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Original Research

The Relationship Between the Resected Colon Length and the Number of Lymph Nodes in Colorectal Cancer: A Retrospective Cohort Study

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ABSTRACT

Objective: The prognostic factors that are important for colorectal cancer are the pathological grade of the tumor and the existence of lymph node involvement. Currently, the curative treatment option is resection of the tumor with adequate length and margin along with complete dissection of lymph nodes draining the site of resection. Our study investigated into retrieving adequate lymph nodes for accurate staging as well as the relationship between lymph nodes and colon and rectum specimen length.

Methods: This retrospective cross-sectional study examined the correlation between resected colon length and lymph node count in patients with colorectal cancer diagnosed between January 2010 and June 2018. We defined a cutoff value for the segment length to be resected to allow adequate staging of the tumor. Furthermore, we examined the relationship between the resected segment lengths and survival.

Results: Of the patients who were included in this study, 211 were men and 169 were women. The mean resected colon length was 26.47±17.09 cm and the mean dissected lymph node count was 29.05±20.84. There was a positive correlation between specimen length and total lymph node count as well as specimen length and the existence of reactive lymph nodes that were statistically significant (r=0.319, p=0.001; r=0.312, p=0.001, respectively). In our study, tumor localization was described in three regions: the right colon, left colon and rectum. The mean right colon region specimen length was 28.8±15.5 cm, while it was 22.0±11.0 cm for the left colon region, and 21.7±10.6 cm for the rectum region. The 5-year overall survival rate was 53.2%, whereas the 5-year disease-specific survival rate was 58.2%.

Conclusion: The mean specimen length to achieve the cutoff value for adequate lymph node retrieval (least 12 lymph nodes) was 16 cm in our study (ROC curve, AUC=0.689±0.05, p=0.001). The resected colon length and the number of retrieved lymph nodes were positively correlated in our study. Based on this confirmation, a cutoff value of 16 cm was calculated to achieve an adequate segment length to be resected.

Keywords: Colorectal cancer, lymph node, prognosis, colon-rectum length, stage

INTRODUCTION

Colorectal cancer is the third most common tumor of the gastrointestinal system [1,2]. It is ranked second among cancer-related deaths [1,2]. The prognostic factors that are important for colorectal cancer are the pathological grade of the tumor and the existence of lymph node involvement. Determining the prognostic factors that affect survival, accurate staging and the treatment of choice is important for colorectal cancer [3]. Currently, the curative treatment option is resection of the tumor with adequate length and margin along with complete dissection of lymph nodes draining the site of resection [3,4]. While a variety of classifications have been used for staging, the TNM staging system is currently used. This staging is determined based on spread to lymph nodes, invasion through the colon wall and metastasis to distant organs. T indicates the degree of invasion, N is related to the metastatic locoregional lymph node count and M signifies whether there is metastasis or not [5]. Following accurate staging, postoperative adjuvant therapy options are determined for patients [6,7].

For accurate staging in patients who have undergone colorectal cancer resection, many institutions, including the American Joint Commission on Cancer (AJCC) guidelines, the National Cancer Institute (NCI), and the American Society of Clinical Oncology (ASCO), state that a minimum of 12 lymph nodes should be dissected [8]. For this reason, an adequate colon length should be resected during surgery. In our research, we aimed to determine the relationship between sufficient lymph node dissection and adequate colon length resection in patients with colorectal cancer.

Main Points;

- The most important two prognostic factors in nonmetastatic resectable colorectal cancer are the grade of the tumor and the involvement of lymph nodes.
- The curative treatment option is the resection of the tumor by resecting the colon at an adequate length to obtain tumor-free margins and the complete dissection of lymph nodes draining the site of resection.
- For accurate staging, a minimum of 12 lymph nodes should be retrieved.
- The retrieval of more than 12 lymph nodes was associated with longer survival compared to the dissection of 11 or fewer lymph nodes.
- Our study has shown the positive and statistically significant correlation between the length of the resected colon specimen and the number of retrieved lymph nodes.
- We found a cut-off value of 16 cm for the specimen length to retrieve an adequate number of lymph nodes.

MATERIALS AND METHODS

This study investigated the relationship between resected colon length and lymph node count retrospectively in patients diagnosed with colorectal cancer who underwent surgery between 01 January 2010 and 20 June 2018 at Gaziantep University Hospital, Department of General Surgery. The study also examined other parameters that affect the lymph node count.

