Effect of tumor size on prognosis in colorectal cancer

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AIM: *This study aimed to reveal the effect of tumor size on overall survival and disease-free survival.*
MATERIAL AND METHODS: *This study retrospectively evaluated the data of 593 patients who underwent colorectal surgery for colorectal cancer (CRC) between May 2012 and December 2018. The patients were divided into two groups based on their tumor size; those with a tumor size <5 cm were grouped as group 1 and those with a tumor size ≥ 5 cm were grouped as group 2.*
RESULTS: *The present study included 222 patients with colorectal adenocarcinoma. The median follow-up period of the patients was 36.0 (1.4-107.4) months, mean tumor size was 5.1±2.3 cm, and number of patients with a tumor size of ≥5 cm was 117 (52.7%). There were statistically significant differences between the groups in terms of overall survival (Log-Rank = 12.559, p<0.001).*
DISCUSSION: *According to the American Joint Committee on Cancer's Cancer Staging Manual (8th edition), the CRC staging system considers the tumor's depth of invasion of the intestinal wall but not the tumor's size. Moreover, it considers the size of the tumors developing in the parenchymal organs (breasts and lungs) but not tumors developing in luminal organs (stomach, colon, etc.).*
CONCLUSIONS: *Tumor size ≥5 cm was found to be a risk factor for poor prognosis. To a certain extent, we believe that this study will aid in elucidating the link between tumor size in and prognosis of patients with CRC.*

KEY WORDS: Colorectal cancer, Prognosis, Tumor size

Introduction

According to the data made available by the World Health Organization, as of the year 2020, colorectal cancer (CRC) was reported as the second most common cancer (9.4%) of all cancers in women, with 865.630 new cases reported, and the third most common cancer (10.6%) of all cancers in men, with 1.065.960 new cases reported [1].

Despite the advances in oncological and surgical treatments, according to the tumor, node, metastasis (TNM) staging system, patients belonging to stages 1 and 2 relapse at a rate of 25% [2]. Varying prognoses of patients at the same stage of the disease led researchers to study the biological behavior of tumors at a molecular level and to conduct more detailed investigations of factors that might potentially have an impact on the prognosis using data available in medical records. Along with studies related to the effect of tumor size on prognosis, there are other studies investigating tumor localization [3], the relationship between tumor growth pattern and tumor size as well as prognosis [4], tumor size, carcinoembryonic antigen (CEA) ratio [5], and tumor size-CRP-prognosis [6].
The 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual was published in 2017 [7]. Although tumor size is a prognostic factor for many cancers (breast, Non-small cell lung cancer [33], gastric cancer [34] , esophageal cancer [35] and renal cell car-

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cinoma), it is not included in the TNM staging for colon cancer [2].

The tumor size is defined as the widest horizontal diameter of the tumor [3]. Unlike previous studies in which no relationship was found between tumor size and prognosis [8-11], recent studies revealed that tumor size affected prognosis [12,13].

While some studies indicate that increased tumor size results in a poor prognosis [2,14-16], other studies indicate that small tumor size leads to poor prognosis [17-19]. In a recent population-based study in which tumor size was investigated, tumor size was found to affect overall survival (OS) [2]. In this study, we aimed to assess the relationship between tumor size and survival in patients with CRC.

Material and Method

Patients and Ethics

The data of 593 patients who underwent colorectal surgery for CRC between May 2012 and December 2018 in our hospital were retrospectively evaluated. The patients' demographic data, including age, sex, pathological records, tumor localization, T stage, N stage, distant metastasis, tumor size, tumor differentiation, venous invasion, perineural invasion, number of lymph nodes, number of metastatic lymph nodes, recurrence, and survival period were identified. Ethical committee approval was obtained for this study (Ethical Committee Number: KAEK/2021.05.150). All study procedures were conducted according to the principles of World Medical Association Declaration of Helsinki.

The patients were grouped based on the tumor size, which was calculated using the maximum tumor diameter reported in the pathological records in each stage of the disease. The dividing value of the tumor size was set at 5 cm, and the stage-based groups were divided into sub-groups as those with a tumor size <5 cm and ≥5 cm.

Inclusion criteria:

1. Patients with pathologically verified colorectal adenocarcinoma
2. Patients undergoing radical R0 surgery
3. Patients undergoing elective surgery
4. Patients with stage 1, 2, 3, and 4 CRC
5. Patients aged over 18 years

Exclusion criteri

1. Patients receiving neoadjuvant chemotherapy and/or radiotherapy
2. Patients with synchronous colorectal tumor
3. Patients with another primary tumor focus
4. Patients who previously underwent surgery but experienced a relapse at the time of their admission
5. Patients with insufficient data regarding pathology
6. Patients who underwent endoscopic resection and whose state of lymph nodes is unknown
7. Patients who underwent emergency surgery because of various reasons, such as ileus and perforation
8. Patients with failed R0 resection
9. Patients who died within the first postoperative month
10. Patients with inherited CRC (hereditary nonpolyposis CRC, familial adenomatous polyposis, etc.)

