European Review for Medical and Pharmacological Sciences 2024; 28: 615-621

Factors affecting survival in stage 2-3 colorectal cancer: a single-center retrospective study

M. KARAHAN[1], F. MULKUT[1], G. OKUT[2]

[1]Department of General Surgery, Health Science University, Istanbul Kartal Lutfu Kırdar City Hospital, Istanbul, Turkey
[2]Department of Gastroenterology Surgery, Health Science University, Izmir Bayraklı City Hospital, İzmir, Turkey

Abstract. – OBJECTIVE: The principal aim of this research is to investigate the variables that exert a discernible impact on the overall survival (OS) of individuals afflicted with colorectal cancer (CRC) harboring pathologic stages 2-3, as delineated within the TNM staging schema tailored to CRC, an established framework governed by the American Joint Committee on Cancer (AJCC).

PATIENTS AND METHODS: Patients with preoperative stages 1 and 4, patients with a history of other organ malignancy, patients who could not undergo curative resection, patients with systemic malignant diseases (leukemia, lymphoma, etc.), patients with synchronous tumors, and patients with positive surgical margins were excluded from the study. Notable pathological parameters, including tumor grade, perforation status, lymphovascular invasion, perineural invasion, the presence of mucinous components, and tumor size, were ascertained through pathological examination of resected specimens.

RESULTS: Curative resection was performed on 241 patients. The mean age of all patients was calculated to be 65.67±16.04. The average tumor size was measured as 5.03±2.22 cm. The 1-year survival rate of the patients was found to be 84.3%, 3-year survival rate was 69.0%, and 5-year survival rate was 52.9%. According to the COX regression analysis, the categorical variables that were found to be significantly associated with OS were grade (p=0.046), emergency surgery (p<0.001), and tumor localization (p=0.015).

CONCLUSIONS: The initial patient and tumor characteristics at baseline have demonstrated substantial predictive capacity regarding patient outcomes following disease recurrence. Survival analyses showed that undergoing emergency surgery, having the tumor located in the rectum, and having a "poor" tumor grade adversely affected survival.

Key Words:
Colon cancer, Rectum cancer, Stage 2, Stage 3.

Introduction

In the year 2022, colorectal cancer (CRC) emerged as the fourth most frequently diagnosed cancer in the United States, and the second leading cause of cancer-related mortality. Surgical resection has established itself as the prevailing standard of care for non-metastatic colorectal cancers[1]. Nonetheless, surgery in isolation is associated with a substantial incidence of locoregional recurrence, particularly in locally advanced rectal cancer patients classified as T3-T4 and N positive according to the tumor/node/metastasis (TNM) staging system devised by the American Joint Committee on Cancer (AJCC)[2]. To mitigate this risk, neoadjuvant or adjuvant radiotherapy (RT) is recommended for eligible patients. The detection of locoregional recurrence in CRC patients significantly diminishes overall survival, underscoring the importance of factors contributing to a higher recurrence rate and a compromised prognosis[3].

Despite the adoption of a standardized treatment regimen involving radical surgery and adjuvant chemotherapy, the survival outcomes in CRC patients exhibit significant heterogeneity and remain unsatisfactory. The 5-year survival rates are markedly disparate, with 90.1% observed among patients with localized CRC, 69.2% among patients with regional lymph node involvement, and a mere 11.7% among patients with distant metastases[4]. Pathologic evaluation of the resected specimen currently serves as the most potent tool for prognostic assessment subsequent to potentially curative surgery[5]. While factors such as tumor invasion depth, the number of positive lymph nodes, and the presence of metastases serve as robust predictors of prognosis, other clinical, molecular, and histological features can independently influence prognosis, regardless of disease stage[5].

Corresponding Author: Gokalp Okut, MD; e-mail: gokalp.okut@gmail.com

The primary objective of this study is to examine the factors that exert an influence on overall survival (OS) in patients diagnosed with CRC at pathologic stages 2-3, as outlined by the TNM staging system for CRC established by the AJCC, who received appropriate treatment comprising neoadjuvant, surgical, and adjuvant modalities.

Patients and Methods

The data of patients who underwent curative surgery for CRC between January 2015 and March 2020 and who were pathologically proven to have cancer were retrospectively evaluated. Approval for this study was obtained from the Ethics Committee of our hospital (364/123/3).

