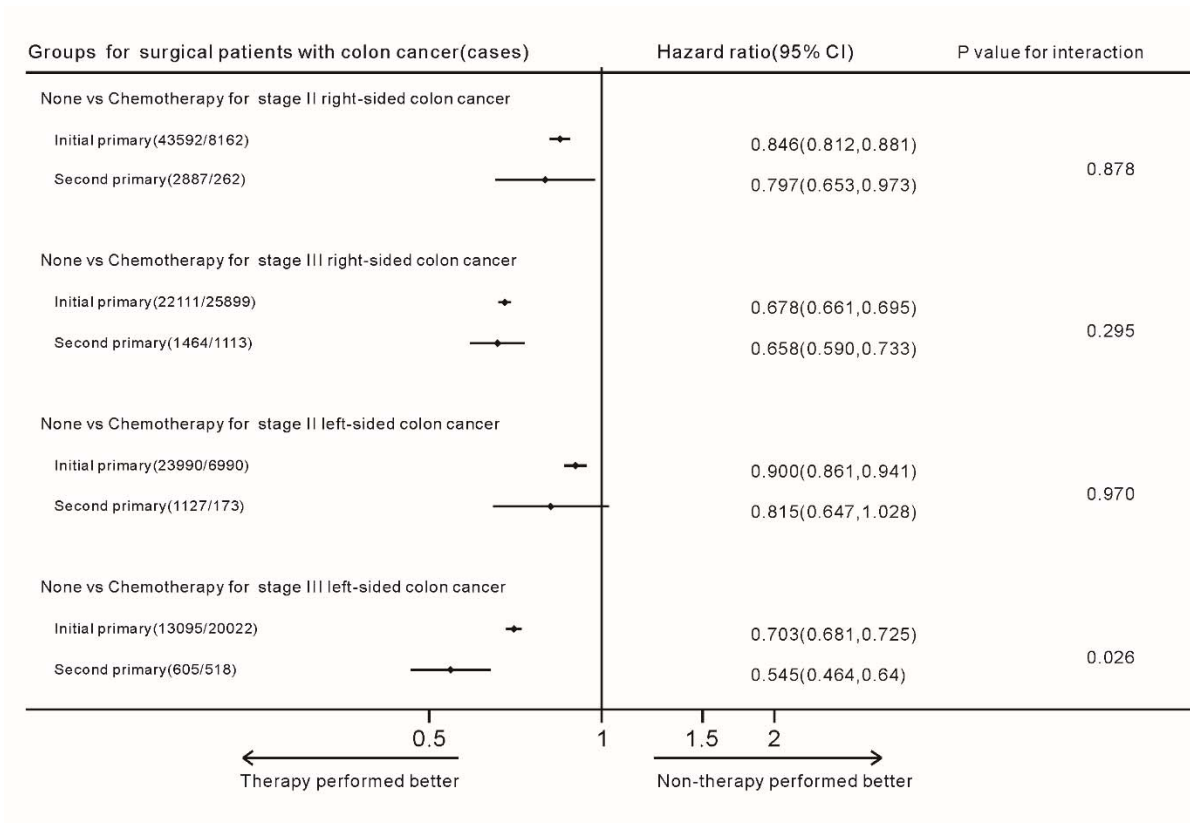
Figure 8 Forest plot of Hazard ratios (HR) and 95% CI in OS different subgroups (Cox proportional hazards model analysis) and interaction comparison between patients with initial and second primary surgical colon cancer.