The study included 380 patients who were diagnosed with colorectal cancer. Age and sex information was used to evaluate their demographic and clinical features. Specimens retrieved from patients who had undergone surgery were evaluated by the department of pathology. The histopathological examination determined colon and rectum specimen length, total lymph node count, existence of reactive lymph nodes, existence of malignant lymph nodes, T staging, N staging, metastasis, overall stage, lymphovascular invasion, and perineural invasion. Tumor localization and the surgical procedures that were performed were determined through operative records. Parameters of age, sex, colon specimen length and lymph node count were compared. For patients diagnosed with malignant disease, overall survival and disease-specific survival analyses were performed. Parameters affecting either type of survival were evaluated separately. Thirty-three patients who died within the early postoperative period due to comorbidities were excluded from disease-specific survival analyses. In patients with malignant disease, differences in sex for specimen length, total lymph node count, existence of reactive lymph nodes and malignant lymph nodes were questioned. Survival analyses were performed with respect to staging. Specimen length and lymph node count were evaluated in relation to the type of surgical procedure performed and tumor localization.

This study was approved by the ethics committee of Gaziantep University on July 4, 2018 with approval number 2018/166.

Statistical Analysis

The distribution of collected data was assessed using the Shapiro–Wilk test. Spearman's rank correlation was used to determine the correlation between variables with a nonnormal

Table 1. Summary of the tested variables; n:number of patients

		n	%
Status	Survivors	270	71.1
	Non-survivors	110	28.9
Gender	Male	211	55.5
	Female	169	44.5
T1234	1	15	3.9
	2	51	13.4
	3	210	55.3
	4	87	22.9
	T *in situ*	17	4.5
N0123	0	219	57.6
	1	94	24.7
	2	67	17.6
M01	0	281	73.9
	1	99	26.1
Stage	0	17	4.5
	1	44	11.6
	2A	105	27.6
	2B	13	3.4
	3A	14	3.7
	3B	88	23.2
	4	99	26
Surgical Procedure	Anterior resection	35	9.2
	Abdominoperineal resection (APR)	38	10.0
	Low anterior resection	101	26.6
	Right hemicolectomy	113	29.7
	Segmental resection	17	4.5
	Sigmoidectomy	20	5.3
	Left hemicolectomy	39	10.3
	Total colectomy	17	4.5
Tumor Region	Right	130	34.2
	Left	92	24.2
	Rectum	142	37.4
	Total	16	4.2
Lymphovascular Invasion	Present	89	23.4
	Absent	291	76.6
Perineural Invasion	Present	47	12.4
	Absent	333	87.6
Type of Surgery	Emergency	48	12.6
	Elective	332	87.4

distribution. For the comparison of features with a nonnormal distribution in the two groups, the Mann–Whitney U test was used. Survival rates were estimated using the Kaplan–Meier method. To determine the factors that impact survival, Cox regression analysis was used. As descriptive statistics, the mean±standard deviation for quantitative variables and the number and percentage for categorical variables were used. Statistical analyses were performed using SPSS for Windows (v 24.0), and $p<0.05$ was accepted as statistically significant.

RESULTS

Of the patients included in this study, 211 were men and 169 were women. The overall mean age with standard deviation was 57.86±14.48. The mean age in men was 56.37±14.59, while it was 59.69±14.15 in women. The mean resected colon length was 26.47±17.09 cm, and the mean dissected lymph node count was 29.05±20.84. In men, the mean dissected lymph node count was 30.51±23.83; while in women, it was 27.22±27.22. In our study, tumor localization was described in three regions: the right colon, left colon and rectum. The rectosigmoid region was included in the rectum region. There were 130 right colon region patients, 92 left colon region patients and 142 rectum region patients. The mean right colon region specimen length was 28.8±15.5 cm, while it was 22.0±11 cm for the left colon region, and 21.7±10.6 cm for the rectum region. Among the majority of the patients with transverse colon tumors, 113 patients underwent right hemicolectomy, 17 patients with central transverse colon tumors underwent segmental resection, 39 patients underwent right hemicolectomy, 20 patients underwent sigmoidectomy, 38 patients underwent abdominoperineal resection (APR), 101 patients underwent low anterior resection, 35 patients underwent anterior resection and 17 patients underwent total colectomy. The mean specimen length for right hemicolectomy was 30±15.6 cm. The segmental colon resection mean specimen length was 29.2±16.8 cm. The mean specimen length for sigmoidectomy was 21.8±11.8 cm. The left hemicolectomy mean specimen length was 27.3±13 cm. For anterior resection, low anterior resection and APR, the mean specimen lengths were 20±7.7 cm, 20±9.6 cm and 25.3±10.6 cm, respectively (Table 1).

