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Should tumor size concern us in nonmetastatic colon adenocarcinoma?

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Ethics Committee Approval
This study was approved by the Kartal Dr. Lütfi Kirdar City Hospital ethics committee (approval date: 09.06.2021; approval number: 2021/514/203/3).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Limited data are evaluating whether tumor diameter and the prognostic criteria are directly related to each other in colon adenocarcinoma cases. This study aimed to evaluate the relationship between tumor diameter and prognostic factors in non-metastatic colon adenocarcinomas.
Methods: Two hundred and sixty patients operated on due to colon adenocarcinoma and followed up in the General Surgery Department of our hospital between January 2015-December 2020 were included in this retrospective cohort study. The relationship between tumor size and lymphovascular invasion, perineural invasion, lymph node metastasis, and N-ratio was evaluated according to localization.
Results: The mean age of the patients was 63.3 (12.3) (min.-max.: 24-94) years. One hundred and sixty (61.5%) patients were male. The tumor was in the right colon (proximal to the splenic flexure) in 31%, and lymph node metastasis was detected in 43.5%. The number of metastatic lymph nodes and N-ratio values were similar according to tumor diameter (P>0.05 for each). Tumor diameter, the number of metastatic lymph nodes, and N-ratio values were not significantly correlated in the groups made according to localization (P>0.05 for each). The median tumor diameter was similar in patients with right colon and left colon cancer with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter (P>0.05 for each).
Conclusion: Our findings show that tumor diameter is not directly related to lymph node metastasis or N-ratio in non-metastatic colon adenocarcinomas and that it does not provide reliable information about lymph node metastasis.

Keywords: Colon adenocarcinoma, Tumor diameter, Lymph node metastasis, N-ratio

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Introduction

Colon adenocarcinomas are one of the most fatal cancer types. In colon adenocarcinomas, a staging system based on the tumor's invasion depth in the tissue (T), lymph node involvement (N), and metastasis (M) status is used to determine the prognosis [1-3]. In recent years, studies investigated whether some findings such as the number of lymph nodes affected, N-ratio expressed as the ratio of this number to the number of lymph nodes removed during the operation, and tumor diameter provide information in predicting prognosis [1-4].

Various research states that the tumor diameter helps in predicting the prognosis in colon adenocarcinomas. It has been suggested that the tumor being large or small indicates a negative prognosis in some stages or some groups of patients, or that its evaluation together with lymph node involvement provides significant data [5-7]. All these reports show uncertainty about the relationship of tumor diameter to prognosis.

Limited data are evaluating whether tumor diameter and the prognostic criteria are directly related in colon adenocarcinoma cases. This study aimed to investigate the relationship between tumor diameter, perineural and lymphovascular invasion, lymph node metastasis, and N-ratio in colon adenocarcinomas.

Materials and methods

This retrospective cohort study was approved by the Kartal Dr. Lütfi Kirdar City Hospital ethics committee on 09.06.2021 with the decision number 2021/514/203/3.

Patients and tests

A total of 260 patients who were operated on with the diagnosis of colon adenocarcinoma and followed up in the General Surgery clinics of our hospital between January 2015-December 2020 were included in this study. Pathology and radiology results of the patients were obtained from the hospital automation system and analyzed.

Patients with unconfirmed diagnoses of adenocarcinoma, metastatic disease (stage 4), and tumors outside the colon (such as stomach, small intestine, and rectum) were excluded from the study.

Statistical analysis

SPSS 25.0 (IBM SPSS, Chicago, USA) was used for statistical analyses. Chi-Square test and Fisher's Exact Test were used for comparisons between groups of categorical variables. The assumption of normality in distribution was assessed with the Kolmogorov-Smirnov Test for continuous variables. The Mann-Whitney U Test and the Kruskal Wallis test were used to analyze the differences between continuous variables and multiple groups, respectively. Spearman's correlation analysis was utilized to analyze the association between continuous variables. The capacity of the number of nuclei to predict the presence of disease in patients was analyzed using receiver operating characteristic (ROC) curve analysis. The results were evaluated within the 95% confidence interval, and $P<0.05$ values were considered significant.

N-ratio was calculated as [4]:

N-ratio= (number of metastatic lymph nodes) / (number of lymph nodes removed).