Patients with preoperative stages 1 and 4, patients with a history of other organ malignancy, patients who could not undergo curative resection, patients with systemic malignant diseases (leukemia, lymphoma, etc.), patients with synchronous tumors, and patients with positive surgical margins were excluded from the study.

According to our clinical protocol, intravenous ceftriaxone and metronidazole were given before surgery in the operating room, and antibiotherapy was continued for 72 hours. If there were signs of infection in the postoperative clinical observation or laboratory tests, the current treatment was extended, or a different antibiotherapy was applied according to the advice of an infectious disease specialist. All patients underwent curative resection according to oncologic principles (lymph node dissection, total mesocolic/mesorectal excision, R0 resection).

The study encompassed an analysis of various demographic characteristics of the patient cohort, as well as an in-depth examination of pathology results, tumor localization, and the impact of treatment modalities on overall prognosis. Notable pathological parameters, including tumor grade, perforation status, lymphovascular invasion, perineural invasion, the presence of mucinous components, and tumor size, were meticulously ascertained through pathological examination of resected specimens. The life span of each patient was sourced from the national data repository, facilitating a comprehensive survival analysis. Tumor localization was systematically categorized into three distinct groups: right colon, left colon, and rectum. Specifically, tumors situated within the proximal two-thirds of the transverse colon were designated as right colon tumors, while those positioned more distally were classified as left colon tumors. Tumors that both received neoadjuvant treatment and were located within the initial 10 centimeters from the anal canal, identified through colonoscopy, were registered as rectal tumors.

Statistical Analysis

All statistical analyses were performed by SPSS 25 software (IBM Corp., Armonk, NY, USA) (Statistical Package for Social Sciences) for Windows 25.0. It was also expressed as numerical (n) and percentage (%). Logistic regression analysis was used to evaluate 1-, 3- and 5-year survival. Cox regression analysis was used to evaluate overall survival. Kaplan-Meier survival analysis was performed for categorical parameters that were significant in Cox regression analysis. $p<0.05$ was considered statistically significant at a 95% confidence interval.

Results

Due to CRC, curative resection was performed on 241 patients, of whom 130 (53.9%) were male and 111 (46.1%) were female. The mean age of all patients was calculated to be 65.67±16.04. The average tumor size was measured as 5.03±2.22 cm.

Among the patients, 22 (13.3%) had high-grade tumors, 175 (72.6%) had intermediate-grade tumors, and 34 (14.1%) had low-grade tumors. Lymphovascular invasion was present in 97 patients (40.2%), perineural invasion in 98 patients (40.7%), and mucinous component in 47 patients (19.5%).

A total of 91 patients (37.8%) underwent emergency surgery, and 26 (10.8%) had tumor perforation. The tumor was located in the right colon in 70 patients (29.0%), the left colon in 143 patients (59.4%), and the rectum in 28 patients (11.6%).

The 1-year survival rate of the patients was found to be 84.3%, 3-year survival rate was 69.0%, and 5-year survival rate was 52.9%. The overall survival (OS) of all patients as of 2022 was determined to be 41.3%.

The survival rates at 1, 3, and 5 years were evaluated. The multivariate analysis of survival with respect to the variables is summarized in Tables I, II, and III.

The subgroup analysis of patients' OS with respect to the variables, based on COX regression analysis, is summarized in Table IV.

Table I. Factors affecting 1-year survival.

	B	95% confidence interval for B		*p* multivariate
		Lower	Upper	
Sex	1.259	0.500	3.167	0.625
Age	0.933	0.899	0.968	**< .000**
Grade				**0.036**
Grade (Moderately)	6.746	1.461	31.155	**0.014**
Grade (Poorly)	12.489	1.524	102.357	**0.019**
Tumor Size (cm)	1.039	0.818	1.320	0.752
Perforation	0.240	0.077	0.748	**0.014**
Lymphovascular Invasion	0.946	0.360	2.486	0.910
Perineural Invasion	0.989	0.382	2.563	0.982
Emergency Surgery	7.270	2.254	23.445	**0.001**
Mucinous Component	1.774	0.337	9.337	0.498
Tumor Location				0.478
Tumor Location (Left)	0.560	0.177	1.771	0.324
Tumor Location (Rectum)	0.306	0.037	2.527	0.272

Logistic regression.

According to the COX regression analysis, the categorical variables that were found to be significantly associated with OS were grade, emergency surgery, and tumor localization. Survival analyses showed that undergoing emergency surgery, having the tumor located in the rectum, and having a "poor" tumor grade adversely affected survival.