For 291 patients, lymphovascular invasion was reported to be negative, while it was positive for 89 patients. For 333 patients, perineural invasion was reported to be negative, while it was positive for 47 patients. According to staging parameters, 17 patients were stage 0, 44 patients were stage 1, 118 patients were stage 2, 102 patients were stage 3, and 99 patients were stage 4. Ninety-nine patients had metastasis. The number of patients with malignant lymph nodes was 161. Of the 380 patients, 332 underwent elective surgery, while 48 underwent emergency surgery. Among patients who had an adequate number of lymph nodes dissected (12 or more), the mean specimen lengths showed a significant difference between elective surgery patients who had a mean specimen length of 35±20.6 cm and emergency surgery patients who had a mean specimen length of 26.7±17.1 cm (Table 1).

According to ACJJ, the minimum adequate dissected lymph node count, was 12. From 329 of our patients, 12 or more lymph nodes were retrieved and the mean specimen length of these patients was 27.61±17.65 cm. From 51 patients, an inadequate number of lymph nodes were retrieved (11 or less). The mean specimen length for these patients was 19.1±10.29 cm.

To calculate a cutoff value for colon specimen length, ROC curve analysis was conducted. In ROC curve analysis, the discrimination threshold is determined based on the AUC value. AUC>0.8 is considered to have excellent discriminating ability. In our study, the AUC was calculated as AUC=0.689±0.05, p=0.001 (Table 2).

This indicates that a resected colon specimen of longer than 16 cm will be associated with an 82% likelihood of having retrieved an adequate number of lymph nodes. However, a specimen length of shorter than 16 cm will be associated with a 53% likelihood of ending in the retrieval of an inadequate number of lymph nodes (Figure 1).

Patient age and specimen length were found to have a weak, negative correlation, which was significant (r=-0.130, p=0.011). Patient age and the number of total retrieved lymph nodes were found to have a weak, negative correlation, which was significant (r=-0.156, p=0.002). Patient age and the existence of reactive lymph nodes were found to have a weak, negative correlation, which was significant (r=-0.149, p=0.004). There was no statistically significant correlation between patient age and other parameters (T, N, and M stage).

There was a positive correlation between specimen length and total lymph node count as well as specimen length and the existence of reactive lymph nodes, which were significant (r=0.319, p=0.001; r=0.312, p=0.001, respectively). There was no significant correlation between specimen length and other

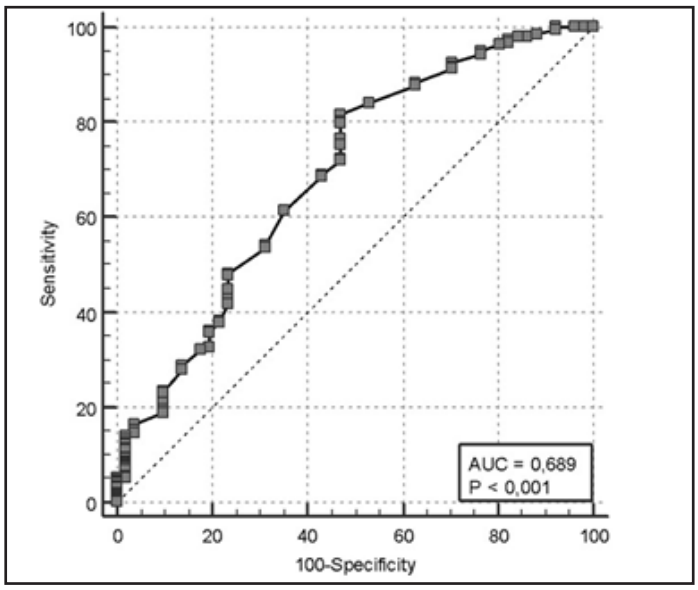

Figure 1. AUC curve for the specificity and the sensivity analysis of a specimen length of >16cm to achieve an adequate number of retrieved lymph nodes.

parameters (the existence of malignant lymph node, T, N, and M stage). There was a positive correlation between total lymph node count and reactive lymph nodes, which was significant (r=0.957, p=0.001). There was no significant correlation between total lymph node count and other parameters (the existence of malignant lymph node, T, N, and M stage). The existence of malignant and reactive nodes was found to have a weak, negative correlation, which was significant (r=-0.144, p=0.005) (Table 3).

