Am J Cancer Res 2025;15(9):4182-4194
www.ajcr.us /ISSN:2156-6976/ajcr0167147

Original Article

A comparative genomic analysis of left- and right-sided colon cancer using real-world data from the AACR project GENIE BPC dataset

Younggwang Kim[1*], Min Ki Kim[2*], Sanghun Lee[1]

[1]Department of Bioconvergence and Engineering, Graduate School, Dankook University, 152 Jukjeon-Ro, Suji-Gu, Yongin-Si 16890, Republic of Korea; [2]Department of Surgery, Hallym Hospital, 722, Jangje-Ro, Gyeyang-Gu, Incheon 21079, Republic of Korea. [*]Equal contributors.

Received July 1, 2025; Accepted September 11, 2025; Epub September 25, 2025; Published September 30, 2025

Abstract: Left- and Right-sided colon cancers (LCC and RCC) are increasingly recognized as distinct clinicopathological and molecular subtypes with divergent prognoses and therapeutic responses. Leveraging a large, multi-institutional cohort from the AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE) Biopharma Collaborative (BPC) (n = 750; LCC: 363 vs. RCC: 387), we conducted a comprehensive analysis of mutational profiles, tumor mutation burden (TMB), and survival outcomes. Our findings revealed a markedly higher TMB in RCC compared to LCC (6.65 ± 11.3 vs. 3.17 ± 4.35; adjusted $P = 3.12\times10^{-32}$), suggesting greater genomic instability in RCC. After applying functional annotation filters (PolyPhen > 0.85, SIFT < 0.05), RCC tumors were significantly enriched for mutations in *BRAF* (23.1% vs. 6.7%), *KMT2D* (8.6% vs. 3.2%), and *SMAD4* (13.1% vs. 7.3%), while *TP53* mutations predominated in LCC (40.6% vs. 31.8%). Multivariate Cox regression analysis identified RCC as an independent predictor of poorer overall survival (OS) relative to LCC (HR: 1.30, 95% CI: 1.02-1.66, $P = 0.033$). Notably, *KRAS* mutations were associated with significantly worse OS in LCC (HR: 1.68, 95% CI: 1.06-2.70, $P = 0.027$), while *BRAF* mutations predicted adverse outcomes in RCC (HR: 1.58, 95% CI: 1.05-2.37, $P = 0.028$). These results underscore the prognostic value of tumor sidedness and specific genetic alterations in colon adenocarcinoma. Our study highlights the need for sidedness-specific molecular profiling to inform precision oncology strategies in colon cancer management.

Keywords: Right-sided colon cancer, left-sided colon cancer, tumor mutation burden, genomic profiling, *KRAS*, *BRAF*, survival analysis

Introduction

Colon cancer is a leading cause of cancer-related deaths in developed countries [1]. It arises from the epithelial lining of the colon and can occur on either the right (proximal) or left (distal) sections of the colon. Tumor location plays a critical role in disease progression and overall survival (OS) [2]. Left-sided colon cancer (LCC) and right-sided colon cancer (RCC) are distinct entities with differing epidemiological, clinicopathological, and molecular characteristics. These distinctions are driven by variations in gene expression profiles, with more than 1,000 genes exhibiting differential expression between LCC and RCC [2]. Specifically, 165 genes exhibit over a two-fold difference, and 49 genes show over a three-fold difference, reflecting intrinsic biological differences established during embryonic development and maintained throughout postnatal life [2].

The genomic landscapes of LCC and RCC further highlight their divergence. RCC is frequently associated with microsatellite instability (MSI)-high tumors and CpG island methylator phenotype (CIMP) positivity, whereas LCC is predominantly characterized by chromosomal instability (CIN-high) [2, 3]. These molecular differences are reflected in histological features: RCC commonly presents with flat morphology, poor differentiation, and mucinous features, which often lead to delayed detection during colonoscopy and advanced tumor stages at

https://doi.org/10.62347/JOGM1897

diagnosis [4]. Conversely, LCC typically exhibits polypoid morphology, making it more amenable to early detection [5]. These differences extend to metastatic patterns, with RCC more frequently associated with peritoneal carcinomatosis, while LCC tends to metastasize to the liver and lungs [6]. These metastatic tendencies are influenced by the anatomical, vascular, and molecular variations driving tumor progression in each type.

Understanding the clinical, molecular, and histological differences between LCC and RCC is critical for tailoring therapeutic strategies and improving prognostic accuracy. While substantial progress has been made in characterizing these distinctions, many prior studies were limited by small sample sizes and a lack of integrative analysis of both clinical and genomic data [7-10]. These issues often resulted in fragmented or conflicting conclusions regarding the molecular and clinical variability between RCC and LCC. To address these challenges, we utilized real-world data from the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) Biopharma Collaborative (BPC) dataset, a platform integrating large-scale genomic and clinical datasets from diverse cohorts [11]. This resource overcomes many of the limitations of traditional studies, providing a robust foundation for high-resolution analysis.

In this study, we investigate the key clinical, molecular, and mutational differences between LCC and RCC using the GENIE BPC dataset. Our analysis aimed to elucidate how these variations influence clinical presentations, including metastatic patterns and patient outcomes. By utilizing this comprehensive dataset, we hope to provide novel insights into the biological variability between LCC and RCC.

Materials and methods

Study population and inclusion criteria

Data of patients with colon cancers were collected from the GENIE BPC CRC v2.0-public dataset. These data were provided by multiple institutions, including Dana-Farber Cancer Institute (DFCI), Memorial Sloan Kettering Cancer Center (MSKCC), Princess Margaret Cancer Centre - University Health Network (UHN), and Vanderbilt-Ingram Cancer Center (VICC). All data were collected under each ethical approval from each institution, and all patients provided informed consent in accordance with the Declaration of Helsinki. Tumors were classified as LCC (descending colon [C18.5], sigmoid colon [C18.6], or rectosigmoid junction [C18.7]) or RCC (cecum [C18.0], ascending colon [C18.2], hepatic flexure [C18.3], or transverse colon [C18.4]) based on site-specific ICD-O-3 codes. Patients aged 18 or older at diagnosis with at least two years of follow-up data were included in the study, and those with ambiguous tumor locations or histologies other than adenocarcinoma (e.g., mucinous or signet ring cell adenocarcinoma) were excluded [12].

Demographic data, including sex, age at diagnosis, race, and ethnicity, and disease data, including tumor stage at initial diagnosis, tumor grade, presence of distant metastases, lymph node involvement, carcinoembryonic antigen (CEA) levels at diagnosis, MSI status, and treatment regimens, were collected from pathology, radiology, and oncology reports using a structured framework.

Genomic analysis

Next-generation sequencing (NGS) data were generated to identify single-nucleotide variants and small insertions/deletions. We used genetic data before and after filtering for functionally significant mutations using a PolyPhen score > 0.85 and a SIFT score < 0.05. Our analysis also focused on frequent genetic alterations reported in colon cancers, including *TP53*, *KRAS*, *PIK3CA*, *SMAD4*, *BRAF*, *FBXW7*, *ATM*, and *KMT2D*. Tumor mutation burden (TMB) was provided as the number of genes with non-synonymous mutations per megabase. We analyzed these genetic alterations according to tumor sidedness and clinical outcomes.

Additionally, genomic profiling leveraged advanced annotation tools such as PolyPhen and SIFT, allowing for the identification of mutations with high pathogenic potential. This systematic integration of clinical and molecular data provides a robust foundation for distinguishing the biological and clinical characteristics unique to LCC and RCC.

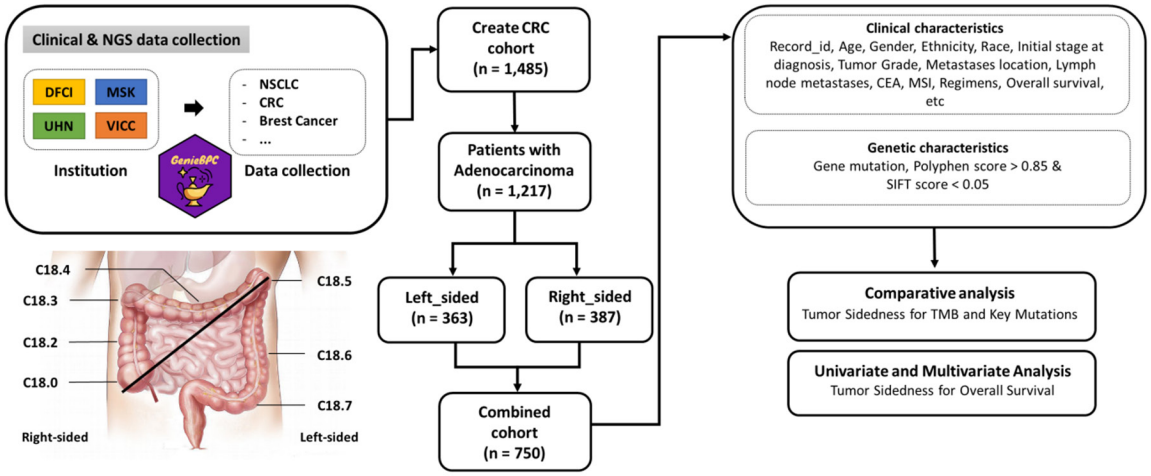


Figure 1. Workflow of patient selection, data annotation, and analysis framework. The flowchart outlines the construction of the colorectal cancer (CRC) cohort from the AACR Project GENIE BPC dataset. After applying clinical filters, 750 patients with histologically confirmed adenocarcinoma were selected and classified into left-sided (n = 363) and right-sided (n = 387) groups based on ICD-0-3 codes. Clinical variables and annotated genomic features (PolyPhen > 0.85, SIFT < 0.05) were integrated for survival and regression analysis.