Tumors of 222 patients meeting the inclusion criteria were staged according to the 8th Edition of the AJCC Cancer Staging Manual [7]. During the postoperative period, the patients were followed up during which they underwent physical examination, evaluation of laboratory parameters (blood count, liver enzymes, CEA, and cancer antigen 19-9), contrast-enhanced abdominal tomography, and colonoscopy at the intervals recommended under the National Comprehensive Cancer Network guidelines. The OS and disease-free survival (DFS) were identified as primary endpoints.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to investigate whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentage (%), whereas quantitative data were expressed as mean ± SD and median (min-max). The mean differences in ages between the groups were compared using the Student's t-test, whereas the Mann-Whitney U test was used for comparing the number of lymph nodes and the metastatic lymph nodes. Pearson's χ^2 test was used in the analysis of categorical data unless otherwise stated. In all 2×2 contingency tables for comparing categorical variables, the continuity corrected χ^2 test was used when one or more of the cells had an expected frequency of 5-25, whereas Fisher's exact test was used when one or more of the cells had an expected frequency ≤5. In all R×C contingency tables to compare categorical variables, the Fisher-Freeman-Halton test was used when ≥¼ of the cells had an expected frequency ≤5. Kaplan-Meier survival analysis via log-rank test was used for determining whether tumor size had a statistically significant effect on prognosis (i.e., recurrence-free survival and OS). Cumulative survival rates for 1, 3, and 5 years, mean expected duration of life, and 95% confidence intervals were computed. Whether the potential risk factors had a statistically significant effect on prognosis or not was investigated using univariate Cox's pro-

portional hazard regression models. Multiple Cox's proportional hazard regression models were established to determine the best independent predictors, which mostly affected prognosis after adjustment for clinically important factors. Besides biological factors, such as age and gender, any variable whose univariate test had a p-value <0.25 was accepted as a candidate for the multivariate model. Hazard ratios (HR), 95% confidence intervals, and Wald statistics for each independent variable were also calculated. Unless otherwise stated, a p-value <0.05 was considered statistically significant. However, for all possible multiple comparisons, the Bonferroni correction was applied for controlling the Type I error.

Results

Clinical Characteristics of the Patients

The present study included 222 patients with colorectal adenocarcinoma. Of these, 138 (62.2%) were male, whereas 84 (37.8%) were female. The mean age was 61.5±12.8, and the majority (71.1%) of the patients had tumor localization in the left colon and rectum. The median CEA level was 4.4 (0.21-255.0). The mean duration of hospital stay was 10 (5–104) days and the median follow-up period was 36.0 (1.4-107.4) months. The incidence rates of complications and postoperative chemotherapy administration were 28 (12.6%) and 128 (57.7%), respectively. In this study, the recurrence rate was 38.7%, and 62.6% of the patients are still alive.

Histopathological Characteristics of the Patients

The mean tumor size was 5.1±2.3 cm and the number of patients with a tumor size ≥5 cm was 117 (52.7%). According to the histopathological studies on the surgically retrieved materials, tumors of 18.8%, 32.5%, 38.7%, and 10.8% of the patients were stages 1, 2, 3, and 4, respectively. In terms of the T stage, the most common was T3 in 49% of the patients, whereas the most common N stage was N0 (53.6%). In terms of tumor differentiation grade, 47.5%, 44.6%, and 7.9% of the patients were grades 1, 2, and 3, respectively. The median number of dissected lymph nodes was 13 (2-78). The rates of invasion, peripheral nervous invasion, and mucinous component were 47.1%, 30.2%, and 11.3%, respectively.

Assessment of the Clinical and Pathological Data Based on Tumor Size

The cut-off values of the tumor size were determined as 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 6.0 cm, and they were investigated for their effect on DFS and OS rates. As the best result was obtained with a cut-off value of 5.0 cm, all of the subsequent assessments were based on <5 cm vs ≥5 cm (Fig. 1).

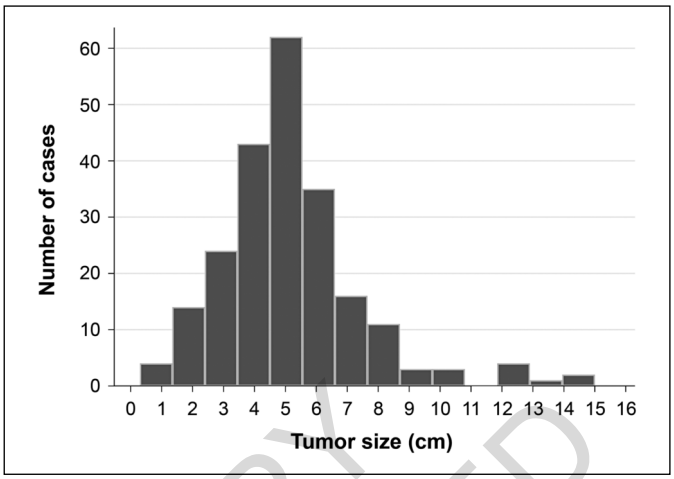

Fig. 1: Frequency distributions of the cases by tumor size. Tumor size is shown on the x-axis and the number of cases is shown on the y-axis.