N stage and the existence of reactive lymph nodes were found to have a weak, negative correlation, which was significant (r=-0.146, p=0.004). N stage and the existence of malignant lymph nodes were found to have a strong, positive correlation, which was significant (r=0.938, p<0.001). N stage and T stage were found to have a strong, positive correlation, which was significant (r=0.261, p<0.001).

Table 2. ROC analysis findings for a specimen length of >16 cm.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>16 cm	81.76	77.2 – 85.8	52.94	38.5 – 67.1	1.74	0.34

Table 3. Correlations between variables

	Correlation	Specimen Length	Total Number of Lymph Nodes	Number of Reactive Lymph Nodes	Number of Malignant Lymph Node	T Staging	N Staging	M Staging	Overall Stage of the Tumor
Age	r	-0.130*	-0.156**	-0.149**	-0.030	-0.048	-0.012	-0.029	0.043
	p	0.011	0.002	0.004	0.554	0.360	0.821	0.568	0.403
Specimen Length	r	1.000	0.319**	0.312**	-0.027	-0.025	-0.049	-0.054	0.054
	p		0.001	0.001	0.601	0.631	0.346	0.294	0.297
Total Number of Lymph Nodes	r		1.000	0.957**	0.055	-0.035	0.032	-0.070	-0.085
	p			0.001	0.287	0.505	0.528	0.171	0.099
Number of Reactive Lymph Nodes	r			1.000	-0.144**	-0.109	-0.146	-0.138	-0.079
	p				0.005	0.038	0.004	0.007	0.124
Number of Malignant Lymph Nodes	r				1.000	0.251	0.938	0.254	0.048
	p					0.000	<0.001	0.001	0.346
T-Staging	r					1.000	0.261	0.382	-0.048
	p						<0.001	0.001	0.364
N-Staging	r						1.000	0.256	0.061
	p							<0.001	0.233
M Staging	r							1.000	0.012
	p								0.811

r:Spearman rank correlation coefficient, *significant for p<0.05; **significant for p<0.01

Colon-rectum specimen length, total lymph count, and the existence of reactive lymph nodes showed significant differences with varying regions (Table 4). According to Dunnett's C multiple comparison test, conducted to determine which groups caused differences: for specimen length, right-left, right-rectum, total-right, and total-left; for total lymph node count, right-left, right-rectum, total-right, total-left, and total-rectum pairs, had significant correlations (Table 5).

Specimen length, total lymph node count, the existence of reactive and malignant lymph nodes, T stage, N stage, M stage, and stage with respect to sex showed no significant difference (p>0.001) (Table 6).

Survival by Tumor Stage and Lymph Node

The numbers of patients with 12 or more lymph nodes retrieved in stages 0, 1, 2, 3, and 4 were 15 (88.2%), 39 (88.6.4%), 105 (88.2%), 86 (85.1%), and 84 (84.8%), respectively. The number of patients with an inadequate number of lymph nodes retrieved in stages 0, 1, 2, 3, and 4 was 2 (11.8%), 5 (11.4%), 14 (11.8%), 15 (14.9%), and 15 (15.2%), respectively. An increase of one node in the number of malignant lymph nodes increased the hazard ratio by a factor of 1.04. An increase in the reactive lymph node number by each unit decreased the hazard ratio by approximately 3%. The M stage positivity increased the hazard ratio by a factor of 2.44. There was no statistically significant difference between sexes in terms of survival rates (Table 6).