Statistical analysis

Descriptive statistics were used to summarize baseline clinical and genetic characteristics. Continuous variables, such as age at diagnosis and OS, were presented as mean and standard deviation (SD), whereas categorical variables, such as tumor sidedness, genetic alterations, and treatment regimens, were reported as counts and percentages. Differences in clinical and genetic characteristics between LCC and RCC were assessed using chi-squared tests. Survival analyses were conducted to evaluate OS, defined as the time from diagnosis to death or last follow-up. Kaplan-Meier survival curves were generated to compare OS between groups, and log-rank tests were used to assess statistical significance. Subgroup analyses were conducted to evaluate differences in OS based on tumor sidedness, sex, age group (≥ 65 years vs. < 65 years), tumor stage at diagnosis (stage IV vs. stages I-III), CEA levels at diagnosis (> 5 ng/mL vs. ≤ 5 ng/mL), TMB, and the presence of somatic mutations. To identify independent predictors of OS, multivariate Cox proportional hazards regression models were constructed. The models incorporated tumor sidedness, sex, age at diagnosis, tumor stage at diagnosis, CEA levels at diagnosis, TMB, and the presence of somatic mutations in key genes associated with colon cancers. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each variable to quantify the strength of associations. The proportional hazards assumption was verified using Schoenfeld residuals, and no significant violations were observed. All statistical analyses were performed using R version 4.3.1. Kaplan-Meier survival analyses and Cox proportional hazards regression models were conducted using the "survival" and "survminer" packages; Oncoplot analyses and visualizations were carried out using the "maftools" and "ggplot2" packages.

Results

Patient selection and LCC vs. RCC stratification

The workflow was illustrated in **Figure 1** outlining the process of patient selection from the AACR Project GENIE BPC database. Initially, 1,485 patients with colon cancers were selected; the cohort was subsequently narrowed to 1,217 patients diagnosed with histologically confirmed adenocarcinoma. After excluding patients younger than 18 at diagnosis and those with insufficient follow-up periods (< 2 years), ambiguous tumor locations, or histologies other than adenocarcinoma, the final group included 750 patients with colon cancers. These were stratified into LCC (n = 363) and RCC (n = 387) groups.

Table 1. Demographic and clinical characteristics of patients with left-sided and right-sided colon cancer (LCC and RCC)

Characteristics	Total (750)	LCC (n = 363)	RCC (n = 387)	*p*-value between LCC and RCC
Age (Mean ± SD)	55.9 ± 12.8	52.9 ± 11.7	58.7 ± 13.1	3.39×10^{-10}
< 65 (%)	546 (72.8)	299 (82.4)	247 (63.8)	1.89×10^{-08}
≥ 65 (%)	204 (27.2)	64 (17.6)	140 (36.2)	
Gender (n, (%))				0.624
Male	384 (51.2)	182 (50.1)	202 (52.2)	
Female	366 (48.8)	181 (49.9)	185 (47.8)	
Ethnicity (n, (%))				0.837
Non-Hispanic White	583 (77.7)	281 (77.4)	302 (78.0)	
Non-Hispanic Black	54 (7.2)	22 (6.1)	32 (8.3)	
Hispanic/Latinx	33 (4.4)	16 (4.4)	17 (4.4)	
AAAPI[a]	32 (4.3)	12 (3.3)	20 (5.2)	
Other	15 (2.0)	14 (3.9)	1 (0.2)	
Unknown[b]	33 (4.4)	18 (4.9)	15 (3.9)	
Race (n, (%))				0.896
White	613 (81.7)	296 (81.5)	317 (81.9)	
Black	57 (7.6)	23 (6.3)	34 (8.8)	
Asian	32 (4.3)	12 (3.3)	20 (5.2)	
Other	15 (2.0)	14 (3.9)	1 (0.2)	
Unknown[b]	33 (4.4)	18 (5.0)	15 (3.9)	
Initial stage at diagnosis (n, (%))				1.12×10^{-04}
I	37 (4.9)	20 (5.5)	17 (4.4)	
II	123 (16.4)	38 (10.5)	85 (22.0)	
III	218 (29.1)	103 (28.4)	115 (29.7)	
IV	372 (49.6)	202 (55.6)	170 (43.9)	
Tumor Grade (n, %)				0.0625
G1	17 (2.3)	11 (3.0)	6 (1.6)	
G2	499 (66.5)	239 (65.8)	260 (67.2)	
G3	131 (17.5)	49 (13.5)	82 (21.2)	
G4	27 (3.6)	11 (3.0)	16 (4.1)	
Unknown[b]	76 (10.1)	53 (14.7)	23 (5.9)	
Tumor Location (n, %)				
C18.0 (Cecum)	171 (22.9)	-	171 (44.2)	
C18.2 (Ascending colon)	115 (15.3)	-	115 (29.7)	
C18.3 (Hepatic flexure of colon)	22 (2.9)	-	22 (5.7)	
C18.4 (Transverse colon)	79 (10.5)	-	79 (20.4)	
C18.5 (Splenic flexure of colon)	26 (3.5)	26 (7.1)	-	
C18.6 (Descending colon)	58 (7.7)	58 (16.0)	-	
C18.7 (Sigmoid colon)	279 (37.2)	279 (76.9)	-	
Metastases (n, %)	579 (77.2)	315 (86.6)	264 (68.2)	4.0×10^{-09}
Liver	280 (37.3)	164 (45.2)	116 (30.0)	0.0514
Lung NOS[d]	54 (7.2)	34 (9.4)	20 (5.2)	0.185
Peritoneum NOS[d]	51 (6.8)	23 (6.3)	28 (7.2)	0.162
CEA[e] (Mean ± SD)	309.0 ± 3287.8	457.1 ± 4586.5	167.8 ± 989.6	0.226
> 5 (n, %)	350 (46.7)	184 (50.7)	166 (42.9)	3.9×10^{-02}
≤ 5 (n, %)	400 (53.3)	179 (49.3)	221 (57.1)	

Lymph node metastasis (n, %)	65 (8.7)	30 (8.3)	35 (9.0)	0.444
N0	30 (4.0)	12 (3.3)	18 (4.7)	
N1	20 (2.6)	9 (2.5)	11 (2.8)	
N2	15 (2.0)	9 (2.5)	6 (1.6)	
Unknown[b]	2 (0.3)	2 (0.6)	0 (0)	
NA[c]	683 (91.1)	331 (91.1)	352 (90.9)	
MSI[f] (n, %)				0.174
MSI-H	5 (0.7)	1 (0.3)	4 (1.0)	
MSI-L/MSS[g]	66 (8.8)	34 (9.4)	32 (8.3)	
Unknown[b]	679 (90.5)	328 (90.3)	351 (90.7)	
Regimens (n, %)				
Chemotherapy	514 (68.5)	231 (63.6)	283 (73.1)	6.6×10^{-03}
Targeted agents with chemotherapy				0.999
Bevacizumab +	141 (18.8)	68 (18.7)	73 (18.9)	
Cetuximab +	16 (2.1)	8 (2.2)	8 (2.1)	
Panitumumab +	11 (1.5)	5 (1.4)	6 (1.6)	
ICI[h]	9 (1.2)	2 (0.6)	7 (1.8)	0.267
NA[c]	443 (59.1)	169 (46.6)	274 (70.8)	
Institution (n, %)				0.299
MSK[i]	409 (54.6)	195 (53.7)	214 (55.3)	
DFCI[j]	241 (32.1)	125 (34.4)	116 (30.0)	
VICC[k]	100 (13.3)	43 (11.9)	57 (14.7)	

AAAPI[a]: Asian, Asian American, and Pacific Islander; Unknown[b]: variable present but value missing in the GENIE BPC dataset; NA[c]: not applicable or not collected in accordance with definitions in the GENIE BPC Analytic Data Guide [33]; NOS[d]: not otherwise specified; CEA[e]: carcinoembryonic antigen; MSI[f]: microsatellite instability; MSS[g]: microsatellite stable; ICI[h]: immune checkpoint inhibitor; MSK[i]: Memorial Sloan Kettering Cancer Center; DFCI[j]: Dana-Farber Cancer Institute; VICC[k]: Vanderbilt-Ingram Cancer Center. *p*-values were calculated using the Chi-square test for categorical variables and the Student's t-test for continuous variables.

Clinical and demographic differences between LCC and RCC

The clinical and demographic characteristics differed significantly by sidedness (**Table 1**). RCC patients were older than LCC patients (58.7 ± 13.1 vs. 52.9 ± 11.7 years, $P = 3.39\times10^{-10}$), with a higher proportion aged ≥ 65 years (36.2% vs. 17.6%). Stage at diagnosis also differed: stage IV was more prevalent in LCC than RCC (55.6% vs. 43.9%, $P = 1.12\times10^{-4}$). Primary-site distributions contrasted, with most LCC in the sigmoid colon (C18.7, 76.9%), whereas RCC was more evenly distributed, predominantly the cecum (C18.0, 44.2%) and ascending colon (C18.2, 29.7%). Liver metastases were more prevalent in LCC (45.2% vs. 30.0%), a borderline difference ($P = 0.0514$). Therapeutic interventions, including chemotherapy and targeted agents, were broadly similar, although chemotherapy use was slightly higher in RCC (73.1% vs. 63.6%).