The groups of patients with a tumor size <5 cm and those with a tumor size ≥5 cm did not have any statistically significant differences in terms of age, the number of metastatic lymph nodes, postoperative chemotherapy, stage, N stage, lymphovascular invasion (LVI), and perineural invasion (PNI), respectively (p>0.05). Compared with the group with tumor size <5 cm, the rate of male patients in the group with tumor size ≥5 cm was found to be statistically significantly higher (p=0.010). The rate of right colon localization was significantly higher and the rate of rectum localization was significantly lower in the group with tumor size ≥5 cm, compared with those in the group with tumor size <5 cm (p=0.011 and p=0.045, respectively). Compared with the group with tumor size <5 cm, the median lymph-node number, grade, and T stage were statistically significantly higher, in the group with tumor size ≥5 cm (p<0.05, respectively; (Fig. 1); (Table I).

Factors affecting OS and DFS

In terms of the OS of all the cases in this study (n=222); the cumulative 1-, 3-, and 5-year OS rates were 88.7%, 70.2%, and 57.3%, respectively, whereas the estimated OS was 66.9 months (95% CI: 59.9-74.0) (Table II). In terms of the DFS of all the cases in this study (n=222), the cumulative 1-, 3-, and 5-year DFS rates were 79.4%, 61.6%, and 55.6%, respectively, whereas the estimated DFS was 60.7 months (95% CI: 54.2-71.8, (Table III).

The cumulative 1-, 3-, and 5-year survival rates in the

TABLE I - *Demographic and clinical characteristics of the cases based on tumor size*

	Tumor size ≥5 cm (n=105)	Tumor size ≥5 cm (n=117)	p-value
Age (year)	61.9±12.0	61.1±13.4	0.649†
Age groups			0.471‡
>50 years	13 (12.6%)	21 (17.9%)	
50–65 years	46 (44.7%)	53 (45.3%)	
>65 years	44 (42.7%)	43 (36.8%)	
Sex			0.010‡
Male	56 (53.3%)	82 (70.1%)	
Female	49 (46.7%)	35 (29.9%)	
Localization			0.034‡
Left colon–Sigmoid colon–Rectosigmoid	49 (46.7%)	49 (41.9%)	
Right colon	17 (16.2%)a	36 (30.7%)a	
Transverse colon	4 (3.8%)	7 (6.0%)	
Rectum	35 (33.3%)b	25 (21.4%)b	
LN number	12 (0–78)	15 (2–53)	0.017¶
Metastatic LN number	0 (0–14)	0 (0–30)	0.443¶
Administration of postoperative CT	65 (61.9%)	63 (53.8%)	0.225‡
Grade			0.015‡
1	55 (57.3%)	41 (38.7%)	
2	37 (38.5%)	53 (50.0%)	
3	4 (4.2%)	12 (11.3%)	
Stage			0.061‡
I	26 (24.8%)	14 (12.0%)	
II	29 (27.6%)	43 (36.8%)	
III	41 (39.0%)	45 (38.6%)	
IV	9 (8.6%)	15 (12.8%)	
T stage			0.006¥
T1	7 (6.7%)	1 (0.9%)	
T2	25 (23.8%)	14 (12.0%)	
T3	48 (45.7%)	61 (52.1%)	
T4	25 (23.8%)	41 (35.0%)	
N stage			0.329‡
N0	58 (55.2%)	61 (52.1%)	
N1	34 (32.4%)	33 (28.2%)	
N2	13 (12.4%)	23 (19.7%)	
LVI	37/78 (47.4%)	38/81 (46.9%)	0.947‡
PNI	22/75 (29.3%)	27/87 (31.0%)	0.949§

† Student's t-test, ‡ Pearson's 2 test, ¶ Mann Whitney U test, ¥ Fisher Freeman Halton test, § Continuity corrected 2 test, a: TM size ≥5 cm vs 5 cm (p=0.011), b: TM size ≥5 cm vs 5 cm (p=0.045).
Abbreviations: LN, lymph node; CT, chemotherapy; LVI, lymphovascular invasion; PNI, perineural invasion; TM, tumor

group with tumor size <5 cm (n=105) were 93.3%, 82.4%, and 65.5%, respectively, whereas the estimated mean survival was 77.6 months (95% CI: 68.0-87.3). The cumulative 1-, 3-, and 5-year survival rates in the group with tumor size ≥5 cm (n=117) were 84.6%, 59.3%, and 50.3%, respectively, whereas the estimated mean survival was 48.5 months (95% CI: 42.3 - 54.7). Thus, there was a statistically significant difference between the groups in terms of OS (Log-Rank=12.559, p<0.001; (Fig. 2A); (Table II)).

