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RESEARCH ARTICLE

Clinicopathological Characteristics and Population-Level Survival Outcomes of Mucinous Adenocarcinoma Across Different Colon Segments: An Analysis Using the Surveillance Epidemiology and End Result Database

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ABSTRACT

Aim: To determine population-level survival differences for patients undergoing curative resection for mucinous adenocarcinoma (MAC) based on specific anatomical colon segment and stage over the last two decades.

Method: The study was conducted using the Surveillance Epidemiology and End Result program. Patients who underwent curative colectomy for MAC between 2004 and 2019 were identified. Demographics and clinical and histopathologic factors were compared for different colon segments, stages, and time periods. Kaplan-Meier survival analysis was conducted for each colon subsite location and stage, and curves were compared using the log-rank test.

Results: A total of 19,427 patients met the inclusion criteria. Patients with proximal colon cancers were significantly older (70.6±12.6 years) and more likely to be female (56.5%) than those with distally located tumor sites (p<0.001). The incidence of MAC was higher in the cecum (30.8%) and ascending colon (27.9%) than at distal sites (3.4-14.6%). The 3-year and 5-year overall survival rates were similar among the different colon sites (3-year survival rate: 66.7-69.9%, 5-year overall survival rate: 54.7-58.7%) for patients at stage 2, 3, and 4. Only patients at stage 1 exhibited significantly different outcomes among colon sites (p=0.018). Patients at stage 1 with MAC in the sigmoid colon exhibited a significantly improved overall survival rate compared with other colon sites (p<0.001). Multivariable Cox regression analysis revealed that age [hazard ratio (HR): 2.2, p<0.001], stage (p<0.001), degree of differentiation (p<0.001), and greater tumor diameter (HR: 1.05, p=0.007) were independently associated with less favorable survival.

Conclusion: In contrast to previous literature, our study revealed that the results of long-term population-level stage-by-stage survival analysis for MAC were similar across seven different colon sites, except for patients at stage 1, who exhibited significantly improved survival for MAC in the sigmoid colon.

Keywords: Surveillance Epidemiology and End Result data, colon cancer, mucinous adenocarcinoma

Introduction

Mucinous adenocarcinoma (MAC) is a less common subtype of colorectal adenocarcinoma that accounts for 5-15% of all cases and is defined by the World Health Organization (WHO) as the presence of extracellular mucin in >50% of the tumor area.[1,2] Many studies have highlighted the distinct clinical and pathological features of MAC, which is regarded as being more advanced at diagnosis and has a less favorable prognosis than non-MAC.[3]

Colorectal cancer encompasses a heterogeneous group of tumors, characterized by significant variations in clinical presentation, genetic configuration, and, ultimately, survival

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rates.[4] Among the numerous factors that contribute to this diversity, the specific localization of the primary colon tumor plays a particularly crucial role. Given the intricate nature of tumor anatomy and location, selecting the appropriate surgical technique and oncological approach is of the utmost importance, as both can profoundly influence disease progression, treatment decision-making, and overall patient care.[5,6] Consequently, contemporary research efforts have increasingly focused on unraveling the molecular, histological, and prognostic implications associated with the precise segments of the colon affected by cancer.[7]

Considering the relatively low prevalence rates of MAC in the setting of colorectal surgery, comprehensive population-level cancer data are essential for generating meaningful insights into the impact of clinical and epidemiological factors, including tumor location, age, sex, and disease stage, on disease outcomes. To the best of our knowledge, there is currently no study that compares the stage-by-stage progression of each colon segment over time. The main objective of this research is, therefore, to comprehensively evaluate population-level survival differences for patients undergoing curative surgery for MAC based on specific anatomical colon segment and stage over the last two decades.

Materials and Methods

Patients who underwent curative colonic resection for stage 1-4 colon MAC between 2004 and 2019 were identified using the Surveillance Epidemiology and End Result (SEER) database and reviewed. Patients who were diagnosed with primary colon MAC were identified according to the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) topography codes (ICD-O-3 codes: 8480 and 8481) and categorized into seven colon anatomical subsegments. The ICD-O-3 topography codes for the anatomical subsegments of the colon, from proximal to distal, were as follows: cecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.3), transverse colon (C18.4), splenic flexure (C18.5), descending colon (C18.6), and sigmoid colon (C18.7). Patients who were initially diagnosed with a second primary cancer in addition to colon cancer, unknown tumor site and stage (T, N), and/or with recurrent/synchronous cancer were excluded from the study. Data were extracted from the SEER database and approved by the Ankara University Institutional Ethics Review Board (approval number: İ07-450-22, date: 15.08.2022).