Mutation landscape before/after functional annotation and by tumor sidedness

Oncoplot analyses before and after PolyPhen and SIFT-based filtering illustrate the mutational landscape (**Figure 2A** and **2B**). Prior to filtering, the most frequently mutated genes were *APC* (72%), *TP53* (67%), *KRAS* (45%), *PIK3CA* (27%), *BRAF* (15%), *KMT2D* (15%), *SMAD4* (15%), and *FBXW7* (15%). After restricting to variants predicted to be deleterious, *TP53* became the most frequent (36%), with adjusted frequencies for *PIK3CA* (17%), *KRAS* (16%), *BRAF* (15%), *SMAD4* (10%), *FBXW7* (8%), and *KMT2D* (6%). *APC* mutations, though initially predominant, were down-ranked due to low pathogenicity, underscoring the utility of functional filtering for prioritizing biologically relevant alterations.

The mutation type distributions also differed by sidedness (**Figure 2C** and **2D**). Missense

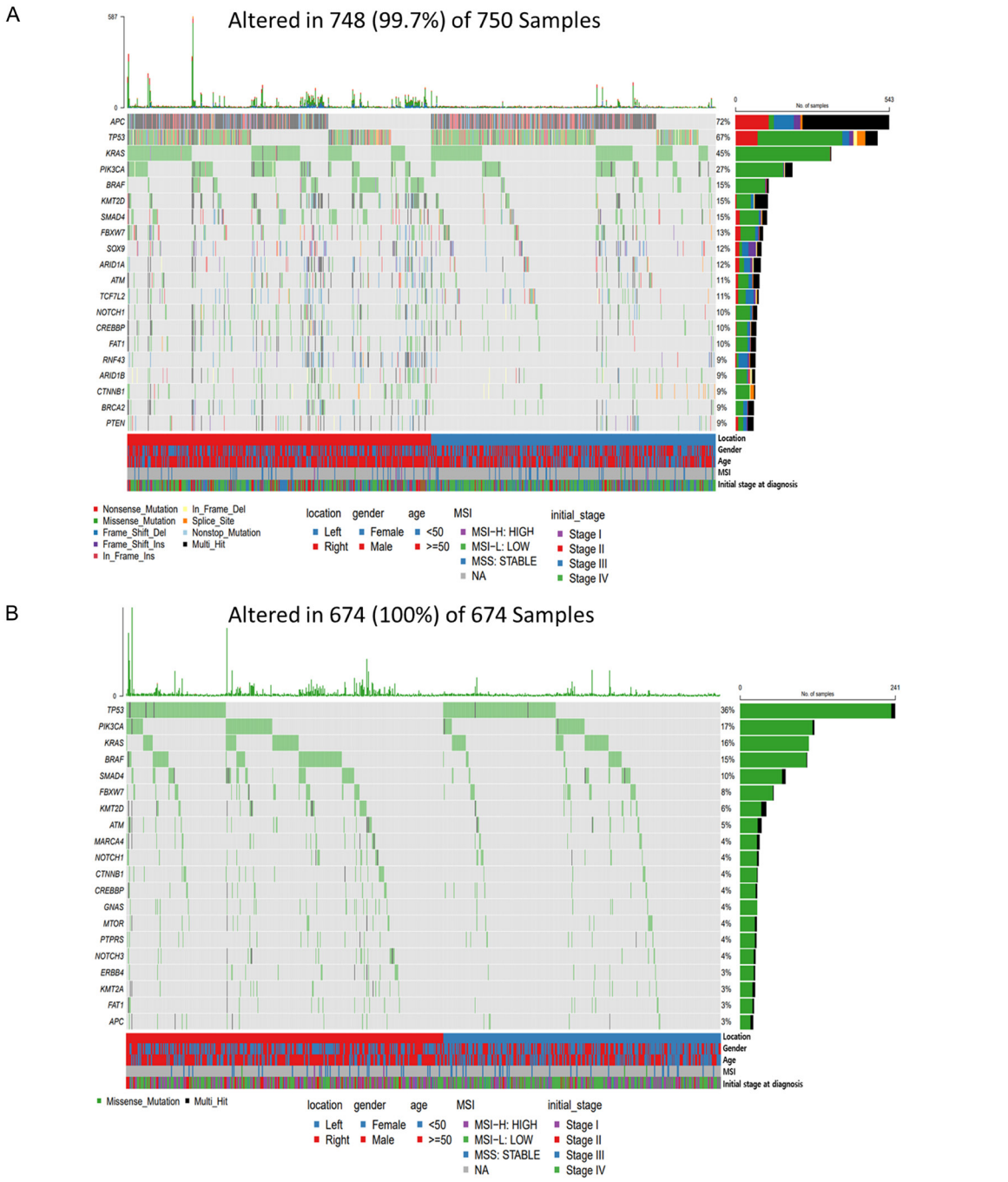

A
Altered in 748 (99.7%) of 750 Samples
APC 72%
TP53 67%
KRAS 45%
PIK3CA 27%
BRAF 15%
KMT2D 15%
SMAD4 15%
FBXW7 13%
SOX9 12%
ARID1A 12%
ATM 11%
TCF7L2 11%
NOTCH1 10%
CREBBP 10%
FAT1 10%
RNF43 9%
ARID1B 9%
CTNNB1 9%
BRCA2 9%
PTEN 9%
Location
Gender
Age
MSI
Initial stage at diagnosis
Nonsense_Mutation
Missense_Mutation
Frame_Shift_Del
Frame_Shift_Ins
In_Frame_Ins
In_Frame_Del
Splice_Site
Nonstop_Mutation
Multi_Hit
location Left Right
gender Female Male
age <50 >=50
MSI MSI-H: HIGH MSI-L: LOW MSS: STABLE NA
initial_stage Stage I Stage II Stage III Stage IV
B
Altered in 674 (100%) of 674 Samples
TP53 36%
PIK3CA 17%
KRAS 16%
BRAF 15%
SMAD4 10%
FBXW7 8%
KMT2D 6%
ATM 5%
MARCA4 4%
NOTCH1 4%
CTNNB1 4%
CREBBP 4%
GNAS 4%
MTOR 4%
PTPRS 4%
NOTCH3 4%
ERBB4 3%
KMT2A 3%
FAT1 3%
APC 3%
Location
Gender
Age
MSI
Initial stage at diagnosis
Missense_Mutation
Multi_Hit
location Left Right
gender Female Male
age <50 >=50
MSI MSI-H: HIGH MSI-L: LOW MSS: STABLE NA
initial_stage Stage I Stage II Stage III Stage IV
C
Mutation Type in LCC
Missense Mutation 67.1%
Nonsense Mutation 11.1%
Frame hift Deletion 8.8%
Splice Site 4.6%
Frame Shift Insertion 3.7%
Other 3.1%
Frame Deletion 1.8%
0 20 40 60
D
Mutation Type in RCC
Missense Mutation 66.9%
Frame hift Deletion 13.6%
Nonsense Mutation 7.7%
Frame Shift Insertion 4.4%
Splice Site 3.8%
Other 2.4%
Frame Deletion 1.3%
0 20 40 60

Figure 2. Mutational landscape and mutation type distribution in left-sided and right-sided colon cancer. A. Oncoplot depicting the most frequently mutated genes in the full colon cancer cohort prior to functional filtering. *APC*, *TP53*, *KRAS*, and *PIK3CA* were among the most common alterations. B. Functionally annotated Oncoplot highlighting mutations with high predicted pathogenicity based on PolyPhen and SIFT scores. *TP53*, *PIK3CA*, *KRAS*, and *BRAF* were most frequently retained after filtering. C. Distribution of mutation types in left-sided colon cancer (LCC), with missense mutations most frequent. D. Distribution of mutation types in right-sided colon cancer (RCC), also dominated by missense mutations but with relatively more frameshift deletions and nonsense mutations, indicating distinct mutational processes compared with LCC.

mutations predominated in both groups (LCC 67.1% vs. RCC 66.9%). Frameshift deletions were more frequent in RCC than LCC (13.6% vs. 8.8%), whereas nonsense mutations were more frequent in LCC (11.1% vs. 7.7%). These patterns suggest distinct mutational processes between LCC and RCC.

Comparative TMB and key mutations by sidedness

We compared TMB and key genetic alterations between LCC and RCC, both before and after PolyPhen/SIFT filtering (**Table 2**). In the unfiltered analysis, RCC had higher TMB than LCC (6.87 ± 12.1 vs. 3.45 ± 4.39, adjusted $P = 1.61\times10^{-30}$). *APC* and *TP53* mutations were more prevalent in LCC than RCC (*APC:* 81.5% vs. 67.2%, adjusted $P = 1.57\times10^{-5}$; *TP53* 73.6% vs. 62.5%, adjusted $P = 1.54\times10^{-3}$). In contrast, *KRAS* (50.1% vs. 40.2%, adjusted $P = 7.31\times10^{-3}$) and *PIK3CA* (32.6% vs. 20.9%, adjusted $P = 6.3\times10^{-5}$) were enriched in RCC. *BRAF* (23.8% vs. 6.6%, adjusted $P = 3.73\times10^{-10}$) and *KMT2D* (22.5% vs. 8.3%, adjusted $P = 2.47\times10^{-7}$), and *SMAD4* (19.9% vs. 10.5%, adjusted $P = 5.13\times10^{-4}$) were also more frequent in RCC than LCC.