The cumulative 1-, 3-, and 5-year DFS rates in the group with tumor size <5 cm (n=105) were 80.6%, 65.7%, and 60.7%, respectively, whereas the estimated mean DFS was 63.9 months (95% CI: 54.6-73.2). The cumulative 1-, 3-, and 5-year DFS rates in the group with tumor size ≥5 cm (n=117) were 78.2%, 57.4%, and 50.3%, respectively, whereas the estimated mean DFS was 49.4 months (95% CI: 42.6-56.1). Thus, there was no statistically significant difference between the groups in terms of DFS (Log-Rank=1.703, p=0.192; (Fig. 2B); (Table III)).

The univariate analyses indicated that the increased number of metastatic lymph nodes, the presence of lymph-node metastasis, stage, each one-degree elevation in the T and N stages, and the presence of PNI were found to have statistically significant effects on the DFS (p<0.05). In the next stage, all factors with p<0.25

TABLE II - *Overall survival results of the cases based on stage and tumor size. The Kaplan–Meier curve demonstrating the survival analysis results*

	N	Survival rates 1-year	3-year	5-year	Follow-up period* (months)	Log-Rank	p-value †
Stage 1						4.556‡	0.033
TM size ≥5 cm	26	100.0	100.0	94.4	91.7 (85.6–97.7)		
TM size 5 cm	14	92.9	78.6	78.6	60.4 (49.0–71.7)		
Total	40	97.5	92.3	88.7	82.6 (72.2–92.9)		
Stage 2						2.235	0.135
TM size ≥5 cm	29	100.0	88.1	88.1	89.9 (73.3–106.4)		
TM size 5 cm	43	88.4	74.0	60.1	60.7 (51.5–69.9)		
Total	72	93.1	79.7	77.4	84.4 (74.0–94.8)		
Stage 3						4.298	0.038
TM size ≥5 cm	41	92.7	75.1	38.2	62.2 (49.9–74.5)		
TM size 5 cm	45	77.8	48.4	42.9	37.9 (30.3–45.6)		
Total	86	84.9	61.1	40.2	52.6 (43.5–61.7)		
Stage 4						0.324	0.569
TM size ≥5 cm	9	55.6	44.4	44.4	31.6 (12.2–50.9)		
TM size 5 cm	15	86.7	33.3	N/A	26.1 (17.5–34.8)		
Total	24	75.0	37.5	12.9	27.7 (19.1–36.4)		
Overall						12.559	<0.001
TM size ≥5 cm	105	93.3	82.4	65.5	77.6 (68.0–87.3)		
TM size 5 cm	117	84.6	59.3	50.3	48.5 (42.3–54.7)		
Total	222	88.7	70.2	57.3	66.9 (59.9–74.0)		

* Data were expressed as mean expected duration of life at 95% confidence interval (CI), † According to the Bonferroni Correction, p<0.0125 was considered statistically significant for the comparisons within each stage.
Legend:TM, tumor; N/A, Not applicable

according to the univariate analyses, as well as biological factors, such as age and sex, were considered as potential risk factors and included in the multivariate Cox's proportional hazards regression model. As there were multiple links between the presence of lymph-node metastasis and the number of metastatic lymph nodes and between the stage and the T and N stages, respectively, out of the above-mentioned factors, only the number of metastatic lymph nodes and the stage were included in the multivariate model. Additionally, because of the problem of missing data, CEA, LVI, and PNI were excluded from the multivariate model (Table IV).

According to the multivariate Cox's proportional hazards regression model, the stage was found to be an independent risk factor for DFS. Independent from other factors, each one-degree elevation in the stage increased the rate of recurrence by 2.054 times (95% CI: 1.528-2.762; p<0.001).

According to the univariate analyses, age, tumor size ≥5 cm, increased number of metastatic lymph nodes, presence of lymph-node metastasis, each one-degree elevation in grade, stage, T and N stages, and the presence of LVI were found to have statistically significant effects on the OS (p<0.05). In the next stage, all factors with p<0.25 as per the univariate analyses, as well as biological factors, such as age and sex, were considered as potential risk factors and included in the multivariate Cox's proportional hazards regression model. As there were multiple links between presence of lymph-node metastasis and the number of metastatic lymph nodes and between the stage and the T and N stages, of the above-mentioned factors, only the number of metastatic lymph nodes and stage were included in the multivariate model. Additionally, because of the problem of missing data, CEA and LVI were excluded from the multivariate model (Table IV).