Discussion

Anatomy-based staging (TNM) remains an important prognostic factor in all cancers. Today, the pathologic stage we reach after resection is the most important factor in determining the survival of CRC[6]. However, rapidly advancing knowledge of cancer biology has shown us that, in some cases, there may be more important factors affecting prognosis[6].

When these factors are examined, tumor spread to venous vessels, non-muscular capillaries, and postcapillary lymphatics is an important prognostic factor[7]. In some published studies[8,9], extramural venous invasion and lymphatic invasion were found to be independent risk factors for survival. In our study, lymphovascular invasion was not found to be an independent risk factor af-

Table II. Factors affecting 3-year survival

B	95% confidence interval for B		*p* multivariate
	Lower	Upper	
0.564	0.276	1.153	0.117
0.969	0.947	0.992	**0.009**
			0.082
2.259	0.702	7.277	0.172
5.917	1.226	28.560	**0.027**
1.089	0.906	1.309	0.361
0.132	0.044	0.395	**< .000**
0.687	0.326	1.446	0.323
1.085	0.516	2.279	0.830
6.989	3.178	15.369	**< .000**
0.902	0.342	2.379	0.835
			0.568
1.359	0.588	3.142	0.473
0.770	0.195	3.038	0.709

Logistic regression.

Table III. Factors affecting 5-years survival.

	B	95% confidence interval for B		p multivariate
		Lower	Upper	
Sex	1.273	0.696	2.328	0.433
Age	0.977	0.957	0.996	**0.019**
Grade				0.799
Grade (Moderately)	1.414	0.507	3.944	0.508
Grade (Poorly)	1.318	0.361	4.820	0.676
Tumor Size (cm)	0.994	0.862	1.145	0.932
Perforation	0.172	0.054	0.552	**0.003**
Lymphovascular Invasion	0.613	0.323	1.162	0.133
Perineural Invasion	0.846	0.448	1.599	0.608
Emergency Surgery	3.166	1.623	6.177	**0.001**
Mucinous Component	0.465	0.213	1.014	0.054
Tumor Location				0.283
Tumor Location (Left)	1.242	0.617	2.501	0.543
Tumor Location (Rectum)	0.563	0.183	1.726	0.314

Logistic regression.

fecting survival at 1, 3 and 5 years (p-value 0.910, 0.323 and 0.133, respectively), but it was found to be close to significance among the factors affecting overall survival (p=0.062). This suggests that lymphovascular invasion is an important parameter that should be considered when evaluating the pathology specimen. According to the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)[10,11], if the lymphovascular invasion is found in the tumor, the tumor should be classified as "high-risk", and adjuvant chemotherapy should be planned accordingly.

The presence of perineural invasion in the tumor has been found to be associated with poor prognosis, according to some studies[12,13]. However, in our study, the perineural invasion was not found to be a factor affecting 1, 3 and 5-year survival and overall survival (p-value 0.982, 0.830, 0.608 and 0.471, respectively). Similar to lymphovascular invasion, ASCO and NCCN[10,11] stated that perineural invasion is a parameter that must be examined in the pathology specimen and the presence of perineural invasion in the tumor should be considered as "high-risk" and adjuvant chemotherapy should be adjusted accordingly.

Table IV. Factors affecting overall survival.

	B	95% confidence interval for B		p multivariate
		Lower	Upper	
Sex	0.840	0.536	1.316	0.446
Age	1.032	1.016	1.049	**< .000**
Grade				**0.046**
Grade (Moderately)	0.540	0.277	1.053	0.070
Grade (Poorly)	0.285	0.105	0.775	**0.014**
Tumor Size (cm)	0.949	0.851	1.059	0.350
Perforation	3.102	1.730	5.565	**< .000**
Lymphovascular Invasion	1.548	0.978	2.450	0.062
Perineural Invasion	1.181	0.751	1.855	0.471
Emergency Surgery	0.310	0.182	0.529	**< .000**
Mucinous Component	1.350	0.741	2.460	0.327
Tumor Location				**0.015**
Tumor Location (Left)	0.747	0.455	1.229	0.251
Tumor Location (Rectum)	2.128	0.972	4.658	0.059

COX regression.