After applying PolyPhen and SIFT filtering criteria, TMB remained higher in RCC (6.65 ± 11.3) than in LCC (3.17 ± 4.35, adjusted $P = 3.12\times10^{-32}$). *TP53* became the most frequent mutation overall (LCC 40.6% vs. RCC 31.8%, adjusted $P = 2.97\times10^{-2}$). *KRAS* mutations were more balanced by sidedness (LCC 16.5% vs. RCC 15.0%, adjusted $P = 0.602$). RCC retained significant enrichment for *BRAF* (23.1% vs. 6.7%, adjusted $P = 1.64\times10^{-8}$), *KMT2D* (8.6% vs. 3.2%, adjusted $P = 9.27\times10^{-3}$), *SMAD4* (13.1% vs. 7.3%, adjusted $P = 2.97\times10^{-2}$), and *PIK3CA* (20.1% vs. 13.7%, adjusted $P = 4.11\times10^{-2}$). Across filtering strategies, RCC consistently exhibited higher TMB and greater enrichment of *BRAF*, *KMT2D*, and *PIK3CA* mutations, whereas LCC was characterized by a higher frequency of *TP53* mutations.

Univariate predictors of OS by tumor sidedness

Advanced stage was strongly associated with inferior OS (Supplementary Table 3 and Supplementary Figure 1): stage IV vs. the others (HR: 1.52, 95% CI: 1.28-1.81, $P = 2.54\times10^{-6}$) and stage III/IV vs. the others (HR: 1.77, 95% CI: 1.36-2.29, $P = 1.66\times10^{-5}$). Elevated CEA (≥ 5 ng/mL) was also highly prognostic (HR: 1.53, 95% CI: 1.28-1.82, $P = 1.86\times10^{-6}$). Age, gender, and most single-gene alterations, were not significant in the combined group.

In the LCC group (Supplementary Table 4 and Supplementary Figure 2), advanced stage remained significant (stage III/IV: HR: 1.79, 95% CI: 1.22-2.64, $P = 0.003$; stage IV: HR: 1.37, 95% CI: 1.07-1.75, $P = 0.014$). Tumor grade III also predicted worse OS (HR: 1.44, 95% CI: 1.04-1.99, $P = 0.030$). Elevated CEA was strongly prognostic (HR: 1.86, 95% CI: 1.44-2.39, $P = 1.46\times10^{-6}$). *BRAF* mutation showed a borderline association (HR: 1.68, 95% CI: 0.99-2.84, $P = 0.054$). In the RCC group (Supplementary Table 5 and Supplementary Figure 3), stage III/IV (HR: 1.77, 95% CI: 1.25-2.51, $P = 0.001$) and stage IV (HR: 1.70, 95% CI: 1.33-2.18, $P = 2.68\times10^{-5}$) predicted worse OS. Elevated CEA remained prognostic (HR: 1.30, 95% CI: 1.01-1.66, $P = 0.038$). *SMAD4* mutation was marginal (HR: 1.41, 95% CI: 1.00-1.99, $P = 0.047$).

Collectively, stage and CEA consistently predict OS across sidedness, whereas the prognostic effect of genetic alterations was not definite between LCC and RCC (borderline *BRAF* in LCC; marginal *SMAD4* in RCC).

Multivariate predictors of OS by tumor sidedness

In the combined group (**Figure 3A**), multivariate analyses identified independent adverse predictors such as age (≥ 65 years; HR: 1.45, 95% CI: 1.13-1.86, $P = 0.003$), stage IV (HR: 3.06, 95% CI: 2.36-3.95, $P < 0.001$), and elevated

Table 2. Comparison of TMB and key genetic alterations between LCC and RCC in non-filtered and PolyPhen/SIFT-filtered analyses

	Genetic alteration (n, %)	Total (750)	LCC (n = 363)	RCC (n = 387)	*p*-value between LCC and RCC	Adjusted *p*-value
PolyPhen/SIFT score non-filtered	TMB (n, Mean ± SD)	3,699 (5.88 ± 10.46)	1,074 (3.45 ± 4.39)	2,625 (6.87 ± 12.1)	1.79×10^{-31}	1.61×10^{-30}
	BRAF	116 (15.5)	24 (6.6)	92 (23.8)	8.28×10^{-11}	3.73×10^{-10}
	KMT2D	117 (15.6)	30 (8.3)	87 (22.5)	8.23×10^{-8}	2.47×10^{-7}
	APC	556 (74.1)	296 (81.5)	260 (67.2)	6.96×10^{-6}	1.57×10^{-5}
	PIK3CA	202 (26.9)	76 (20.9)	126 (32.6)	3.5×10^{-5}	6.3×10^{-5}
	SMAD4	115 (15.3)	38 (10.5)	77 (19.9)	3.42×10^{-4}	5.13×10^{-4}
	TP53	509 (67.9)	267 (73.6)	242 (62.5)	1.2×10^{-3}	1.54×10^{-3}
	KRAS	340 (45.3)	146 (40.2)	194 (50.1)	6.5×10^{-3}	7.31×10^{-3}
	Genetic alteration (n, %)	Total (674)	LCC (n = 315)	RCC (n = 359)	*p*-value	Adjusted *p*-value
PolyPhen/SIFT score filtered	TMB (n, Mean ± SD)	3,351 (5.64 ± 9.80)	976 (3.17 ± 4.35)	2,375 (6.65 ± 11.3)	3.47×10^{-33}	3.12×10^{-32}
	BRAF	104 (15.4)	21 (6.7)	83 (23.1)	3.64×10^{-9}	1.64×10^{-8}
	KMT2D	41 (6.1)	10 (3.2)	31 (8.6)	3.09×10^{-3}	9.27×10^{-3}
	TP53	242 (35.9)	128 (40.6)	114 (31.8)	1.65×10^{-2}	2.97×10^{-2}
	SMAD4	70 (10.4)	23 (7.3)	47 (13.1)	1.39×10^{-2}	2.97×10^{-2}
	PIK3CA	115 (17.1)	43 (13.7)	72 (20.1)	2.74×10^{-2}	4.11×10^{-2}

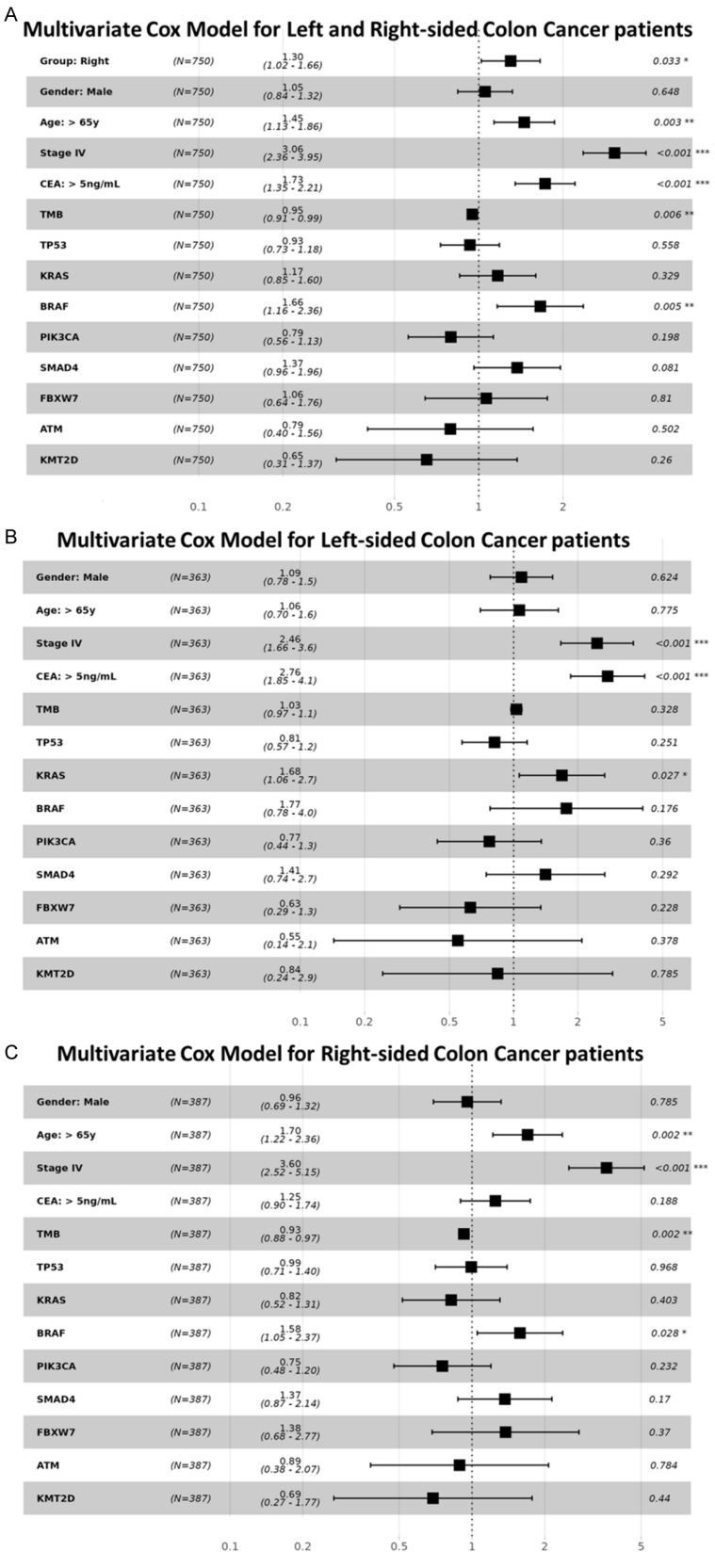


Figure 3. Multivariate Cox regression analysis of overall survival (OS) in colon adenocarcinoma patients. Forest plots display hazard ratios (HR) with 95% confidence intervals for clinical and genetic variables in three groups. A. Combined group (n = 750) including both left-sided and right-sided colorectal cancers. Right-sided tumor location, age ≥ 65, stage IV disease, elevated CEA levels (> 5 ng/mL), and *BRAF* mutations were significantly associated with worse OS. B. Left-sided CRC group (LCC; n = 363), where stage IV disease, age ≥65, and BRAF mutations were associated with worse OS, while higher tumor mutation burden (TMB) was associated with improved survival. C. Right-sided CRC group (RCC; n = 387), where stage IV disease, elevated CEA, and *KRAS* mutations were significantly associated with poorer outcomes. **p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001.