According to the multivariate Cox's proportional hazards regression model, the most crucial factors for prognosis were stage, age, number of metastatic lymph nodes, tumor size ≥5 cm, and number of dissected lymph nodes <12. Independent from other factors, each one-degree elevation in the stage increased the mortality rate (HR=2.214, 95% CI: 1.609-3.046, p<0.001). Advanced age statistically significantly increased the mortality rate (HR=1.037, 95% CI: 1.016-1.057, p<0.001). Independent from other factors, a tumor size ≥5 cm statistically significantly increased the mortality rate by 1.867 times (95% CI: 1.102-3.162) (p=0.020). Lymph-node number <12 (HR=1.708, 95% CI: 1.043-2.797, p=0.033) and increased number of metastatic lymph nodes (HR=1.059, 95% CI: 1.011-1.108, p=0.015) also statistically significantly increased the mortality rate. Among the cases belonging to the 4 stages, the 2 groups did not differ statistically significantly in terms of their DFS and OS rates based on the Bonferroni correction (p>0.05). Among the cases with stage 1, stage 2, stage 3, and stage 4 cancer, Bonferroni correction revealed no statistically significant differences in recurrence-free sur-

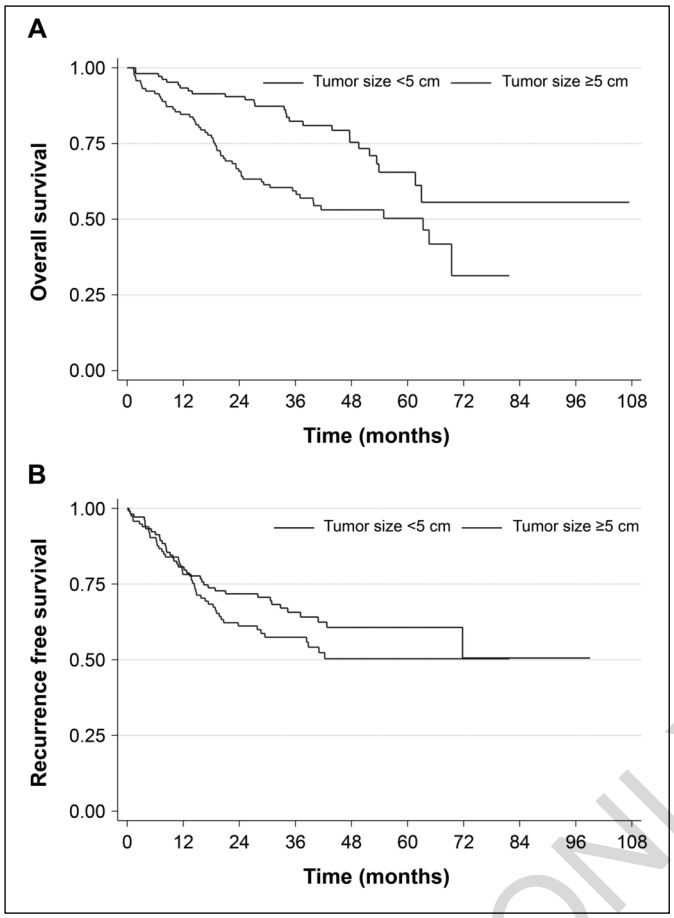

Fig. 2: Kaplan-Meier curve showing the overall survival and disease-free survival rates of the cases based on tumor size.
A: Kaplan-Meier curve showing the overall survival rates of the cases based on tumor size.
The cumulative 1-, 3- and 5-year survival rates of the group with a tumor size of <5 cm (n=105) were 93.3%, 82.4%, and 65.5%, respectively, whereas the estimated mean survival was 77.6 months (95% CI: 68.0-87.3). The cumulative 1-, 3- and 5-year survival rates of the group with a tumor size of 5 cm (n=117) were 84.6%, 59.3%, and 50.3%, respectively, whereas the estimated mean survival was 48.5 months (95% CI: 42.3-54.7). There were statistically significant differences between the groups in terms of overall survival (Log-Rank=12.559, p<0.001).

B: Kaplan-Meier curve showing the disease-free survival rates of the cases based on tumor size.
The cumulative 1-, 3- and 5-year disease-free survival rates of the group with a tumor size of <5 cm (n=105) were 80.6%, 65.7% and 60.7%, respectively, whereas the estimated mean disease-free survival was 63.9 months (95% CI: 54.6-73.2). The cumulative 1-, 3- and 5-year disease-free survival rates of the group with a tumor size of 5 cm (n=117) were 78.2%, 57.4% and 50.3%, respectively, whereas the estimated mean disease-free survival was 49.4 months (95% CI: 42.6-56.1). No statistically significant difference was found between the groups in terms of disease-free survival (Log-Rank=1.703, p=0.192).