Table 4. Colon specimen length by tumor stages

T Stage	Colon Specimen Length (cm) Mean±SD
0	23.23±17.11
1	26.33±15.82
2	25.49±14.85
3	25.79±16.31
4	28.96±20.61

Table 5. Mean number of retrieved lymph nodes and mean specimen length by tumor location

Tumor Location	Mean Number of Total Lymph Nodes	Specimen Length
Right	33.1±18.9	28.8±15.5
Left	23.7±17.4	22.0±11.0
Rectum	25.6±15.8	21.7±10.6
Total	58.1±49.0	75.6±23.6
P	<0.001	<0.001

Table 6. Cox regression analysis. Evaluation of the effects of the specimen length, the total number of retrieved lymph nodes, the presence of reactive and malignant lymph nodes, the T-stage, N-stage, and M-stage of the tumor, and the effect of gender on overall survival.

Variable	HR(95% CI)	P
Specimen Length	1.01 (0.99 -1.02)	0.092
Total Number of Lymph Nodes	0.98 (0.97 -1)	0.010*
Number of Reactive Lymph Nodes	0.97 (0.95 -0.98)	<0.001*
Number of Malignant Lymph Nodes	1.04 (1-1.08)	0.036*
T-Stage	1.01 (0.75 -1.35)	0.943
N-Stage	0.36 (1.03 -1.80)	0.029*
M-Stage	2.44 (1.61 -3.68)	<0.001*
Gender	1.35 (0.92 -1.98)	0.123

HR: Hazard Ratio, CI: Confidence Interval, * significant for p<0.05.

Patients with 12 or more lymph nodes dissected showed better long-term survival than patients with 11 or fewer lymph nodes dissected (log-rank test p=0.03) (Figure 2).

The survival rates for patients were as follows: 94.1% for stage 0, 84.1% for stage 1, 85.6% for stage 2, 65.7% for stage 3, and 49.5% for stage 4. The 1-year survival rates, 2-year survival rates and 5-year survival rates were 89.2%, 82%, and 75%, respectively for stage 0. However, these rates were 87.2%, 80%, and 68% for stage 1; 89%, 84%, and 72% for stage 2; 89.2%, 84%, and 72% for stage 3; and 81%, 73.5%, and 65% for stage 4, respectively.

Our results indicated a decrease in survival rates with advanced disease (p=0.001) (Table 7) (Figure 3). Overall survival rates were not different with respect to the location of the tumor (on the right side, left side, or in the rectum) (log-rank test. p=0.759).

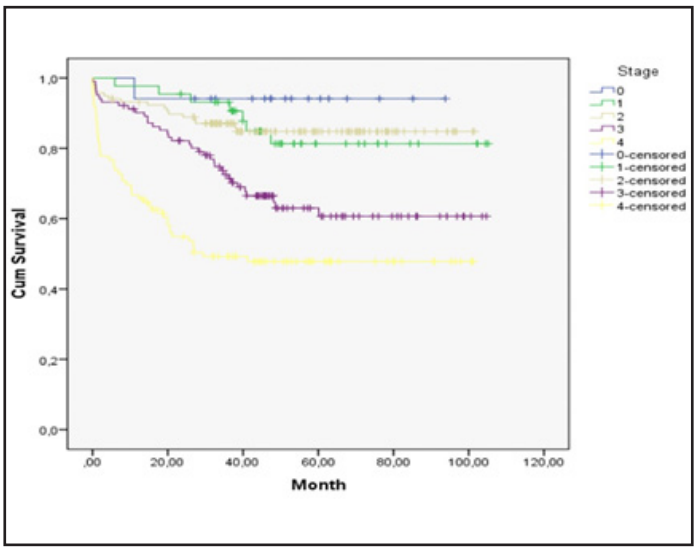

Figure 3. Kaplan-Meier survival depending on stages log-rank test P:0.001

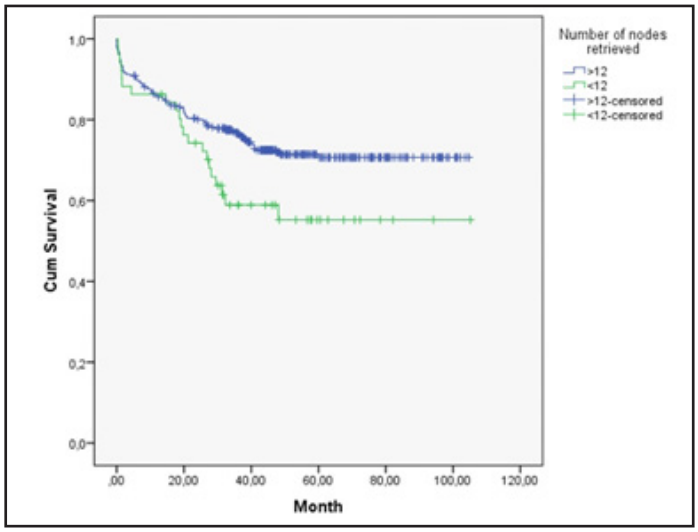

Figure 2. Kaplan-Meier survival analysis with respect to the number of dissected lymph nodes. Patients with 12 or more lymph nodes dissected appeared to have better long-term survival than patients with 11 or fewer lymph nodes dissected (Log-rank test, p:0.03).