CEA (HR: 1.73, 95% CI: 1.35-2.21, $P < 0.001$). Notably, RCC was significantly associated with poorer OS compared to LCC (HR: 1.30, 95% CI: 1.02-1.66, $P = 0.033$). Among genetic mutations, *BRAF* independently predicted worse OS (HR: 1.66, 95% CI: 1.16-2.36, $P = 0.005$). *TP53*, *KRAS*, *PIK3CA*, *SMAD4*, *FBXW7*, *ATM*, *KMT2D*, and the total number of gene alterations were not significant.

In the LCC group (**Figure 3B**), stage IV (HR: 2.46, 95% CI: 1.66-3.6, $P < 0.001$) and elevated CEA (HR: 2.76, 95% CI: 1.85-4.1, $P < 0.001$) were the most significant predictors of poorer OS. *KRAS* mutation was also significantly associated with worse OS (HR: 1.68, 95% CI: 1.06-2.7, $P = 0.027$). Other variables, including gender, age, TMB, *BRAF*, and *SMAD4*, were not significant in the LCC group. In the RCC group (**Figure 3C**), stage IV (HR: 3.60, 95% CI: 2.52-5.15, $P < 0.001$) and age ≥ 65 years (HR: 1.70, 95% CI: 1.22-2.36, $P < 0.001$) were the strongest

predictors of poorer OS. *BRAF* mutation was also significantly associated with worse OS (HR: 1.58, 95% CI: 1.05-2.37, $P = 0.028$), while higher TMB was associated with better OS (HR: 0.93, 95% CI: 0.88-0.97, $P = 0.002$). Other variables were not significant in the RCC model. Taken together, multivariable results underscore strong clinical drivers (stage, CEA, age) with sidedness-specific genomic effects: *KRAS* confers risk in LCC, whereas *BRAF* and lower TMB confer risk in RCC.

Discussion

The biological distinction between RCC and LCC is shaped by the interplay of developmental, immunologic, epigenetic, and microbial factors [13-18]. From an embryologic standpoint, the RCC originates from the midgut (cecum to proximal transverse colon) and LCC from the hindgut (distal transverse colon to upper anal canal) [15]. These developmental differences, together with regional variation in immune activity, epigenetic regulation, and microbiome composition, provide the basis for the distinct biology observed between LCC and RCC [13, 14, 16-18]. Clinically, multiple cohorts report worse survival for RCC versus LCC across stages [19, 20]. A large population-based study from England including 167,606 patients reported that 5-year OS was significantly worse for RCC compared with LCC, both in unmatched cohorts (58.8% vs. 66.7%, $P < 0.001$) and after propensity-score matching (62.6% vs. 66.8%, $P < 0.001$) [19]. Similarly, a retrospective study of 2,475 surgically treated patients found that RCC consistently exhibited higher mortality and inferior OS and RFS compared with LCC across stages I-IV (all $P < 0.05$) [20]. Consistent with these reports, despite fewer stage IV cases (**Table 1**), RCC showed inferior OS in our data (**Figure 3A**) suggesting that stage alone does not account for the survival gap and implicating sidedness-specific biology.

To probe molecular contributors, we integrated functional variant annotation and cohort-wide genomic features. APC appeared most frequent before filtering, but PolyPhen/SIFT deprioritized many APC variants, indicating limited predicted pathogenicity and avoiding overestimation of APC's impact (**Table 2**). This is concordant with genomic analyses reporting that only a small subset of nonsynonymous APC substitutions are predicted to be pathogenic [21]. Therefore, we adopted PolyPhen/SIFT filtering for functional annotation to avoid overestimating its impact.

At the macro-genomic level, RCC had higher TMB than LCC, in line with prior evidence that RCC is enriched for MSI-high and serrated-pathway carcinogenesis [2, 22]. Consistently, our dataset confirmed that RCC exhibited significantly higher TMB than LCC (**Table 2**). Importantly, higher TMB was independently associated with better OS in RCC, but not in LCC (**Figure 3B** and **3C**), consistent with the hypothesis that increased neoantigen load augments tumor immunogenicity and antitumor activity despite genomic instability [23, 24]. Concordantly, frameshift deletions - characteristic of dMMR/MSI-H tumors - were more frequent in RCC (**Figure 2C**, **2D**). MSI-H tumors generate numerous frameshift neoantigens that correlate with tumor-infiltrating lymphocyte density and may influence tumor behavior [25, 26]. This biology often co-occurs with *BRAF* mutations and *MLH1* promoter hypermethylation, yielding sporadic MSI-H cancers via the serrated pathway (sessile serrated lesions, CIMP positivity) [27-29]. Experimental evidence also supports that *BRAF* initiated the serrated pathway, with lesions progressing from hyperplastic polyps to adenocarcinomas [30]. In our dataset, *BRAF* mutations were significantly enriched in RCC (**Table 2**) and independently associated with worse OS, highlighting their poor prognostic role in RCC (**Figure 3C**).

Driver-specific effects were sidedness dependent. *KRAS* mutations conferred inferior OS in LCC but not RCC (**Figure 3B**), aligning with large registry studies showing that the prognostic impact of KRAS is modified by laterality (worse outcomes predominantly in LCC). Specifically, population-based studies have consistently shown a prognostic disadvantage of *KRAS* predominantly in LCC. Another analysis of 5,292 patients with stage I-III colon cancer (2010-2016) reported that laterality modified the prognostic role of *KRAS* among patients with *KRAS*-mutated tumors, LCC were associated with worse survival compared with RCC (HR: 1.30, 95% CI: 1.03-1.63), whereas in *KRAS* wild-type cancers, LCC had better survival than RCC (HR: 0.81, 95% CI: 0.67-0.97) [31].

Similarly, a SEER-based study of 22,542 patients with stage IV colon cancer (2010-2013) found that *KRAS* mutations were linked to an increased risk of death in LCC (HR: 1.19, 95% CI: 1.05-1.33), but not in RCC [32]. Together, these findings reinforce that tumor location conditions both the genomic landscape (MSI/TMB, serrated features, driver frequencies) and the prognostic meaning of specific alterations (*BRAF*, *KRAS*).

This study has several limitations. First, as a secondary analysis of the GENIE BPC dataset, the study was inherently constrained by incomplete or missing clinical and genomic information. Key variables, such as MSI/MMR status, detailed treatment histories, and performance status, were inconsistently captured. Within stages (I-III or IV), systemic therapy patterns did not differ by sidedness (Supplementary Table 1), while certain regimen types, such as bevacizumab- and panitumumab-containing therapies, were significantly different between localized and metastatic disease (Supplementary Table 2). These suggest that treatment is unlikely to explain the sidedness survival gap. Second, locoregional treatment modalities, including surgery and radiation, were not captured, preventing a comprehensive assessment of their contribution to survival outcomes. Third, the dataset lacked racial and ethnic diversity, as the majority of patients were of Caucasian background. This limits the generalizability of our findings across global populations. Finally, microbiome composition and other omics data, such as transcriptomics, proteomics, or metabolomics, were not available, precluding integrative analyses.

In conclusion, RCC is characterized by higher TMB, more frameshift deletions, and enrichment of serrated-pathway alterations, particularly *BRAF*, and has poorer OS independent of stage. In contrast, *KRAS* confers a prognostic disadvantage chiefly in LCC. These results indicate that tumor sidedness modifies both genomic architecture and the prognostic significance of key drivers, with implications for risk stratification and therapeutic decision-making. Multi-omic, and more demographically diverse cohorts are needed to refine location-specific mechanisms and clinical translation.

Acknowledgements

This research utilized data generated by the AACR Project GENIE consortium. The authors recognize the invaluable efforts of all consortium members who have advanced collaborative data sharing in cancer research. We further acknowledge the support provided by the AACR, including its financial and infrastructural contributions. The present research was supported by the research fund of Dankook University in 2025.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Address correspondence to: Sanghun Lee, Department of Bioconvergence and Engineering, Graduate School, Dankook University, 152 Jukjeon-ro, Suji-gu, Yongin-Si 16890, Republic of Korea. E-mail: shlee92@dankook.ac.kr

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, DeNobile J, Soballe P, Simon R, Wright G, Lynch P, Patterson S, Lynch H, Gallinger S, Buchbinder A, Gordon G, Hawk E and Kirsch IR. Distinguishing right from left colon by the pattern of gene expression. Cancer Epidemiol Biomarkers Prev 2003; 12: 755-762.

[3] Carethers JM. One colon lumen but two organs. Gastroenterology 2011; 141: 411-412.

[4] Nitsche U, Stögbauer F, Späth C, Haller B, Wilhelm D, Friess H and Bader FG. Right sided colon cancer as a distinct histopathological subtype with reduced prognosis. Dig Surg 2016; 33: 157-163.

[5] Gualco G, Reissenweber N, Cliché I and Bacchi CE. Flat elevated lesions of the colon and rectum: a spectrum of neoplastic and nonneoplastic entities. Ann Diagn Pathol 2006; 10: 333-338.