In order to determine the grade of the tumor, in our study, evaluation was made according to the well, moderately, and poorly differentiated classification used by the World Health Organization[14] in determining the prognosis of digestive system tumors. However, since the histologic grading system is based on the subjective evaluation of the pathologist, the outcome is open to debate. In our study, we found that grade was an independent risk factor affecting 1-year survival and over-survival (p=0.036 and 0.046, respectively); poorly differentiated compared to well or intermediately differentiated was an independent risk factor affecting 3-year survival (p=0.027). In some previous studies[15,16], tumor differentiation was also considered as an independent risk factor, but there is no widely accepted grading system today, so the grade remains subjective data.

Many tumors can secrete intracellular (signet ring cell) or extracellular mucin. Extracellular mucin is secreted out of the colon wall and acts as a factor that helps the tumor spread[17]. The tumor may secrete varying amounts of mucin, and if this amount is more than 50% of the tumor size, then it is a mucinous carcinoma rather than a mucinous component. While signet ring cell carcinoma is associated with a poor prognosis, the relationship of the extracellular mucinous component with prognosis is unclear, and current data are confusing[18]. In our study, mucinous components were not found to be an independent risk factor in the evaluation of survival. The p-values for 1, 3 and 5-year survival and overall survival were 0.498, 0.835, 0.054 and 0.327, respectively.

Localization of the tumor (Left-Right) has been found to be a prognostic factor in most studies in the literature. In a 2016 meta-analysis[19] of 66 studies, left colon tumors (from the splenic flexure to the rectum) were associated with a reduced risk of death. In addition, tumor localization may also be associated with genetic mutation. In one study[20], *BRAF* or *KRAS* (genes associated with worse prognosis) mutations were more common in tumors originating from the right colon, while mutations were less common in tumors originating from the left colon. In our study, left colon tumors were also found to have a better prognosis in accordance with the literature. In a European study[21] comparing the survival of patients with rectal and colon cancer, it was reported that rectal cancer had a lower survival rate than colon cancer. In our study, it was found that rectal cancer had a worse prognosis than left and right colon cancer in terms of overall survival (p=0.015).

There are studies[22,23] suggesting that obstruction or perforation of the tumor at the time of diagnosis or during treatment is associated with poor prognosis. There are also studies[24] that suggest that perforated or obstructed tumors have a worse prognosis because they are more advanced and associated with worse histological findings. In our study, patients who underwent emergency surgery for obstruction or perforation had worse 1,3 and 5-year survival and overall survival, consistent with the literature (p-values were 0.001, <0.001, 0.001 and <0.001, respectively).

The age of the patient has an important role in CRC prognosis. In many studies in the literature conducted in different age groups, it has been reported that advanced age affects the prognosis of the disease in a bad way. In a study[25] published in 2016, a statistically significant value was obtained when the 5-year OS of patients over and under 50 years of age at the same stage was compared. In another study[26], a significant difference was found in the survival of stage 1-3 patients under and over 35 years of age. In our study, age was found to be an independent risk factor for 1, 3 and 5-year and overall survival (p-values were <0.001, 0.009, 0.019 and <0.001, respectively).

Women are known to have better survival in some cancer types. For CRC, the female gender was previously said to be a good prognostic factor[27,28]. Recent studies[29,30] suggest that gender may be a risk factor affecting survival in the early stage of CRC, especially in the elderly population, where randomized trials of more than 1,000 patients suggest that current conventional treatment has a better outcome in women compared to men. In our study, we concluded that gender had no effect on 1-, 3- and 5-year survival and overall survival (p-values were 0.625, 0.117, 0.433 and 0.446, respectively).

In a recent study[31] of 4,057 patients, tumor size was found to be an independent risk factor for overall survival. In the same study[31], when patients were grouped according to macroscopic growth pattern, tumor size was found to be an independent risk factor for over-survival in both infiltrative and ulcerative groups, whereas it was found to be an independent risk factor affecting disease-free survival only in the infiltrative group. In another study[32], in metachronous tumors, patients with primary tumor size great-

er than 6.5 cm had worse survival. In another study[33] published in 2021, small tumor size was evaluated as a factor positively affecting survival in univariate analysis. In this study, tumor size was not found to be a factor affecting overall survival (p=0.350).

Limitations

The limitations of the study include its retrospective nature, the fact that preoperative carcinoembryonic antigen (CEA) was not analyzed, genetic tests were not performed, and disease-free survival was not analyzed.