The present study utilized data sourced from the National Cancer Institute SEER program database, renowned for its comprehensive and diverse compilation of cancer-related data spanning multiple regions across the United States. The SEER database, accessible at https://seer.cancer.gov/, is an integral component of the SEER program at the National Cancer Institute, dedicated to gathering both incidence and survival data from all participating areas.[8]

Demographics, histopathological outcomes, and long-term overall survival rates were assessed and compared among different colon segments over different time intervals. Survival analysis was conducted for each colon location and stage. The primary endpoint of this study is to reveal the impact of tumor localization on overall survival.

Parameters

The location of primary colon MAC and its histology were defined according to the criteria in ICD-O-3 (8480, 8481). Each colon segment was localized and coded based on the location indicated in a priority order of preoperative imaging, surgery report, and pathology report. The following variables were included in our study: age, gender, year of diagnosis, American Joint Committee on Cancer stage (T, N), histologic grade (well differentiated, moderately differentiated, poorly differentiated/undifferentiated/anaplastic), number of lymph nodes retrieved, metastatic lymph nodes, and chemotherapy status. The negative lymph node number was calculated as the difference between the total lymph node number and metastatic lymph node number. The study time period was categorized into four subgroups (2004-2007, 2008-2011, 2012-2015, and 2016-2019), and changes over the years were evaluated.

Statistical Analysis

Statistical analysis was performed using descriptive statistics, including mean, standard deviation, median, minimum, and maximum values. The chi-square test or Fisher's exact test was used to compare categorical variables among the groups, the Student's t-test was used for continuous variables, and the Mann-Whitney U test was used for non-normally distributed continuous or ordinal variables. Kaplan-Meier survival analysis and the log-rank test were used for univariate analysis, and Cox proportional hazards regression was used for multivariate analysis. Variables with a p value <0.25 in the univariate Cox proportional hazards regression were selected as candidates for the multivariate model along with all variables of known clinical importance. The final model was constructed using variables with a p value <0.05, which was considered statistically significant. Statistical analysis was performed using Jamovi statistical software (version: 2.3.1) and R version 4.3.1.

Results

A total of 33,497 patients were initially identified from the 2004-2019 SEER dataset. After applying the exclusion criteria, which included cases with unknown stage (n=8,480), appendix involvement (n=3,440), colon not otherwise specified (n=770), overlapping lesions of the colon (n=515),

and patients with signet-ring cell histology (n=75,456), 28,772 patients remained. Among them 24,922 patients had undergone surgery. After further refining the dataset to include only cases with complete dates and a minimum survival duration greater than 0 days, as well as excluding patients with missing TNM stages and those with follow-up periods greater than 0 months, a final cohort of 19,427 patients met the inclusion criteria for analysis.

The comparison of demographics and pathological characteristics among different colon segments is presented in Table 1. Patients with proximal colon cancer exhibited a significantly higher average age of 70.6 years (±12.6) and a greater likelihood of being female (56.5%) than those with distally located tumors (p<0.001). The incidence of MAC was notably elevated in the cecum (30.8%) and ascending colon (27.9%) in contrast to the lower rates observed at distal sites (ranging from; 3.4% to 14.6%) (Figure 1). Histopathological tumor stage, T-stage, N-stage, and grade of differentiation were statistically different among the study groups (p<0.001). Chemotherapy rates were significantly higher in more proximally located MAC (cecum: 66.3%, ascending colon: 70.9%) compared with more distal sites (sigmoid colon: 58.9%, descending colon: 62.5%) (p<0.001).

Regarding overall survival rates, this study found remarkable similarity among different colon sites. For different colon segments, the 3-year survival rates ranged from 66.7% to 69.9%, and the 5-year survival rates ranged from 54.7% to 58.7% (Figure 2). The Kaplan-Meier survival curves comparing different colon segments at each stage are presented in Figure 3. The overall survival rates were comparable among different colon segments in patients at stage 2, 3, and 4. Notably, significant differences in outcomes were observed only among patients at stage 1 across the different colon sites (p=0.018). In patients at stage 1, the sigmoid colon was associated with significantly improved overall survival rate compared with the other colon sites (p<0.001). To delve deeper into the factors influencing long-term survival, we conducted a comprehensive multivariable Cox regression analysis across the entire cohort (Table 2). This analysis revealed several independent factors that were associated with poorer survival outcomes, including age [hazard ratio (HR): 2.2, p<0.001), cancer stage (p<0.001), degree of differentiation (p<0.001), and greater tumor diameter (HR: 1.05, p=0.007).