TABLE III - *Disease-free survival results of the cases based on stage and tumor size—The Kaplan–Meier curve demonstrating the survival analysis results*

	N	Survival rates 1-year	3-year	5-year	Follow-up period* (months)	Log-Rank	p-value †
Stage 1						1.686	0.194
TM size ≥5 cm	26	92.3	92.3	92.3	88.1 (79.2–97.1)		
TM size 5 cm	14	100.0	77.9	77.9	59.3 (45.2–73.4)		
Total	40	90.0	87.4	87.4	84.0 (75.2–92.9)		
Stage 2						0.040	0.842
TM size ≥5 cm	29	82.8	66.3	66.3	52.9 (42.1–63.7)		
TM size 5 cm	43	81.1	73.5	64.9	58.5 (48.1–69.0)		
Total	72	81.7	70.5	65.6	56.8 (48.5–65.1)		
Stage 3						0.004	0.948
TM size ≥5 cm	41	80.1	55.9	41.3	52.7 (38.7–66.7)		
TM size 5 cm	45	81.7	51.8	41.9	40.0 (31.3–48.3)		
Total	86	81.0	54.2	42.0	53.2 (43.3–63.1)		
Stage 4						0.508	0.476
TM size ≥5 cm	9	38.1	19.0	N/A	17.0 (7.0–26.9)		
TM size 5 cm	15	50.9	N/A	N/A	13.2 (9.0–17.4)		
Total	24	46.6	8.7	N/A	14.9 (10.2–19.5)		
Overall						1.703	0.192
TM size ≥5 cm	105	80.6	65.7	60.7	63.9 (54.6–73.2)		
TM size 5 cm	117	78.2	57.4	50.3	49.4 (42.6–56.1)		
Total	222	79.4	61.6	55.6	60.7 (54.2–71.8)		

*Data were expressed as mean expected recurrence-free duration of life at 95% CI, † According to the Bonferroni Correction, p<0.0125 was considered statistically significant for the comparisons within each stage.
Legend:TM, tumor; N/A, Not applicable

Table IV – *Results from the univariate and multivariate Cox proportional-hazard regression analysis related to all potential factors thought to affect non-recurrent and overall survival*

	Non-recurrent survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.002 (0.985–1.020)	0.832	1.012 (0.994–1.030)	0.197	1.030 (1.010–1.050)	0.003	1.037 (1.016–1.057)	<0.001
Male factor	1.330 (0.847–2.088)	0.215	1.158 (0.727–1.843)	0.537	1.200 (0.764–1.885)	0.429	1.138 (0.684–1.894)	0.618
CEA	1.003 (0.999–1.008)	0.177	-	-	1.004 (0.999–1.009)	0.110	-	-
Right colon	1.011 (0.587–1.744)	0.967	-	-	1.413 (0.802–2.489)	0.232	-	-
Transverse colon	1.242 (0.488–3.160)	0.650	-	-	1.474 (0.571–3.806)	0.423	-	-
Rectum	1.046 (0.625–1.749)	0.865	-	-	1.508 (0.901–2.525)	0.118	-	-
Tumor size ≥5 cm	1.327 (0.866–2.033)	0.193	1.132 (0.713–1.797)	0.598	2.248 (1.419–3.562)	<0.001	1.867 (1.102–3.162)	0.020
LN number	1.008 (0.989–1.028)	0.413	-	-	1.005 (0.983–1.027)	0.678	-	-
LN number <12	1.086 (0.703–1.678)	0.709	-	-	1.358 (0.878–2.101)	0.169	1.708 (1.043–2.797)	0.033
Metastatic LN number	1.092 (1.055–1.130)	<0.001	1.042 (0.997–1.089)	0.066	1.094 (1.058–1.133)	<0.001	1.059 (1.011–1.108)	0.015
LN metastasis	2.037 (1.331–3.118)	<0.001	-	-	2.286 (1.478–3.536)	<0.001	-	-
Grade	1.358 (0.952–1.936)	0.091	1.317 (0.793–2.189)	0.287	1.528 (1.066–2.191)	0.021	1.195 (0.795–1.797)	0.390
Stage	2.297 (1.755–3.007)	<0.001	2.054 (1.528–2.762)	<0.001	2.415 (1.840–3.170)	<0.001	2.214 (1.609–3.046)	<0.001
T stage	1.974 (1.444–2.698)	<0.001	-	-	2.347 (1.679–3.281)	<0.001	-	-
N stage	1.842 (1.407–2.411)	<0.001	-	-	2.191 (1.669–2.875)	<0.001	-	-
LVI	1.547 (0.849–2.820)	0.154	-	-	2.496 (1.378–4.523)	0.003	-	-
PNI	2.217 (1.224–4.017)	0.009	-	-	1.185 (0.660–2.128)	0.571	-	-

Legend:: LN, lymph node; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; HR: Hazard ratio, CI: Confidence interval

vival and OS between those with a tumor size of <5 cm and those with a tumor size of ≥5 cm (p>0.0125). Across the sub-groups of T1N0, T2N0, T3N0, and T4N0, the two groups of patients did not differ statistically significantly in terms of their DFS and OS rates (p>0.05). Of all the N0 cases (with no distinction of the T stage), the cases with a tumor size ≥5 cm had statistically significantly poorer prognosis in terms of their OS, compared with that in those with a tumor size <5 cm (p=0.010).