[6] Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I and Lippert H. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010; 53: 57-64.

[7] Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO and Clark SK. Is right-sided colon

cancer different to left-sided colorectal cancer? - A systematic review. Eur J Surg Oncol 2015; 41: 300-308.
[8] Dekker E, Tanis PJ, Vleugels JLA, Kasi PM and Wallace MB. Colorectal cancer. Lancet 2019; 394: 1467-1480.
[9] Qiu MZ, Pan WT, Lin JZ, Wang ZX, Pan ZZ, Wang FH, Yang DJ and Xu RH. Comparison of survival between right-sided and left-sided colon cancer in different situations. Cancer Med 2018; 7: 1141-1150.
[10] Hanna DL and Lenz HJ. How we treat left-sided vs. right-sided colon cancer. Clin Adv Hematol Oncol 2020; 18: 253-257.
[11] AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017; 7: 818-831.
[12] Kehl KL, Riely GJ, Lepisto EM, Lavery JA, Warner JL, LeNoue-Newton ML, Sweeney SM, Rudolph JE, Brown S, Yu C, Bedard PL, Schrag D and Panageas KS. Correlation between surrogate end points and overall survival in a multiinstitutional clinicogenomic cohort of patients with non-small cell lung or colorectal cancer. JAMA Netw Open 2021; 4: e2117547.
[13] Kwak HD and Ju JK. Immunological differences between right-sided and left-sided colorectal cancers: a comparison of embryologic midgut and hindgut. Ann Coloproctol 2019; 35: 342-346.
[14] Kneis B, Wirtz S, Weber K, Denz A, Gittler M, Geppert C, Brunner M, Krautz C, Siebenhüner AR, Schierwagen R, Tyc O, Agaimy A, Grützmann R, Trebicka J, Kersting S and Langheinrich M. Colon cancer microbiome landscaping: differences in right- and left-sided colon cancer and a tumor microbiome-ileal microbiome association. Int J Mol Sci 2023; 24: 3265.
[15] Yang S, Cho M and Kim N. Difference between right-sided and left-sided colorectal cancers: from embryology to molecular subtype. Expert Review of Anticancer Therapy 2018; 18: 1-8.
[16] Qi GX, Zhao RX, Gao C, Ma ZY, Wang S and Xu J. Recent advances and challenges in colorectal cancer: from molecular research to treatment. World J Gastroenterol 2025; 31: 106964.
[17] Li S, Peppelenbosch MP and Smits R. Bacterial biofilms as a potential contributor to mucinous colorectal cancer formation. Biochim Biophys Acta Rev Cancer 2019; 1872: 74-79.
[18] Ou S, Wang H, Tao Y, Luo K, Ye J, Ran S, Guan Z, Wang Y, Hu H and Huang R. Fusobacterium nucleatum and colorectal cancer: From phenomenon to mechanism. Front Cell Infect Microbiol 2022; 12: 1020583.
[19] Hodges N, Mackenzie H, D'Souza N, Brown G and Miskovic D. Survival outcomes for right-versus left-sided colon cancer and rectal cancer in england: a propensity-score matched population-based cohort study. Eur J Surg Oncol 2022; 48: 841-849.
[20] Asghari-Jafarabadi M, Wilkins S, Plazzer JP, Yap R and McMurrick PJ. Prognostic factors and survival disparities in right-sided versus left-sided colon cancer. Sci Rep 2024; 14: 12306.
[21] Salih S, Abdelhag I, Abdalla W, Mosad S and Hassan M. Computational detection of deleterious single nucleotide polymorphisms in human adenomatous polyposis coli gene the gate-keeper of colorectal carcinoma. Int J Comput Bioinfo In Silico Model 2014; 3: 531-537.
[22] Salem ME, Battaglin F, Goldberg RM, Puccini A, Shields AF, Arguello D, Korn WM, Marshall JL, Grothey A and Lenz HJ. Molecular analyses of left- and right-sided tumors in adolescents and young adults with colorectal cancer. Oncologist 2020; 25: 404-413.
[23] Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.
[24] Wang P, Chen Y and Wang C. Beyond tumor mutation burden: tumor neoantigen burden as a biomarker for immunotherapy and other types of therapy. Front Oncol 2021; 11: 672677.
[25] Antoniotti C, Korn WM, Marmorino F, Rossini D, Lonardi S, Masi G, Randon G, Conca V, Boccaccino A, Tomasello G, Passardi A, Swensen J, Ugolini C, Oberley M, Tamburini E, Casagrande M, Domenyuk V, Fontanini G, Giordano M, Abraham J, Spetzler D, Falcone A, Lenz HJ and Cremolini C. Tumour mutational burden, microsatellite instability, and actionable alterations in metastatic colorectal cancer: next-generation sequencing results of TRIBE2 study. Eur J Cancer 2021; 155: 73-84.
[26] Tougeron D, Fauquembergue E, Rouquette A, Le Pessot F, Sesboüé R, Laurent M, Berthet P, Mauillon J, Di Fiore F, Sabourin JC, Michel P, Tosi M, Frébourg T and Latouche JB. Tumor-infiltrating lymphocytes in colorectal cancers with microsatellite instability are correlated with the number and spectrum of frameshift mutations. Mod Pathol 2009; 22: 1186-1195.
[27] Fang M, Ou J, Hutchinson L and Green MR. The BRAF oncoprotein functions through the transcriptional repressor MAFG to mediate the CpG Island Methylator phenotype. Mol Cell 2014; 55: 904-915.
[28] Kadowaki S, Kakuta M, Takahashi S, Takahashi A, Arai Y, Nishimura Y, Yatsuoka T, Ooki A, Yamaguchi K, Matsuo K, Muro K and Akagi K. Prognostic value of KRAS and BRAF mutations in curatively resected colorectal cancer. World J Gastroenterol 2015; 21: 1275-1283.

[29] Harvey NT and Ruszkiewicz A. Serrated neoplasia of the colorectum. World J Gastroenterol 2007; 13: 3792-3798.
[30] Rad R, Cadiñanos J, Rad L, Varela I, Strong A, Kriegl L, Constantino-Casas F, Eser S, Hieber M, Seidler B, Price S, Fraga MF, Calvanese V, Hoffman G, Ponstingl H, Schneider G, Yusa K, Grove C, Schmid RM, Wang W, Vassiliou G, Kirchner T, McDermott U, Liu P, Saur D and Bradley A. A genetic progression model of Braf(V600E)-induced intestinal tumorigenesis reveals targets for therapeutic intervention. Cancer Cell 2013; 24: 15-29.
[31] Tran CG, Goffredo P, Mott SL, Hart A, You YN, Vauthey JN, Weigel RJ and Hassan I. The impact of KRAS mutation, microsatellite instability, and tumor laterality on the prognosis of nonmetastatic colon cancer. Surgery 2022; 171: 657-665.
[32] Charlton ME, Kahl AR, Greenbaum AA, Karlitz JJ, Lin C, Lynch CF and Chen VW. KRAS testing, tumor location, and survival in patients with stage IV colorectal cancer: SEER 2010-2013. J Natl Compr Canc Netw 2017; 15: 1484-1493.
[33] Lavery JA, Brown S, Curry MA, Martin A, Sjoberg DD and Whiting K. A data processing pipeline for the AACR project GENIE biopharma collaborative data with the {genieBPC} R package. Bioinformatics 2022; 39: btac796.

Supplementary Table 1. Treatment regimens for stage IV colon cancer patients, stratified by LCC and RCC, including targeted therapies and chemotherapy across different treatment lines

Regimen Type	Line	Stage I-III LCC	Stage I-III RCC	Stage IV LCC	Stage IV RCC
Bevacizumab +	1st	8	11	69	66
	2nd	29	38	79	56
	3rd	31	24	59	38
Cetuximab +	1st	0	0	2	0
	2nd	2	3	5	1
	3rd	6	5	9	5
Panitumumab +	1st	1	0	3	3
	2nd	2	1	4	1
	3rd	2	5	13	5
ICI	1st	2	1	0	0
	2nd	0	2	0	2
	3rd	0	4	0	5
Chemotherapy	1st	131	159	121	94
	2nd	65	72	88	83
	3rd	35	52	76	59
NA	1st	19	46	7	7
	2nd	63	101	26	27
	3rd	87	127	45	58

NA: not applicable.