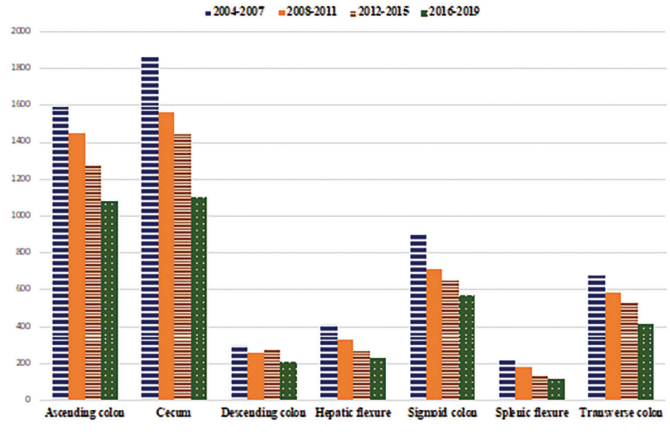
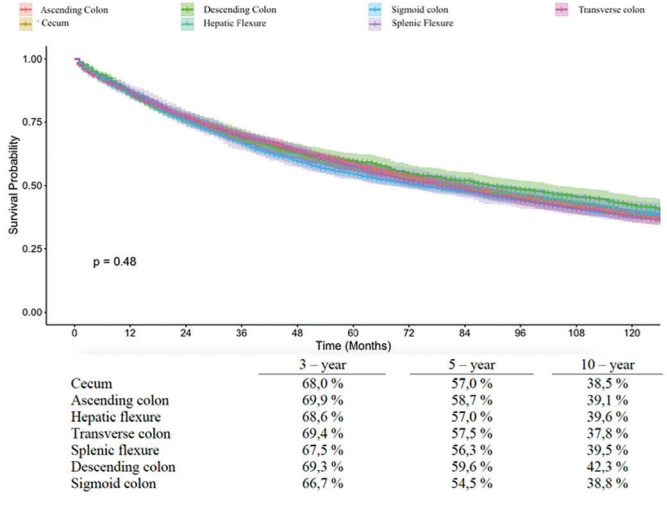


Figure 1. Prevalence of mucinous adenocarcinoma by years and different colon locations. Rate of mucinous adenocarcinoma by tumor locations (in blue rectangles)

Discussion

This study represents one of the most extensive investigations to date on the demographics and histopathological characteristics of colon MAC based on anatomical colon segment locations. Our research provides a novel perspective by performing a detailed long-term survival analysis, conducted at a population level and evaluated stage by stage, across seven distinct anatomical sites within the colon. The findings revealed that survival outcomes for MAC were largely consistent across the different locations. However, a significant exception was identified among patients at stage 1 - those with tumors located in the sigmoid colon exhibited markedly high survival rates. The reason for significant survival differences among each colon location for patients at stage 1 could be molecular and biological differences. This unique finding underscores the value of considering the anatomical site of the tumor, particularly for early-stage MAC, in understanding prognosis and guiding treatment strategies.

Consistent with our results, MAC was more frequently documented in women, located in the proximal right colon, and presented with advanced stages;[9,10] MAC located at more proximal colon segments generally present with more advanced tumor stages and poorer differentiation, consistent with findings from several other studies.[11] The underlying reasons for this pattern are not yet fully understood, but



	3 – year	5 – year	10 – year
Cecum	68,0 %	57,0 %	38,5 %
Ascending colon	69,9 %	58,7 %	39,1 %
Hepatic flexure	68,6 %	57,0 %	39,6 %
Transverse colon	69,4 %	57,5 %	37,8 %
Splenic flexure	67,5 %	56,3 %	39,5 %
Descending colon	69,3 %	59,6 %	42,3 %
Sigmoid colon	66,7 %	54,5 %	38,8 %

Figure 2. Kaplan-Meier survival curve by different colonic location

Table 1. Demographics and pathological characteristics of mucinous adenocarcinoma by different colon locations