Discussion

CRC remains an important health problem that results in certain rates of morbidity and mortality across the world [1]. In the literature, there are numerous studies on CRC etiopathogenesis, carcinogenesis, and surgical as well as medical treatment methods. In addition to the results of these studies, surgeons and clinicians also report that increased tumor size can be an early- and late-term negative risk factor because of the difficulty in intraop-

erative dissection caused by increased tumor volume and potential invasion of some of the important tissues or organs, such as the duodenum, pancreas, and ureters. Uncertainties remain in studies comparing the relationship between the tumor size or volume and prognosis [2,3,5,6].

The 8th edition of the AJCC Cancer Staging Manual was published in 2017 (7). The CRC staging system considers the tumor's depth of invasion of the intestinal wall but not the tumor's size [20, 21]. The AJCC considers the size of the tumors developing in the parenchymal organs (breasts and lungs) but does not consider tumors developing in organs with a lumen (stomach, colon, etc.) [20, 22-24]. The maximum horizontal tumor diameter has been demonstrated to be an important prognostic factor [25]. The tumor size is not considered in perihilar and distal biliary tumors, whereas the intrahepatic biliary tract tumors >5 cm and <5 cm that do not present with vascular invasion are staged as T1a and T1b [26].

There is an ongoing controversy owing to the variability of the clinical course of patients who are considered to be early-stage patients according to the TNM staging system. A sub-group was identified using the definition of high-risk stage 2 according to the parameters that were not included in the TNM staging system and adjuvant therapy was recommended for this sub-group [27]. Is the tumor size worth being included in the high-risk patient definition in the TNM system or in terms of OS or DFS? We aimed to answer this question in this study. Although early-stage CRC might have a good prognosis, lymphatic metastasis can occur in some T2 CRC cases. Patients with T1 and T2 tumors have 85% node-negativity; however, this rate was found to be >50% in patients with a tumor size >4 cm. Therefore, it is recommended that T1 and T2 patients with a tumor size >4 cm are staged >stage 1 according to the AJCC staging system [2]. A sub-group of poorer prognosis can also be defined according to this staging, wherein tumor depth is combined with tumor size; this sub-group can also be considered for adjuvant therapy [2]. These studies excluded the tumors diagnosed as pathological T1 tumors after the polypectomy.

Moreover, a study reported that patients with tumor sizes <4 cm and those with tumor sizes =4 cm had similar rates of OS, cancer specific survival (CSS), and DFS, whereas smaller tumor size was an independent risk factor for CSS in patients with stage 1–3 CRC and for OS and CSS in patients with right colon tumors [3]. The 5-year local recurrence rates were 1.40% and 23.00% in patients with tumor size <5 cm and ≥5 cm, respectively. The 5-year OS rates were 82.60% and 71.20% in patients with tumor size <5 cm and ≥5 cm, respectively [16]. Kornprat et al. stated that the tumor size could be a negative prognostic factor for colon cancer but not for rectal cancer [13].

There are studies investigating the correlation between tumor size and pathological data to subsequently evaluate how the tumor size affects tumor aggressiveness. There are studies reporting that the tumor size is correlated with grade, T stage, and N stage and inversely correlated with survival [2]. The tumor size is positively correlated with significant prognostic factors and has had an adverse effect on survival [2]. As the tumor size increased, the 5-year OS decreased [2]. In 1984, Wolmark et al. showed that depth of tumor penetration was related with both tumor size and positive local lymph-node ratio [9]. However, the tumor size and positive lymph-node ratio were not found to be correlated [9]. Adachi et al. showed that patients with tumor sizes >6 cm had an increased number of positive lymph nodes (42% vs 22%) [28]. The tumor size and the tumor grade were also found to be correlated [13]. In a study by Takeuchi et al., poorly-, moderately-, and well-differentiated tumor sizes were reported to be 72.3 mm, 52.2 mm, and 42.2 mm, respectively [29]. On the other hand, although some of the studies investigating tumor size and tumor aggressiveness emphasize that large tumor sizes negatively affect survival, some also report tumor aggressiveness with small tumor sizes. It is hypothesized that small tumors with a high T stage present more aggressive courses [19]. Takahashi et al. also showed that small tumor sizes (<4 cm) had higher recurrence rates [30]. In a study conducted with 1734 patients with CRC penetrating through the serosa (T4bN0-2M0), decreased tumor size (≤4 cm, 4-7 cm, ≥7 cm) was found to be related with lower rates of CSS. In the sub-group analyses, tumor size and CSS were found to be significantly correlated in patients with T4bN0 than in those with T4bN1 and T4bN2 [18].

Although the stage is the best indicator of long-term survival at the time of diagnosis, long-term survival rates vary among the stages. Evaluation of the tumor size and aggressiveness at the time of CRC diagnosis may lead to inaccurate results. This is because the time taken for the tumor to reach its current size and that taken for it to metastasize to the lymph nodes is unknown. However, a small sized metastatic tumor may be more aggressive. In this study, the univariate and multivariate analyses revealed that a tumor size of ≥5 cm did not affect recurrence-free survival ($p>0.05$) but did affect OS ($p<0.05$) (Table IV). We did not detect any significant difference in DFS between the two groups with different tumor sizes (≥5 cm, <5 cm). Considering all the stages, no significant difference was found in terms of the DFS rates between the two groups. When each cancer stage group was evaluated in terms of tumor size (≥5cm, <5cm), no significant difference was found in terms of OS ($p>0.05$). However, when all the stages were evaluated together, a tumor size of ≥5 cm resulted in worse OS than a tumor size of <5 cm (Log-Rank=12.559, $p<0.001$).