Supplementary Table 2. Comparison of treatment regimens between Stage I-III and Stage IV colon cancer patients, including targeted therapies and chemotherapy across different treatment lines

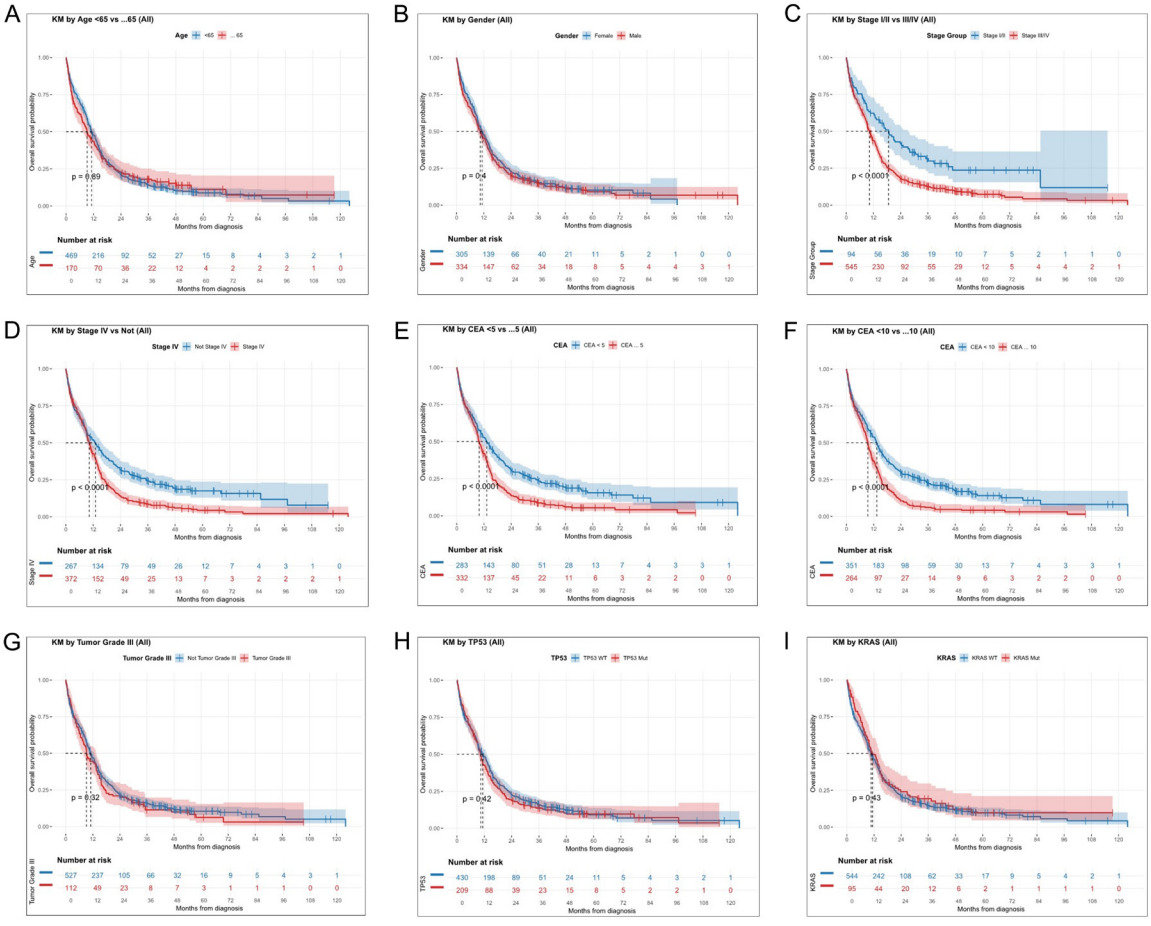
Regimen Type	Stage I-III (n)	Stage IV (n)	*p*-value
Bevacizumab +	128	207	1.6×10^{-4}
Cetuximab +	4	14	5.39×10^{-2}
Panitumumab +	6	20	1.61×10^{-2}
ICI	1	5	2.23×10^{-1}
Chemotherapy	231	285	1.91×10^{-1}
NA	169	78	

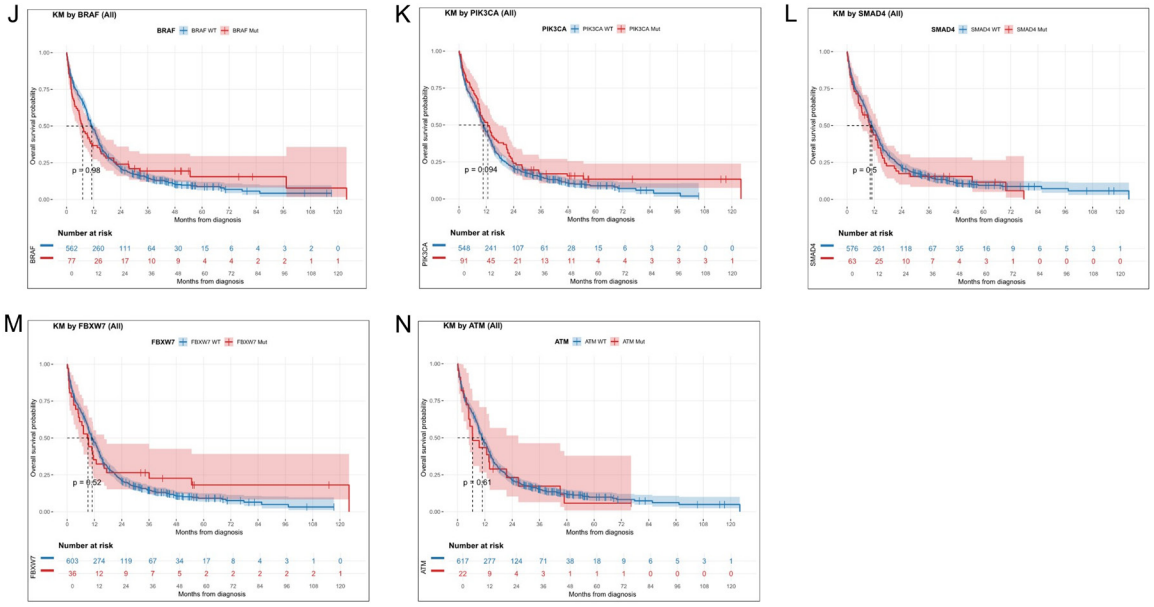
Patient counts and *p*-values are shown for group comparisons.

Supplementary Table 3. Univariate analysis of overall survival in the combined group

Variables	HR	95% CI	*p*-value
Male	1.07	0.91-1.27	0.403
Age ≥ 65	1.01	0.84-1.23	0.892
Stage III/IV	1.77	1.36-2.29	1.66×10^{-5}
Stage IV	1.52	1.28-1.81	2.54×10^{-6}
Tumor Grade III	1.12	0.90-1.38	0.320
CEA ≥ 5 ng/mL	1.53	1.28-1.82	1.86×10^{-6}
CEA ≥ 10 ng/mL	1.63	1.37-1.94	3.08×10^{-8}
TP53	1.08	0.90-1.28	0.416
KRAS	0.91	0.71-1.15	0.431
PIK3CA	0.81	0.64-1.04	0.096
BRAF	1.00	0.77-1.31	0.975
SMAD4	1.10	0.83-1.46	0.501
FBXW7	0.88	0.60-1.29	0.519
ATM	1.12	0.71-1.78	0.615

HR: Hazard ratios, CI: 95% confidence intervals, and *p*-values are shown for each clinical and genomic variable in the combined group of colon cancer patients (n = 750).