Characteristics	Right-sided colon cancer				Left-sided colon cancer			p value
	Cecum, (n=5,975)	Ascending colon, (n=5,414)	Hepatic flexure, (n=1,248)	Transverse colon, (n=2,218)	Splenic flexure, (n=669)	Descending colon, (n=1,059)	Sigmoid colon, (n=2,844)	
Age (years), mean (SD)	70.6 (12.6)	71.0 (12.5)	70.0 (13.3)	69.8 (13.4)	67.9 (13.4)	65.4 (14.4)	66.0 (13.7)	<0.001
Age (years), median (interquartile range)	73 (19)	74 (19)	72 (19)	73 (19)	70 (20)	67 (22)	67 (22)	
Gender, n (%)								
Male, (%)	2,598 (43.5)	2,367 (43.7)	624 (50.0)	1,021 (46.0)	349 (52.2)	593 (56.0)	1,569 (55.2)	<0.001
Female, (%)	3,377 (56.5)	3,047 (56.3)	624 (50.0)	1,197 (54.0)	320 (47.8)	466 (44.0)	1,275 (44.8)	
Year of diagnosis, n (%)								
2004-2007	1,867 (31.2)	1,603 (29.6)	418 (33.5)	680 (30.7)	226 (33.8)	305 (28.8)	906 (31.9)	0.026
2008-2011	1,565 (26.2)	1,451 (26.8)	334 (26.8)	587 (26.4)	185 (27.6)	260 (24.6)	713 (25.1)	
2012-2015	1,443 (24.2)	1,276 (23.6)	267 (21.4)	534 (24.1)	139 (20.8)	282 (26.6)	652 (22.9)	
2016-2019	1,100 (18.4)	1,084 (20.0)	229 (18.3)	417 (18.8)	119 (17.8)	212 (20.0)	573 (20.1)	
Tumor stage, n (%)								
Stage 1	820 (13.7)	857 (15.8)	181 (14.5)	276 (12.4)	76 (11.4)	131 (12.4)	360 (12.7)	<0.001
Stage 2	2,354 (39.4)	2,288 (42.3)	533 (42.7)	1,003 (45.2)	281 (42.0)	455 (43.0)	1,024 (36.0)	
Stage 3	2,137 (35.8)	1,844 (33.1)	424 (34.0)	722 (32.6)	247 (36.9)	348 (32.8)	1,118 (39.3)	
Stage 4	664 (11.1)	425 (7.8)	110 (8.8)	217 (9.8)	65 (9.7)	125 (11.8)	342 (12.0)	
Grade, n (%)								
Well differentiated	561 (9.4)	547 (10.1)	133 (10.7)	214 (9.7)	66 (9.9)	151 (14.3)	412 (14.5)	<0.001
Moderately differentiated	4,083 (68.3)	3,646 (67.3)	829 (66.4)	1,500 (67.6)	472 (70.6)	721 (68.1)	1,896 (66.7)	
Poorly differentiated	1,128 (18.9)	1,050 (19.4)	248 (19.9)	426 (19.2)	115 (17.2)	163 (15.4)	478 (16.8)	
Undifferentiated	203 (3.4)	171 (3.2)	38 (3.0)	78 (3.5)	16 (2.3)	24 (2.2)	58 (2.0)	
T-stage, n (%)								
T1	178 (3.0)	231 (4.3)	34 (2.7)	80 (3.6)	22 (3.3)	37 (3.5)	144 (5.1)	<0.001
T2	904 (15.1)	818 (15.1)	186 (14.9)	255 (11.5)	72 (10.7)	120 (11.3)	340 (12.0)	
T3	3,594 (60.2)	3,573 (66.0)	857 (68.7)	1,508 (68.0)	457 (68.3)	693 (65.5)	1,705 (59.9)	
T4	1,299 (21.7)	792 (14.6)	171 (13.7)	375 (16.9)	118 (17.7)	209 (19.7)	655 (23.0)	
N-stage, n (%)								
N0	3,259 (54.5)	3,218 (59.4)	733 (58.7)	1,322 (59.6)	368 (55.0)	611 (57.7)	1,449 (50.9)	<0.001
N1	1,519 (25.4)	1,281 (23.7)	298 (23.9)	520 (23.9)	186 (27.8)	273 (25.8)	798 (28.1)	
N2	1,197 (20.1)	915 (16.9)	217 (17.4)	366 (16.5)	115 (17.2)	175 (16.5)	597 (21.0)	