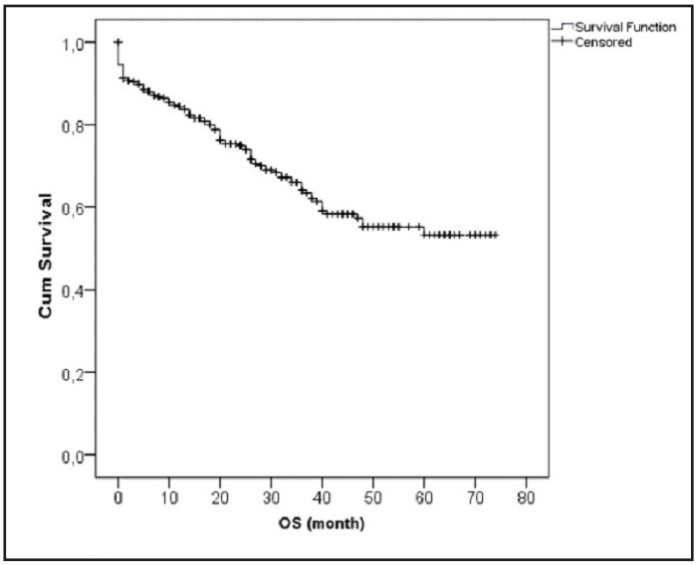

Figure 4. Overall survival rates

Table 7. Correlation between tumor stages and survival

Tumor Stage	Mean[a]			
	Estimated Survival Rate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
0	88.967	4.719	79.718	98.217
1	91.555	4.691	82.361	100.748
2	88.370	2.948	82.591	94.149
3	73.634	4.240	65.324	81.944
4	53.655	4.720	44.405	62.905
Overall	77.748	2.205	73.425	82.070

Log-Rank test. P=0.001

Overall Survival

Of the 380 patients with malignant disease, 71.1% were survivors and 28.9% were nonsurvivors at the time of the analysis. For these patients, the mean duration of survival was 49.87±1.82 months, the one-year survival rate was estimated to be 84.4%, and the 5-year survival rate was estimated to be 53.2% (Figure 4).

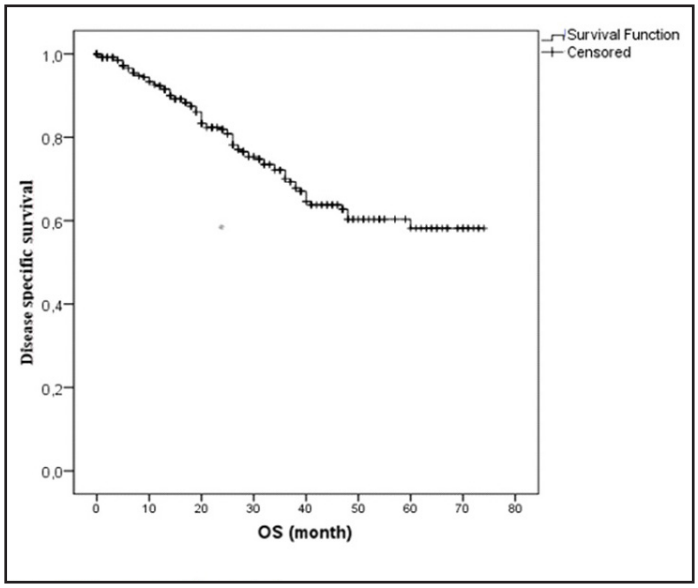

Figure 5. Disease spesific survival

Disease-Specific Survival

Of the 347 patients with malignant disease, 77.8% were survivors and 22.2% were nonsurvivors at the time of the analysis. For the survivors by the time of the analysis, the mean duration of survival was 56.91±1.33 months, the one-year survival was estimated to be 92.3%, and the 5-year survival was estimated to be 58.2% (Figure 5).

