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RESEARCH ARTICLE

Factors Associated with Poor Lymph Node Dissection of Colon Neoplasm

Kolon Kanseri Cerrahisinde Yetersiz Lenf Nodu Çıkarılması ile İlişkili Risk Faktörleri

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ABSTRACT

Aim: Dissection of ≥12 lymph nodes is recommended for curative surgery of colon neoplasms. The aim was to determine the clinicopathological factors associated with poor lymph node dissection.

Method: Patient hospital records in those undergoing surgery due to stage 1-3 colon neoplasm, between January 2009 and December 2017, were retrospectively evaluated. Univariate and multivariate analyses were performed to evaluate the clinical and pathological risk factors associated with poor lymph node dissection.

Results: The patient population during the study period numbered 388. Of these, <12 lymph nodes were dissected in 21.9%. Tumor location in the left colon, large tumors, deep penetrating tumors and short surgical margins were found to be independent risk factors for poor lymph node dissection by univariate analysis. Male gender, left colon location, large-sized tumors and deep penetrating tumors were confirmed as being independent markers for poor lymph node dissection by multivariate analysis.

Conclusion: Adequate lymph node dissection for colon neoplasm patients has prognostic significance. Male patients, advanced pT stage neoplasm, and left colon tumors had an increased risk of poor lymph node dissection. Therefore, lymph node dissection should be undertaken particularly meticulously in these patients.

Keywords: Colon cancer, colectomy, poor lynph node dissection

ÖZ

Amaç: Kolon kanserinin küratif cerrahisinde ≥12 lenf nodunun diseke edilmesi önerilmektedir. Bu çalışmada yetersiz lenf nodu diseksiyonuna etki eden klinikopatolojik faktörleri belirlemeyi amaçladık.

Yöntem: Ocak 2009-Aralık 2017 tarihleri arasında evre 1-3 kolon kanseri tanısıyla opere ettiğimiz hastalar retrospektif olarak incelenmiştir. Yetersiz lenf nodu diseksiyonu için risk faktörü olan klinik ve patolojik veriler tek değişkenli ve çok değişkenli analizlerle değerlendirilmiştir.

Bulgular: Çalışmaya 388 evre 1-3 kolon kanseri hasta dahil edilmiştir. Hastaların %21,9'da <12 lenf nodu diseke edildiği tespit edilmiştir. Tek değişkenli analizde sol kolon lokalizasyonunun, büyük tümörlerin, derin penetrasyon gösteren tümörlerin ve kısa cerrahi sınırın yetersiz lenf nodu diseksiyonu için bağımsız risk faktörleri olduğu tespit edilmiştir. Çok değişkenli analizde ise erkek cinsiyetin, sol kolon lokalizasyonunun, büyük tümörlerin ve derin penetrasyon gösteren tümörlerin yetersiz lenf nodu diseksiyonu açısından bağımsız belirteçler olduğu tespit edilmiştir.

Sonuç: Hastaların büyük kısmında yeterli lenf nodu diseksiyonun sağlandığı çalışmamızda büyük, pT evresi ileri, sol kolon yerleşimli tümöre sahip erkek hastaların yetersiz lenf nodu diseksiyonu açısından artmış riske sahiptir.

Anahtar Kelimeler: Kolon kanseri, kolektomi, yetersiz lenf nodu disseksiyonu

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Introduction

Colon neoplasms are the most common malignant tumor of the gastrointestinal system worldwide and the leading cause of cancer-related morbidity and mortality in Western countries. Approximately 70-80% of colon neoplasms are diagnosed at localized disease level, and surgical resection is the treatment of choice.[1] Curative surgery of colon neoplasms should include complete tumor resection with involved bowel segment and its mesentery with dissection of the draining lymph nodes.

Currently, the most important prognostic factors for colon neoplasm are the tumor node metastasis (TNM) staging system and the presence of residual tumor after resection. The presence of nodal metastasis is not only the most important prognostic factor but also the primary factor for adjuvant therapy decision making.[2]

Detection of all positive lymph nodes is essential for accurate staging, as inadequate lymph node dissection poses an absolute risk for inaccurate staging and thus deprivation of appropriate adjuvant therapy which has a significant effect on survival.[3,4,5]

There are different views on the minimum number of lymph nodes for adequate staging.[5,6,7] However, many studies suggest that at least 12 lymph nodes should be examined for nodal evaluation of colon cancer.[8,9,10]

Institutional guidelines, including the American Joint Committee on Cancer, the American Society of Clinical Oncology, the National College of Surgeons, the National Quality Forum, and the National Comprehensive Cancer Network, state that at least 12 lymph nodes are required for the correct staging of colon neoplasm patient.[11,12,13] Several factors have been shown to influence the number of lymph nodes removed. These include patient-specific and surgeon-specific factors and others related to pathological evaluation, not all of which can be optimized.[14,15]

The aim of this study was to determine the clinicopathological factors affecting inadequate lymph node dissection in patients with curative resection of colon neoplasms.