Table 1. Continued

Characteristics	Right-sided colon cancer			Transverse colon, (n=2,218)	Left-sided colon cancer			p value
	Cecum, (n=5,975)	Ascending colon, (n=5,414)	Hepatic flexure, (n=1,248)		Splenic flexure, (n=669)	Descending colon, (n=1,059)	Sigmoid colon, (n=2,844)	
M stage, n (%)								
M0	5,311 (88.9)	4,989 (92.1)	1,138 (91.2)	2,001 (90.2)	604 (90.3)	934 (88.2)	2,502 (88.0)	<0.001
M1	664 (11.1)	425 (7.9)	110 (8.8)	217 (9.8)	65 (9.7)	125 (11.8)	342 (12.0)	
Number of retrieved regional lymph nodes, n (%)								
<12 lymph nodes	381 (6.4)	263 (4.9)	77 (6.2)	179 (8.1)	61 (9.1)	71 (6.7)	247 (8.7)	<0.001
>12 lymph nodes	5,594 (93.6)	5,151 (95.1)	1,171 (93.8)	2,039 (91.9)	608 (90.9)	988 (93.3)	2,597 (91.3)	
Number of positive regional lymph nodes, mean (SD)	2.2 (4.2)	1.8 (3.8)	1.8 (4.0)	1.8 (3.9)	2.3 (4.2)	1.81 (3.6)	2.3 (4.4)	0.008
Tumor size (mm), mean (SD)	60.0 (40.6)	57.8 (40.5)	55.5 (27.0)	55.0 (36.1)	57.5 (33.8)	54.6 (29.2)	53.2 (41.9)	<0.001
Chemotherapy, n (%)								
Yes	2,016 (66.3)	1,575 (70.9)	377 (69.8)	698 (68.5)	233 (65.2)	397 (62.5)	1169 (58.9)	<0.001
No/unknown	3,959 (33.7)	3,839 (29.1)	871 (30.2)	1,520 (31.5)	436 (34.8)	662 (37.5)	1,675 (41.1)	

CI, confidence interval; SD, standard deviation

molecular and genetic factors such as microsatellite instability and mismatch repair deficiency, which are linked to MAC, might play a role. Microsatellite instability has been associated with poor differentiation and advanced tumor stages in multiple reports. Due to the lack of detailed molecular data in the SEER database, microsatellite instability could not be accounted for in this analysis, which is a limitation of the study.[12,13] The rate of MAC decreased over the study period, potentially due to colorectal cancer screening programs implemented in the United States. It is widely accepted that cancer screening, including colonoscopy and polypectomy, reduces mortality by detecting tumors at an earlier stage.[14] Because MAC is typically detected at a more advanced stage, the effective screening and removal of polyps might result in fewer MAC cases being identified in later study periods. Additionally, the widespread adoption of the histologic criteria for MAC defined by the WHO could have contributed to the reduction in MAC diagnoses over time.

Despite the distinct clinicopathologic characteristics of right-sided MAC compared with that of the left colon, our long-term population-level survival analysis in this study revealed similar outcomes across different colon locations. The complex interplay between clinicopathologic features and tumor location in colon cancer may partly account for the contradictory findings in the literature regarding survival comparisons.[6,9,15-17] Some studies have reported higher survival rates on the left side compared with the right, whereas others have found no significant relationship between colon location and survival. Considering these conflicting results in the literature, we hypothesized that survival comparisons between the right and left colon may vary depending on specific contexts characterized by different mutation profiles despite having the same histological type. This variability underscores the need for further research to elucidate the molecular underpinnings that contribute to survival disparities observed across different anatomical locations within the colon.