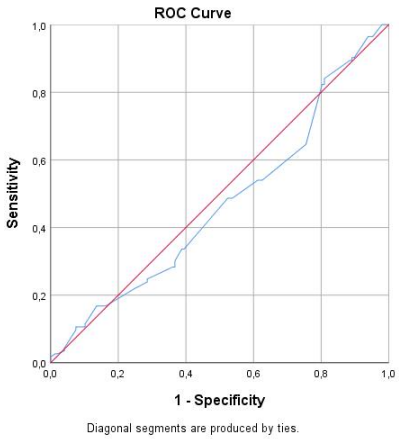
Power analysis was performed with G*Power Version 3.1.9.6 (Franz Faul, Universitaet Kiel, Germany), resulting in a need of 120 participants for 0.95 power with an effect size of 0.66.

Results

The mean age of the patients was 63.3 (12.3) (median: 63; interquartile range: 16; min.-max.: 24-94) years. One hundred and sixty patients (61.5%) were male. The tumor was in the right colon in 31% of the cases, and 14.6% were poorly differentiated. Perineural invasion was detected in 38.8%, lymphovascular invasion, in 45.8%, and lymph node metastasis, in 43.5% (Table 1).

ROC analyses revealed that a cut-off value of 44.5 mm for tumor diameter had a sensitivity of 54.0% and a specificity of 58.8% in predicting lymph node metastasis (AUC: 0.47; P=0.402; LB:0.399; UB: 0.541; CI 95%) (Figure 1).

Figure 1: ROC analysis. The cut-off value of 44.5 mm for tumor diameter had a sensitivity of 54.0% and a specificity of 58.8% in predicting lymph node metastasis (AUC: 0.47; P=0.402; LB:0.399; UB: 0.541; CI 95%).



In this study, the rate of patients with a tumor diameter above 44.5 mm was significantly higher among patients with a tumor in the right colon (P=0.004), while the rate of patients with a tumor diameter of less than 44.5 mm was significantly higher among stage 1 patients (P=0.031) (Table 1).

Table 1: Distribution of some variables by tumor diameter in all patients

	Tumor diameter (mm) <44.5 (n=109)		>44.5 (n=151)		Total	*P*-value
	n	%	n	%	n	
Gender						0.812
Male	68	42.5	92	57.5	160	
Female	41	41.0	59	59.0	100	
Localization						0.004
Right colon	24	28.9	59	71.1	83	
Left colon	85	48.0	92	52.0	177	
T						0.106
T1	4	80.0	1	20.0	5	
T2	13	56.5	10	43.5	23	
T3	67	41.4	95	58.6	162	
T4	25	35.7	45	64.3	70	
Differentiation						0.787
Well	14	37.8	23	62.2	37	
Moderately	80	43.2	105	56.8	185	
Poorly	15	39.5	23	60.5	38	
N						0.472
N0	57	38.8	90	61.2	147	
N1	29	47.5	32	52.5	61	
N2	23	44.2	29	55.8	52	
Stage						0.031
Stage 1	15	60.0	10	40.0	25	
Stage 2	42	34.4	80	65.6	122	
Stage 3	52	46.0	61	54.0	113	
Lymph node metastasis	52	46.0	61	54.0	113	0.241
Perineural invasion	45	44.6	56	55.4	101	0.493
Lymphovascular invasion	49	41.2	70	58.8	119	0.823

Chi square test was used.

The median tumor diameter of stage 1 patients with tumors in the left colon was significantly lower than those of stage 2 and 3 patients (P=0.005) (Table 2).

Metastatic lymph node count and N-ratio values were similar according to tumor diameter cut-off groups (P>0.05 for each) (Table 3).

Table 2: Comparison of median values

Stage		Age (years)	Tumor diameter (mm)
In all patients			
Stage 1	Mean	65.7	41.0
(n=27)	SD	12.7	22.1
	Median	65.0	40.0
Stage 2	Mean	63.4	54.3
(n=181)	SD	11.8	21.6
	Median	63.0	50.0
Stage 3	Mean	62.6	51.1
(n=52)	SD	12.6	23.6
	Median	63.0	45.0
P-value		0.478	0.016
Post-hoc			1<2; *P*=0.007
			1~3; *P*=0.072
			2~3; *P*=0.11
In the right colon-tumor patients			
Stage 1	Mean	72.8	68.0
(n=6)	SD	10.2	22.8
	Median	74.0	60.0
Stage 2	Mean	62.8	63.5
(n=53)	SD	13.3	21.9
	Median	62.0	60.0
Stage 3	Mean	62.2	56.1
(n=24)	SD	10.9	27.2
	Median	58.0	50.0
P-value		0.123	0.148
In the left colon-tumor patients			
Stage 1	Mean	64.0	34.2
(n=21)	SD	12.9	16.3
	Median	62.5	36.5
Stage 2	Mean	63.5	51.2
(n=128)	SD	11.4	20.7
	Median	64.0	47.0
Stage 3	Mean	62.8	47.6
(n=28)	SD	13.8	20.2
	Median	64.5	40.0
P-value		0.959	0.005
Post-hoc			1<2; *P*=0.001
			1<3; *P*=0.018
			2~3; *P*=0.202