Conclusions

Age, grade, tumor perforation, and emergen cy surgery were identified as factors that independently affect 1-year survival. Similarly, age, poorly differentiated tumor, perforation, and emergency surgery were identified as independent risk factors for 3-year survival. Age, tumor perforation, and emergency surgery were found to be independent risk factors for 5-year survival. Lastly, age, grade, perforation, emergency surgery, and tumor localization were identified as independent risk factors for overall survival.

Survival analysis showed that being operated for emergency conditions was associated with worse survival than being operated for elective conditions, being operated for rectal cancer was associated with worse survival than being operated for colon cancer, and having poorly differentiated tumors was associated with worse survival than other types.

Conflict of Interest

The authors declare that they have no conflict of interests.

Funding

The authors declare that this study has received no financial support.

Ethics Approval

Approval for this study was obtained from the Ethics Committee of the Health Science University, İstanbul Kartal Lutfu Kirdar City Hospital (approval number: 364/123/3).

Informed Consent

All participants provided written informed consent.

Data Availability

F.M., M.K., and G.O.: conceptualization, methodology, software. F.M. and M.K.: data curation, original draft preparation. F.M. and M.K.: visualization, investigation. G.O.: supervision. F.M., M.K.: software, validation. G.O. and F.M.: writing, reviewing, editing.

ORCID ID

Fırat Mulkut: 0000-0003-4049-7595
Mehmet Karahan: 0000-0003-2385-938X
Gokalp Okut: 0000-0002-3641-5625

References

1) Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33.
2) Baek JY, Yu JI, Park HC, Choi DH, Yoo GS, Cho WK, Lee WY, Yun SH, Cho YB, Park YA, Kim HC. Risk factors for locoregional recurrence in patients with pathologic T3N0 rectal cancer with negative resection margin treated by surgery alone. Radiat Oncol J 2019; 37: 110-116.
3) Elferink MA, Visser O, Wiggers T, Otter R, Tollenaar RA, Langendijk JA, Siesling S. Prognostic factors for locoregional recurrences in colon cancer. Ann Surg Oncol 2012; 19: 2203-2211.
4) Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62: 220-241.
5) Compton CC. Pathology and prognostic determinants of colorectal cancer. 2023. Available at: https://www.uptodate.com/contents/pathology-and-prognostic-determinants-of-colorectal-cancer.
6) Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17:1471-1474.
7) Hogan J, Chang KH, Duff G, Samaha G, Kelly N, Burton M, Burton E, Coffey JC. Lymphovascular invasion: a comprehensive appraisal in colon and rectal adenocarcinoma. Dis Colon Rectum 2015; 58: 547-555.
8) Takebayashi Y, Aklyama S, Yamada K, Akiba S, Aikou T. Angiogenesis as an unfavorable prognostic factor in human colorectal carcinoma. Cancer 1996; 78: 226-231.
9) Amri R, England J, Bordeianou LG, Berger DL. Risk Stratification in Patients with Stage II Colon Cancer. Ann Surg Oncol 2016; 23: 3907-3914.
10) Baxter NN, Kennedy EB, Bergsland E, Berlin J, George TJ, Gill S, Gold PJ, Hantel A, Jones L, Lieu C, Mahmoud N, Morris AM, Ruiz-Garcia E, You YN, Meyerhardt JA. Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. J Clin Oncol 2022; 40: 892-910.

11) Levy MH, Back A, Benedetti C, Billings JA, Block S, Boston B, Bruera E, Dy S, Eberle C, Foley KM, Karver SB, Knight SJ, Misra S, Ritchie CS, Spiegel D, Sutton L, Urba S, Von Roenn JH, Weinstein SM. NCCN clinical practice guidelines in oncology: palliative care. J Natl Compr Canc Netw 2009; 7: 436-473.

12) Liebig C, Ayala G, Wilks J, Verstovsek G, Liu H, Agarwal N, Berger DH, Albo D. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009; 27: 5131-5137.

13) Alotaibi AM, Lee JL, Kim J, Lim SB, Yu CS, Kim TW, Kim JH, Kim JC. Prognostic and Oncologic Significance of Perineural Invasion in Sporadic Colorectal Cancer. Ann Surg Oncol 2017; 24: 1626-1634.

14) WCoTE B. Digestive system tumours. WHO Classification of Tumours, 5th ed IARC 2019.