In the multivariate analysis, we found that location was not an independent prognostic factor in the whole population. Other studies have used the SEER database or SEER-Medicare database to explore the role of location on survival, with numerous studies investigating the impact of primary colon cancer location on long-term overall survival.[5,7-11] For instance, Benesch et al.[9] conducted a rigorous 10-year overall survival analysis focusing on all histopathological types of colon cancer, examining the influence of tumor location on survival outcomes, and revealed similar results. Moreover, a comprehensive analysis by Wu et al.[18] encompassing a cohort of patients with colon cancer across various demographics, cancer stages, study durations, and chemotherapy protocols, highlighted a significant association between tumor location and mortality. These collective findings underscore the

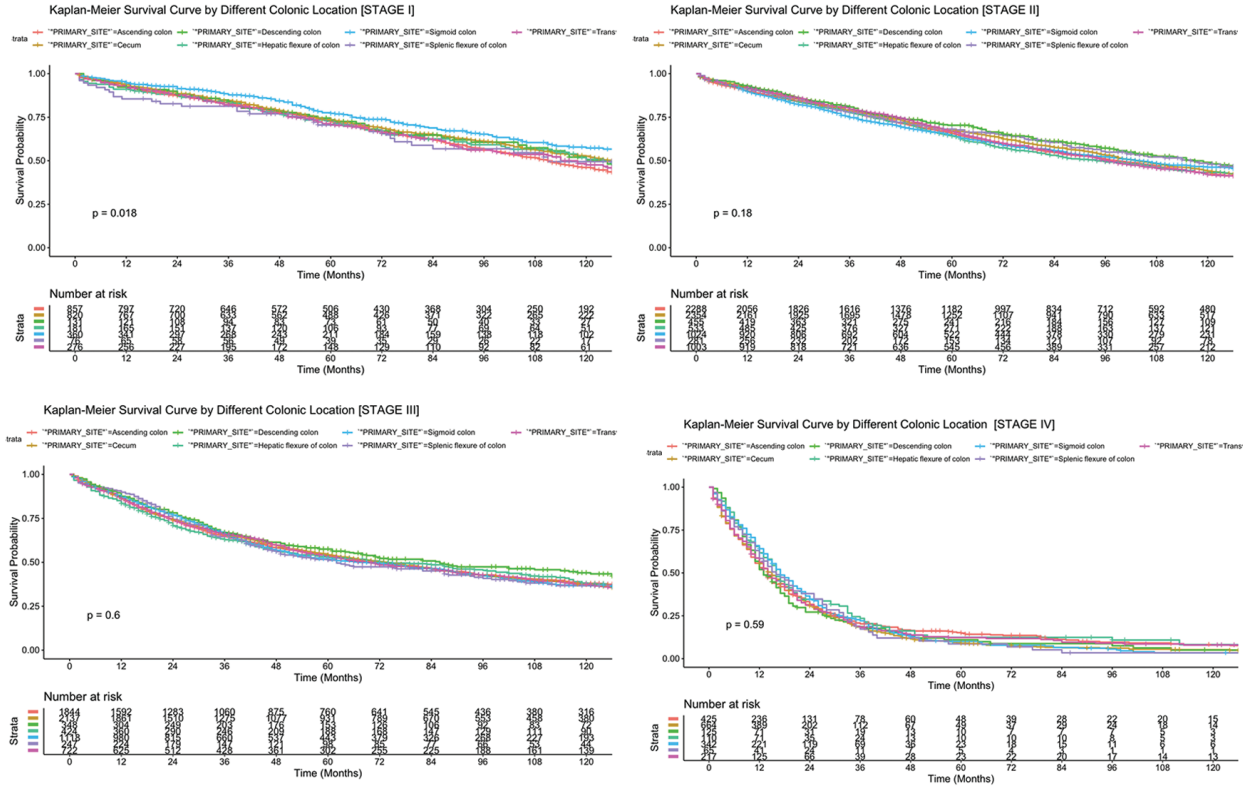


Figure 3. Kaplan-Meier survival curves for stage 1, 2, 3, and 4

complexity of how tumor location within the colon impacts survival outcomes, warranting further exploration into the underlying mechanisms driving these disparities.

Study Limitations

Our study has some limitations that should be considered before interpreting the findings. First, the SEER database lacks detailed information on certain pathological parameters, such as neural or vascular invasion, and treatment-related data, including the quality of surgery and whether a case was elective or an emergency. These factors are known to be closely linked to survival outcomes and could have influenced our results. Second, the absence of molecular cancer profiles prevented us from exploring the intrinsic mechanisms underlying survival differences among various subgroups.[7,19] Such molecular data could have provided valuable insights into the underlying biology driving survival disparities. Additionally, the inclusion of new centers in the SEER database throughout the study period could have introduced variability in treatment modalities and approaches, potentially impacting outcomes. Changes in staging systems also need to be considered. Moreover, because our study relied on a database, some patients were excluded from the statistical analysis due to missing or incomplete data, which could have introduced bias. Certain demographic data, symptoms, treatments, and disease-related information were not available, limiting the depth of our analysis. Furthermore, due to the general nature of some data, we were unable to conduct more in-depth analyses on certain aspects. Finally, the lack of a definitive definition for each colon segment, coded according to the ICD coding system, makes it challenging to assess and compare results from each center. Despite these limitations, we believe that the substantial size of our study cohort and the extended follow-up period compensate to some extent for these drawbacks. This study represents one of the largest and most comprehensive investigations to date, providing a valuable epidemiological overview of colon cancer. While acknowledging these limitations, we trust that our findings contribute key insights to the field of colon cancer research and further understanding of this complex disease.