Kruskal Wallis test was used for general comparison, and Mann-Whitney U test was used for comparisons between each pair. SD: Standard deviation.

Table 3: Comparison of median values according to tumor diameter groups

Tumor diameter		Age (years)	Number of metastatic lymph nodes	N-ratio
In all patients				
<44.5 mm	Mean	62.9	1.8	10.6
(n=109)	SD	11.5	3.0	18.4
	Median	64.0	0.0	0.0
>44.5 mm	Mean	63.5	2.1	11.1
(n=151)	SD	12.8	4.0	21.8
	Median	63.0	0.0	0.0
P-value		0.824	0.449	0.385
In patients with right colon tumor				
<44.5 mm	Mean	62.8	2.5	13.6
(n=24)	SD	11.2	2.7	20.3
	Median	60.5	1.5	5.8
>44.5 mm	Mean	63.2	3.0	15.1
(n=59)	SD	12.3	5.0	24.6
	Median	62.0	1.0	2.0
P-value		0.58	0.375	0.441
In patients with left colon tumor				
<44.5 mm	Mean	62.9	1.7	9.7
(n=85)	SD	11.7	3.1	17.8
	Median	65.0	0.0	0.0
>44.5 mm	Mean	63.7	1.5	8.5
(n=92)	SD	13.2	3.2	19.6
	Median	64.0	0.0	0.0
P-value		0.939	0.359	0.285

Mann-Whitney U test was used. N-ratio was calculated as: N-ratio=(number of metastatic lymph nodes) / (number of lymph nodes removed). SD: Standard deviation.

Tumor diameter, the number of metastatic lymph nodes, and N-ratio values were not significantly correlated according to localization (P>0.05 for each) (Table 4).

The median tumor diameter was similar among patients with right colon cancer and left colon cancer with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter (P>0.05 for each).

Median tumor diameter was similar in patients with and without perineural invasion (P=0.741). The median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with perineural invasion than in those without (P>0.001 for both) (Table 5).

The median tumor diameter was similar between patients with and without lymphovascular invasion (P=0.58). The median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with lymphovascular invasion compared to those without (P>0.001 for both) (Table 5).

Table 4: Correlation analyzes

		Tumor diameter (mm)
In all patients		
Number of metastatic lymph nodes	r	0.071
	P-value	0.253
N-Ratio	r	0.050
	P-value	0.424
In the right colon-tumor patients		
Number of metastatic lymph nodes	r	-0.056
	P-value	0.613
N-Ratio	r	-0.098
	P-value	0.376
In the left colon-tumor patients		
Number of metastatic lymph nodes	r	0.107
	P-value	0.157
N-Ratio	r	0.104
	P-value	0.168

Pearson's correlation anaysis was used.

Table 5: Comparison of median values according to perineural and lymphovascular involvement

		Tumor diameter (mm)	Number of metastatic lymph nodes	N-Ratio
Perineural invasion				
Present	Mean	51.6	3.6	19.4
(n=101)	SD	24.8	4.7	25.0
	Median	50	2	10
Absent	Mean	51.7	0.9	5.5
(n=159)	SD	21.5	2.2	14.6
	Median	50	0	0
P-value		0.58	<0.001	<0.001
Lymphovascular invasion				
Present	Mean	52.6	3.6	18.9
(n=119)	SD	23.7	4.4	23.7
	Median	50	2	10.3
Absent	Mean	50.8	0.6	4.1
(n=141)	SD	22	2.0	14.1
	Median	48	0	0
P-value		0.741	<0.001	<0.001

Mann-Whitney U test was used. N-ratio was calculated as: N-ratio=(number of metastatic lymph nodes) / (number of lymph nodes removed). SD: Standard deviation.