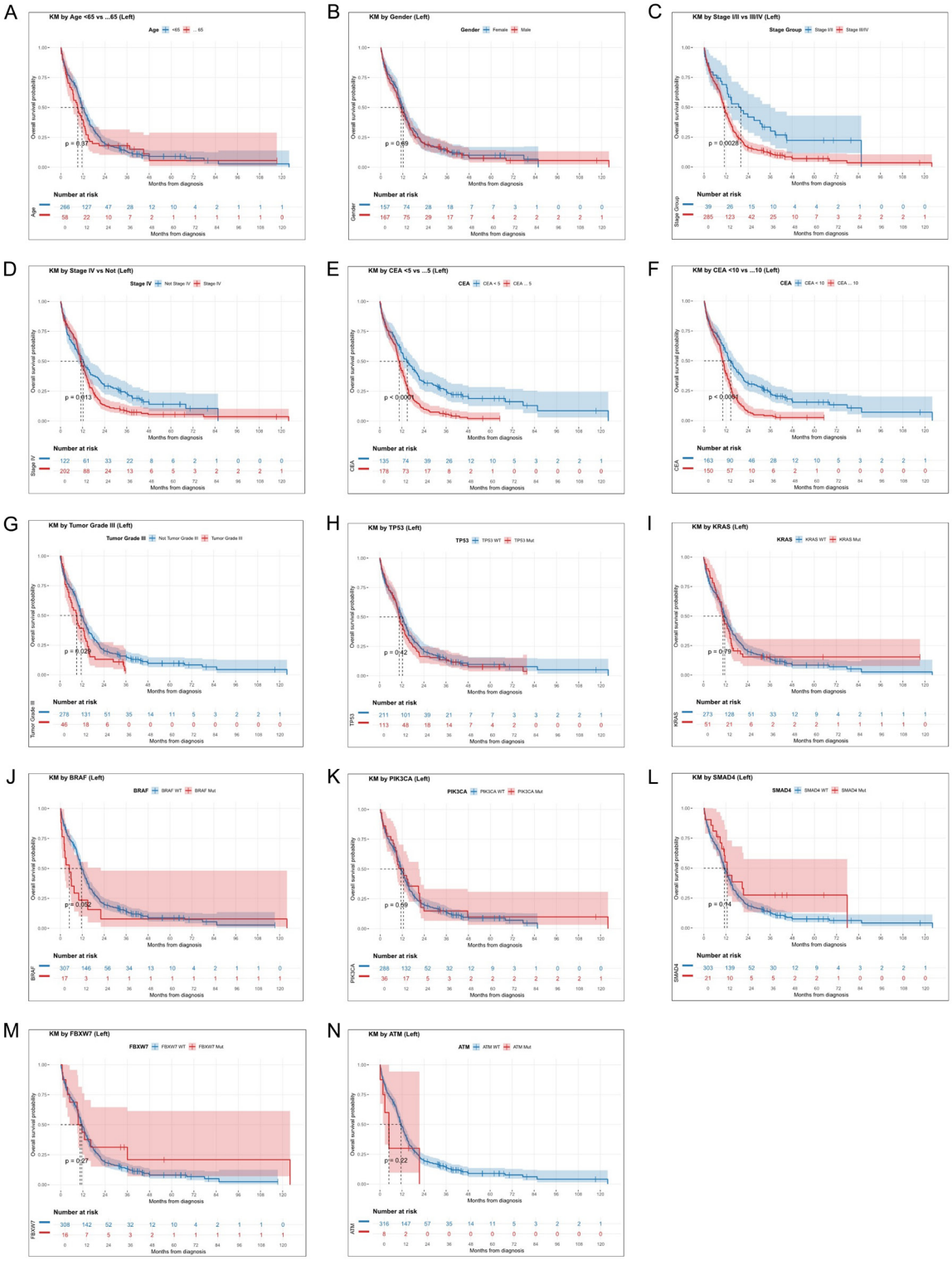


Supplementary Figure 1. Kaplan-Meier analyses of overall survival in the combined group of colon cancer patients (n = 750). Curves are shown for age (A, ≥ 65 vs. < 65), gender (B, male vs. female), stage (C, I/II vs. III/IV), stage IV (D, yes vs. no), CEA ≥ 5 ng/mL (E, ≥ 5 vs. < 5), CEA ≥ 10 ng/mL (F, ≥ 10 vs. < 10), tumor grade III (G, grade III vs. grades I-II), *TP53* mutation (H, mutant vs. wild type), *KRAS* mutation (I, mutant vs. wild type), *BRAF* mutation (J, mutant vs. wild type), *PIK3CA* mutation (K, mutant vs. wild type), *SMAD4* mutation (L, mutant vs. wild type), *FBXW7* mutation (M, mutant vs. wild type), and *ATM* mutation (N, mutant vs. wild type).

Supplementary Table 4. Univariate analysis of overall survival in the left-sided colon cancer group

Variable	HR	95% CI	*p*-value
Male	1.05	0.83-1.32	0.692
Age ≥ 65	1.15	0.85-1.57	0.366
Stage III/IV	1.79	1.22-2.64	0.00323
Stage IV	1.37	1.07-1.75	0.0137
Tumor Grade III	1.44	1.04-1.99	0.0297
CEA ≥ 5 ng/mL	1.86	1.44-2.39	1.46×10^{-6}
CEA ≥ 10 ng/mL	1.88	1.47-2.40	5.65×10^{-7}
TP53 mutation	1.11	0.87-1.41	0.417
KRAS mutation	1.05	0.75-1.46	0.785
PIK3CA mutation	0.90	0.62-1.32	0.598
BRAF mutation	1.68	0.99-2.84	0.0542
SMAD4 mutation	0.68	0.40-1.14	0.143
FBXW7 mutation	0.72	0.40-1.29	0.274
ATM mutation	1.65	0.73-3.71	0.227

HR: Hazard ratios, CI: 95% confidence intervals, and *p*-values are shown for each clinical and genomic variable in the left-sided colon cancer patients (n = 363).

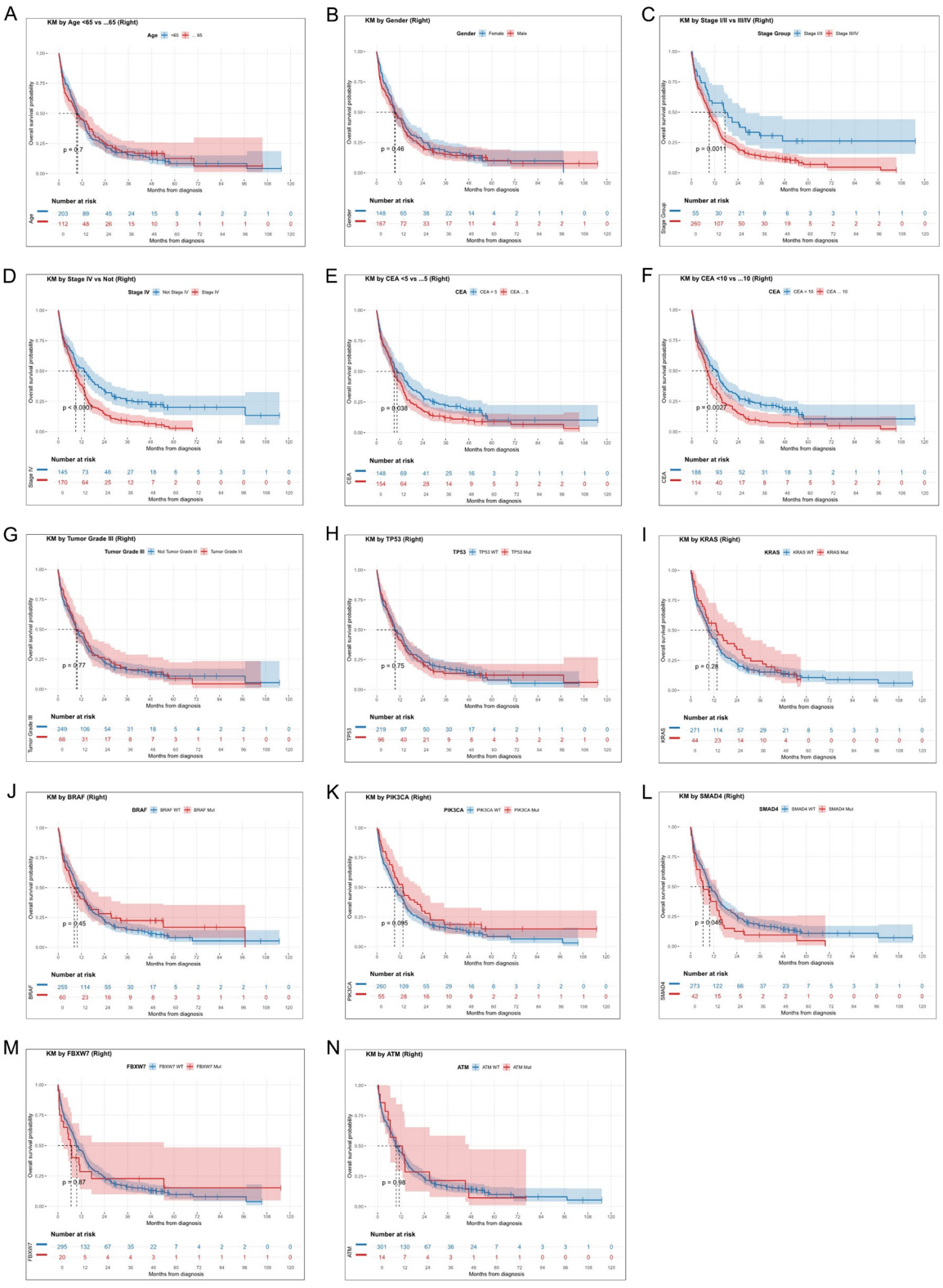


Supplementary Figure 2. Kaplan-Meier analyses of overall survival in the left-sided group of colon cancer patients (n = 363). Curves are shown for age (A, ≥ 65 vs. < 65), gender (B, male vs. female), stage (C, I/II vs. III/IV), stage IV (D, yes vs. no), CEA ≥ 5 ng/mL (E, ≥ 5 vs. < 5), CEA ≥ 10 ng/mL (F, ≥ 10 vs. < 10), tumor grade III (G, grade III vs. grades I-II), *TP53* mutation (H, mutant vs. wild type), *KRAS* mutation (I, mutant vs. wild type), *BRAF* mutation (J, mutant vs. wild type), *PIK3CA* mutation (K, mutant vs. wild type), *SMAD4* mutation (L, mutant vs. wild type), *FBXW7* mutation (M, mutant vs. wild type), and *ATM* mutation (N, mutant vs. wild type).

Supplementary Table 5. Univariate analysis of overall survival in the right-sided colon cancer group

Variable	HR	95% CI	*p*-value
Male	1.10	0.86-1.39	0.456
Age ≥ 65	0.95	0.74-1.23	0.702
Stage III/IV	1.77	1.25-2.51	0.00128
Stage IV	1.70	1.33-2.18	2.68×10^{-5}
Tumor Grade III	0.96	0.72-1.28	0.770
CEA ≥ 5 ng/mL	1.30	1.01-1.66	0.0382
CEA ≥ 10 ng/mL	1.46	1.14-1.88	0.00286
TP53 mutation	1.04	0.81-1.35	0.750
KRAS mutation	0.83	0.58-1.17	0.279
PIK3CA mutation	0.76	0.55-1.05	0.096
BRAF mutation	0.89	0.65-1.21	0.449
SMAD4 mutation	1.41	1.00-1.99	0.0471
FBXW7 mutation	1.04	0.63-1.74	0.866
ATM mutation	0.99	0.57-1.73	0.976

HR: Hazard ratios, CI: 95% confidence intervals, and *p*-values are shown for each clinical and genomic variable in the right-sided colon cancer patients (n = 387).



Supplementary Figure 3. Kaplan-Meier analyses of overall survival in the right-sided group of colon cancer patients (n = 387). Curves are shown for age (A, ≥ 65 vs. < 65), gender (B, male vs. female), stage (C, I/II vs. III/IV), stage IV (D, yes vs. no), CEA ≥ 5 ng/mL (E, ≥ 5 vs. < 5), CEA ≥ 10 ng/mL (F, ≥ 10 vs. < 10), tumor grade III (G, grade III vs. grades I-II), *TP53* mutation (H, mutant vs. wild type), *KRAS* mutation (I, mutant vs. wild type), *BRAF* mutation (J, mutant vs. wild type), *PIK3CA* mutation (K, mutant vs. wild type), *SMAD4* mutation (L, mutant vs. wild type), *FBXW7* mutation (M, mutant vs. wild type), and *ATM* mutation (N, mutant vs. wild type).