Conclusion

Our study offers new insights that contrast with the existing literature on colon MAC. Specifically, our comprehensive long-term population-level analysis examined survival rates stage by stage across seven distinct colon sites. Unlike previous findings, our results demonstrated that survival outcomes were remarkably consistent across these different sites for most stages of MAC. However, a notable exception was observed for patients at stage 1, who exhibited significantly better survival

Table 2. Univariate and multivariate analysis

Mucinous adenocarcinoma	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (ref = ≤65 years old)						
>65 years old	2,285	(2,185, 2,391)	<0.001	2,270	(2,167, 2,378)	<0.001
Gender (ref = Female)						
Male	1,002	(0.965, 1,041)	0.91			
Year of diagnosis (ref = 2004-2007)						
2016-2019	0.87	(0.981, 1,076)	<0.001			
2012-2015	0.99	(0.936, 1.04)	0.61			
2008-2011	1.02	(0.98, 1,076)	0.26			
Primary location (ref = descending colon)						
Cecum	1,092	(0.998, 1,195)	0.054			
Ascending colon	1,059	(0.967, 1,159)	0.22			
Hepatic flexure	1,051	(0.94, 1,175)	0.38			
Transverse colon	1,075	(0.972, 1,188)	0.158			
Splenic flexure	1,050	(0.921, 1,197)	0.46			
Sigmoid colon	1,095	(0.994, 1,206)	0.067			
Primary side (ref = left-sided colon cancer)						
Right-sided colon cancer	1,008	(0.964, 1,053)	0.74			
Tumor stage (ref = stage 1)						
Stage 2	1,174	(1,101, 1,251)	<0.001	1,244	(1,164, 1,328)	<0.001
Stage 3	1,528	(1,433, 1,629)	<0.001	2,121	(1,978, 2,275)	<0.001
Stage 4	5,718	(5,310, 6,157)	<0.001	8,452	(7,790, 9,168)	<0.001
Grade (ref = well differentiated)						
Moderately differentiated	1,136	(1,065, 1,212)	<0.001	1,087	(0.920, 1,019)	0.012
Poorly differentiated	1,481	(1,377, 1,593)	<0.001	1,246	(0.803, 1,157)	<0.001
Undifferentiated	1,677	(1,492, 1,885)	<0.001	1,468	(0.681, 1,652)	<0.001
Tumor size (ref = 50 mm)						
≥50 mm	1,141	(1,098, 1,185)	<0.001	1,056	(1,015, 1,099)	0.007
Chemotherapy (ref = no)						
Yes	0.85	(0.818, 0.887)	<0.001	0.609	(0.580, 0.639)	0.987

HR: Hazard Ratio, CI, confidence interval

rates for MAC in the sigmoid colon. This finding highlights the unique behavior of stage 1 MAC in the sigmoid colon and underscores the importance of site-specific considerations in the management and prognosis of colon cancer. This manuscript underscores the critical need for future studies aimed at deepening our understanding of the behavior of colon cancers. Such research is essential for refining treatment strategies and improving patient outcomes across different tumor stages and locations.

Ethics

Ethics Committee Approval: This study was approved by the Ankara University Ethics Committee (approval number: İ07-450-22, date: 15.08.2022).

Informed Consent: It wasn't obtained.

Authorship Contributions

Surgical and Medical Practices: Ç.B., E.G., M.A.K., Concept: Ç.B., M.E., E.G., M.A.K., Design: Ç.B., M.E., Data Collection

or Processing: Ç.B., M.E., Analysis or Interpretation: Ç.B., M.E., Literature Search: Ç.B., M.E., Writing: Ç.B., M.E., E.G., M.A.K.

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