Discussion

Colon adenocarcinoma, one of the most common cancers in the world, has a high mortality rate [8, 9]. The relationship between findings such as tumor diameter, lymph node metastasis, and N-ratio in colon adenocarcinomas has not been demonstrated [4-7]. We examined the relationship between these data and observed that lymph node metastasis was not related to the size of the tumor.

Tumor diameter can reportedly provide significant information in predicting distant metastasis and prognosis in colon adenocarcinomas [5, 10]. A study reported that the prognosis was worse in cases with large tumors in the presence of lymph node metastasis [11], while another study stated that smaller tumor diameter was associated with a worse prognosis in the presence of lymph node metastasis [12]. In some studies, smaller tumor diameter was associated with worse survival or more frequent recurrence in T4 [6], T4b [13], stage 2 [14], stage 2a [7, 15, 16], and stage 1-3 [17] cancers. Another study reported

that tumor diameter was associated with survival in stage 3 cases but did not provide significant information about prognosis in stage 2 cases [18]. These data show that the relationship of tumor size with prognosis has not yet been clarified. In our study, the rate of patients with a tumor diameter of less than 44.5 mm was significantly higher among those with stage 1 cancer, and the median tumor diameter was significantly lower among stage 1 patients with tumors in the left colon than in stage 2 and 3 patients. Tumor size may be associated with stage, especially in left colon tumors, and a smaller tumor size can be expected in the early stages in these cases.

There may be an increase in the number of involved lymph nodes as the tumor diameter increases in colon adenocarcinomas, which can be expected because larger tumors may cause a greater inflammatory response in the mesentery [19-22]. Some studies report that as the N stage increases, the median tumor diameter increases, and tumor diameter is associated with lymph node metastasis [23, 24]. However, another study revealed that the tumor diameter decreased as the N stage increased [17]. In a study, no relationship was found between tumor diameter and the number of metastatic lymph nodes [19]. Another study reported that the lymph nodes involved were larger due to the more intense immune reaction in cases with large tumor diameters [25]. These data do not prove a direct relationship between tumor diameter and lymph node metastasis. However, in one study, tumor diameter and the presence of lymph node metastases were significantly correlated [26]. In our study, the number of metastatic lymph nodes and N-ratio values did not differ with tumor diameter. In the groups made according to localization, there was no correlation between tumor diameter, the number of metastatic lymph nodes, and N-ratio values. The median tumor diameter was similar in both right colon cancer patients and left colon cancer patients with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter. Our ROC analysis showed that the threshold value determined for tumor diameter in predicting lymph node metastasis had a very low level of reliability. All these findings show that there is no direct relationship between tumor diameter and lymph node metastasis.

Perineural invasion, the tumor invading the neurons around the organ, may indicate an unfavorable prognosis [13, 14, 16, 25]. In some studies, the tumor diameter did not differ according to the presence of perineural invasion [13, 16, 17]. In the present study, both the proportion of patients with large-size tumors and the median tumor diameter were similar in patients with and without perineural invasion, which indicates that perineural invasion is not directly related to tumor diameter.

Various studies state that the number of metastatic lymph nodes is significantly higher in patients with perineural invasion [17, 19, 25]. In ours, the median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with perineural invasion than in those without. This shows that perineural invasion and lymph node metastasis are directly related and more lymph nodes are involved in those with perineural invasion.

Lymphovascular invasion is the tumoral invasion of the lymphatic and vascular structures around the organ and may show an unfavorable prognosis [13, 14, 25]. Some studies showed that tumor diameter distribution does not differ according to the presence of lymphovascular invasion [13, 16, 17]. In our study, both the proportion of patients with large tumors with and without lymphovascular invasion and the median tumor diameter were similar. This finding indicates that lymphovascular invasion is not directly related to tumor size.

According to various research, the number of metastatic lymph nodes is significantly higher in patients with lymphovascular invasion [17, 19, 25]. We found that the median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with lymphovascular invasion than in those without, which reveals that lymphovascular invasion and lymph node metastasis are directly related, and more lymph nodes are involved in those with lymphovascular invasion.

Limitations

Direct prognostic data such as survival and recurrence were not included in the study because we aimed to examine the relationship between tumor size, lymph node metastasis, and other histopathological findings that affect prognosis.

Conclusions

There is no direct relationship between tumor diameter and lymph node metastasis and N-ratio in colon adenocarcinomas, and tumor diameter does not provide reliable information about lymph node metastasis. Our findings indicate that perineural and lymphovascular invasion are not directly related to tumor diameter but may be associated with lymph node metastasis.

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