15) Hermanek P, Guggenmoos-Holzmann I, Gall FP. Prognostic factors in rectal carcinoma. A contribution to the further development of tumor classification. Dis Colon Rectum 1989; 32: 593-599.

16) Jessup JM, Stewart AK, Menck HR. The National Cancer Data Base report on patterns of care for adenocarcinoma of the rectum, 1985-95. Cancer 1998; 83: 2408-2418.

17) Green JB, Timmcke AE, Mitchell WT, Hicks TC, Gathright JB Jr, Ray JE. Mucinous carcinoma--just another colon cancer? Dis Colon Rectum 1993; 36: 49-54.

18) Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, Rodriguez-Bigas MA, Cormier JN, Chang GJ. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol 2012; 19: 2814-2821.

19) Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, Passalacqua R, Sgroi G, Barni S. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2017; 3: 211-219.

20) Sinicrope FA, Mahoney MR, Yoon HH, Smyrk TC, Thibodeau SN, Goldberg RM, Nelson GD, Sargent DJ, Alberts SR; Alliance for Clinical Trials in Oncology. Analysis of Molecular Markers by Anatomic Tumor Site in Stage III Colon Carcinomas from Adjuvant Chemotherapy Trial NCCTG N0147 (Alliance). Clin Cancer Res 2015; 21: 5294-5304.

21) Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, Hackl M, Eisemann N, Brenner H; EUROCARE-5 Working Group:. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. Eur J Cancer 2015; 51: 2158-2168.

22) Ho YH, Siu SK, Buttner P, Stevenson A, Lumley J, Stitz R. The effect of obstruction and perforation on colorectal cancer disease-free survival. World J Surg 2010; 34: 1091-1101.

23) Chen HS, Sheen-Chen SM. Obstruction and perforation in colorectal adenocarcinoma: an analysis of prognosis and current trends. Surgery 2000; 127: 370-376.

24) Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of Incorporation of Pretreatment Serum Carcinoembryonic Antigen Levels Into AJCC Staging for Colon Cancer on 5-Year Survival. JAMA Surg 2015; 150: 747-755.

25) Abdelsattar ZM, Wong SL, Regenbogen SE, Jomaa DM, Hardiman KM, Hendren S. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening. Cancer 2016; 122: 929-934.

26) Shen L, Mo M, Jia L, Jia H, Li Q, Liang L, Shi D, Zhang Z, Cai S, Li X, Zhu J. Poorer prognosis in young female patients with non-metastatic colorectal cancer: a hospital-based analysis of 5,047 patients in China. Cancer Manag Res 2018; 10: 653-661.

27) Paulson EC, Wirtalla C, Armstrong K, Mahmoud NN. Gender influences treatment and survival in colorectal cancer surgery. Dis Colon Rectum 2009; 52: 1982-1991.

28) McArdle CS, McMillan DC, Hole DJ. Male gender adversely affects survival following surgery for colorectal cancer. Br J Surg 2003; 90: 711-715.

29) Smith RE, Colangelo L, Wieand HS, Begovic M, Wolmark N. Randomized trial of adjuvant therapy in colon carcinoma: 10-year results of NSABP protocol C-01. J Natl Cancer Inst 2004; 96: 1128-1132.

30) Giacchetti S, Dugué PA, Innominato PF, Bjarnason GA, Focan C, Garufi C, Tumolo S, Coudert B, Iacobelli S, Smaaland R, Tampellini M, Adam R, Moreau T, Lévi F; ARTBC International Chronotherapy Group. Sex moderates circadian chemotherapy effects on survival of patients with metastatic colorectal cancer: a meta-analysis. Ann Oncol 2012; 23: 3110-3116.

31) Dai W, Li Y, Meng X, Cai S, Li Q, Cai G. Does tumor size have its prognostic role in colorectal cancer? Re-evaluating its value in colorectal adenocarcinoma with different macroscopic growth pattern. Int J Surg 2017; 45: 105-112.

32) Kato T, Alonso S, Muto Y, Perucho M, Rikiyama T. Tumor size is an independent risk predictor for metachronous colorectal cancer. Oncotarget 2016; 7: 17896-17904.

33) Alese OB, Zhou W, Jiang R, Zakka K, Huang Z, Okoli C, Shaib WL, Akce M, Diab M, Wu C, El-Rayes BF. Predictive and Prognostic Effects of Primary Tumor Size on Colorectal Cancer Survival. Front Oncol 2021; 11: 728076.