DISCUSSION

Accurate staging is crucial for colorectal cancer. For accurate staging, a minimum of 12 lymph nodes must be retrieved. Other studies in the literature have shown that patients with more than 12 lymph nodes dissected had longer survival than patients who had 11 or fewer lymph nodes dissected [9,10,11]. In our study, an adequate number (12 or more) of lymph nodes were retrieved from 329 patients. Patients with an adequate number (12 or more) of lymph nodes dissected had longer survival than patients with an inadequate number (11 or less) of lymph nodes dissected (Kaplan–Meier survival analysis, log-rank test p=0.03).

Pages et al. have shown that the number of malignant lymph nodes does not increase or the number of reactive lymph nodes increases as the length of the resected colon increases, despite having performed colorectal surgeries on different patients using the same techniques, due to biological differences in the lymph nodes of the operated portion of the colon mesentery and differences in the immunological response of the body [12,13]. In our study, specimen length showed a positive correlation with total and reactive lymph node counts (r=0.319, p=0.001; r=0.312, p=0.001, respectively). Specimen length showed no correlation of statistical significance with other parameters.

In the present study, lymph node count was correlated with age. This correlation between total lymph node count and age was an inverse correlation (r=-0.156, p=0.002). The lymph node count decreases with increasing age [14-16]. Our study has revealed similar results. Reasons for this may be weaker immunological response and the unwillingness of surgeons to perform wide resections on older patients.

While some studies in the literature have reported an increased number of lymph nodes in women [17-19], in our study, more lymph nodes were retrieved from men. However, this difference in our study was not significant.

Important prognostic factors for colorectal cancer include stage and the existence of metastatic lymph nodes [20]. In our study, with more advanced stages, survival rates decreased through Kaplan–Meier survival analysis with the log-rank test (p=0.001).

Many factors are known to affect overall survival, such as tumor localization, stage, tumor differentiation and lymph node involvement [21]. In our study, while metastatic lymph nodes affected survival, varying tumor localization showed no significant difference (log-rank test p=0.759).

There are various published studies on the relationship of specimen length and lymph nodes for colorectal cancer. F. Stracci et al. reported inadequate lymph node dissection in the case of specimen lengths less than 20 cm [22]. In our study, contrary to the literature, the cutoff value of mean specimen length for the retrieval of an adequate number (12 according to ACJJ) of lymph nodes was calculated as 16 cm (ROC curve, AUC=0.689±0.05, p=0.001). In 79.73% (n=303) of patients, as a result of operations where correct surgical techniques were applied, a minimum specimen length of 16 cm was achieved. This length and at least 12 lymph nodes are recommended for

all oncological colon resections, regardless of the location of the tumor.

Limitations

Although our study was a single center and retrospective study with important limitations, there is a positive correlation between resected colon specimen length and the number of lymph nodes retrieved.

CONCLUSIONS

The mean specimen length to achieve the cutoff value for adequate lymph node retrieval (the retrieval of at least 12 lymph nodes for an adequate pathological examination as defined by AJCC) was 16 cm in our study (ROC curve, AUC=0.689±0.05, p=0.001). Furthermore, the length of the resected colon specimen and the number of retrieved lymph nodes were positively correlated. Based on this confirmation, a cutoff value of 16 cm achieved an adequate segment length to be resected.

There was a positive correlation between the number of lymph nodes evaluated after surgical resection and the survival of patients with colon cancer. The results indicate that the number of lymph nodes analyzed should be considered as an indicator of the level of quality in colon cancer management. Our findings indicate that the removal of the colon can have a significant impact when following oncological surgical standards. In this study, we concluded that colorectal tumor surgery would be effective when performed by expert surgeons by applying correct techniques.

Conflict of Interest: None

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Ethical Committee Approval: We obtained the ethics committee approval of Gaziantep University Medical Faculty (04.07.2018, No:2018/166).

Author Contributions: Conception: UK, LY, AA; Design: UK, LY, AA; Supervision: UK, LY, AA; Materials: UK, LY; Data Collection and/or Processing: UK, LY; Analysis and/or lnterpretation: UK, LY; Literature Review: UK, LY, AB; Writing: UK, LY, AA, AB; Critical Review: UK, LY, AB.

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