The effect of tumor localization on tumor size and how this effect influences tumor aggressiveness was investigated. It takes longer to diagnose right colon tumors

than left colon tumors due to the width of the right colon and its liquid content. In a study by Tomoda et al., the mean tumor diameters of right colon tumors were found to be larger than those of the left colon tumors (6.1 vs. 4.8 cm) [31]. In a study on mucinous colon tumors, right colon tumors were found to be larger than left colon tumors [32]. In another study conducted with 381 CRC patients, the median tumor size was found to be 4.5 cm (0.6-15), and the varying cut-off values of the tumor size for different parts of the large intestine were identified (cut-off values were 5 cm for the entire colon, 5.3 cm for the right colon, 3.9 cm for the left colon, and 3.4 cm for the rectum) [13]. The incidence rate of right colon tumor was higher in the group with a tumor size of ≥5 cm compared with the group with a tumor size of <5cm (30.7%, p=0.011), whereas the incidence rate of rectal tumors was significantly lower in the group with a tumor size of ≥5 cm compared with the group with a tumor size of <5cm (21.4%, p=0.045). The present study has some limitations. The retrospective nature of the study and the small sample size are considerable limitations of this study. In this study, administration of postoperative chemotherapy was excluded from the multivariate analysis of the risk factors affecting long-term survival as the data available was not homogenous.

Conclusion

In this study, increased tumor size, especially a tumor size of ≥5 cm, was found to be a risk factor that affected the OS adversely. We believe that this finding will aid in elucidating the link between tumor size and prognosis further.

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Riassunto

Obiettivo: Sono in corso discussioni sulla relazione tra le dimensioni del tumore e la prognosi dei pazienti con cancro del colon-retto (CRC). Questo studio mirava a rivelare l'effetto delle dimensioni del tumore sulla sopravvivenza globale e sulla sopravvivenza libera da malattia.
Materiali e Metodi: Questo studio ha valutato retrospettivamente i dati di 593 pazienti sottoposti a chirurgia colorettale per CRC tra maggio 2012 e dicembre 2018. I pazienti sono stati analizzati in termini di età, sesso, localizzazione del tumore, stadio T, stadio N, metastasi a distanza, dimensione del tumore, differenziazione del tumore, invasione venosa, invasione perineurale, numero di linfonodi, numero di linfonodi metastatici, recidiva e periodo di sopravvivenza. I pazienti sono stati divisi in 2 gruppi in base alle dimensioni del tumore; quelli con una dimensione del tumore <5 cm sono stati raggruppati come gruppo 1 e quelli con una dimensione del tumore >5 cm sono stati raggruppati come gruppo 2.
Risultati: Il presente studio ha incluso 222 pazienti con adenocarcinoma del colon-retto. Il periodo di follow-up mediano dei pazienti è stato di 36,0 (1,4–107,4) mesi, la dimensione media del tumore è stata di 5,1±2,3 cm e il numero di pazienti con una dimensione del tumore ≥5 cm è stato di 117 (52,7%). Un totale del 18%, 32,5%, 38,7% e 10,8% dei pazienti apparteneva rispettivamente agli stadi 1, 2, 3 e 4. I tassi cumulativi di sopravvivenza a 1, 3 e 5 anni del gruppo di pazienti con una dimensione del tumore ≥5 cm (n=117) erano rispettivamente dell'84,6%, 59,3% e 50,3%, mentre la sopravvivenza media stimata era 48,5 mesi (intervallo di confidenza 95% (CI): 42,3-54,7). Ci sono state differenze statisticamente significative tra i gruppi in termini di sopravvivenza globale (Log-Rank=12.559, p<0.001). Indipendentemente da altri fattori, una dimensione del tumore ≥5 cm ha influenzato negativamente la sopravvivenza globale (HR 2.248; 95% CI: 1.419-3.562) (p<0.001). Inoltre, una dimensione del tumore ≥5 cm (HR 1,867; 95% CI: 1,102-3,162; p=0,02), età, numero inadeguato di linfonodi dissezionati, numero di linfonodi metastatici e stadio sono risultati fattori di rischio per prognosi infausta.
Conclusioni: l'aumento delle dimensioni del tumore, in particolare una dimensione del tumore ≥5 cm, è risultato essere un fattore di rischio per una prognosi infausta. In una certa misura, riteniamo che questo studio aiuterà a chiarire il legame tra le dimensioni del tumore e la prognosi dei pazienti con CRC.

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