Materials and Methods

This study was a retrospective, single-centre study, comprised of colon cancer patients who underwent emergency and elective surgery between January 2009 and December 2017. Rectal neoplasms, synchronous colon neoplasms, colon neoplasms of familial polyposis, metastatic disease, palliative surgery patients, and patients who did not have adenocarcinoma following histopathological examination were excluded from the study. Only patients with stage 1-3 colon cancer were evaluated.

Preoperative laboratory analysis, colonoscopy, and imaging procedures including chest radiography and computed tomography, were performed in all elective surgery patients. The local Ethics Committee of University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt, Training and Research Hospital approved the study (date: 25.12.2017, no: 44/24). Written patient consent was not obtained because of the retrospective nature of the study.

All surgical specimens were fixed in 10% formalin solution and then routinely placed in paraffin. Conventional methods of visual inspection and palpation were used to detect lymph nodes. Hematoxylin-eosin stained sections of all lymph nodes were examined microscopically. If mucin constituted >50% of tumor volume histopathologically, the tumor was defined as mucinous carcinoma. Vascular invasion was defined as the presence of tumor cells along the venous endothelial surface, thrombosis of the venous lumen with tumor cells or destruction of the venous wall by tumor cells. The extraneural appearance of tumor cells was defined as “perineural invasion”. In all pathology reports, tumor size and differentiation, proximal and distal surgical margins, pT staging, the total number of removed lymph nodes and the total number of involved lymph nodes were reported.

Neoplasms located in the region from the ileocecal valve to the distal of the transverse colon were defined as right colon neoplasms, and neoplasms located in the region from splenic flexure to rectosigmoid junction (15 cm proximal from the anal canal) were defined as left colon neoplasm. Central vascular ligation was performed for both side neoplasms.

Neoplasms were pathologically classified according to the 8th American Joint Committee on Cancer (AJCC) TNM classification. Samples with <12 removed lymph nodes constituted the inadequate dissection group.[16]

Statistical Analysis

The Shapiro-Wilk test was used to assess normality of distribution of data sets. Numerical variables are presented as mean ± standard deviation and median (minimum to maximum range) while categorical variables are presented as number (percentage).

A univariate logistic regression model was used to calculate the effect of independent variables on the likelihood of obtaining an insufficient number of lymph nodes. As a result of univariate logistic regression analysis of clinically predicted variables that affected inadequate lymph node removal, variables with an error level below 0.25 ($p<0.25$) were identified as candidate variables for the multivariate model. A multivariate logistic regression model (Backward Wald) was established for candidate variables. In each step, the probability of entry into the logistic regression

model was 0.05, and the probability of exclusion from the model was 0.10. In addition, 95% confidence intervals were determined for the odds ratio (OR) values obtained by logistic regression.

Statistical Analysis

Statistical analyses and calculations were performed using SPSS, version 21.0 (IBM Inc., Armonk, NY, USA) and MS-Excel 2007. Statistical significance level was accepted as $p < 0.05$.

Results

Between January 2009 and December 2017, a total of 761 colorectal neoplasm patients were operated. After assessment of fit with the study inclusion criteria, 388 of 761 (50.98%) stage 1-3 colon cancer patients were included in the study population (Figure 1).

Demographic characteristics of patients are shown in Table 1. Two hundred and four patients (52.6%) were younger than 65 years, and 232 (59.8%) were male. Adequate lymph node dissection (≥12 nodes) was performed in 303 (78.1%) and inadequate (<12 nodes) was performed in 85 (21.9%). The statistical numerical variables are shown in Table 2.

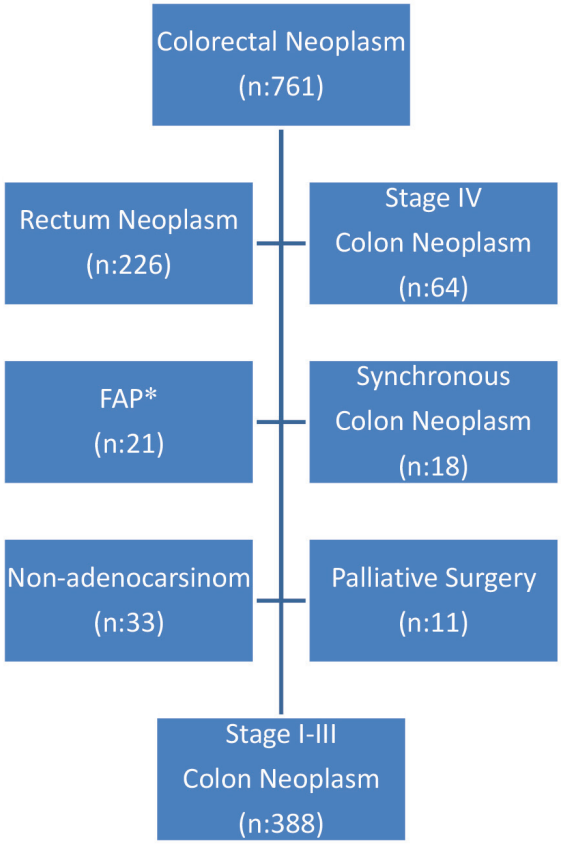

Figure 1. Selection of colorectal neoplasm patients' criterias
(*Familial adenomatous polyposis)

The relationship between univariate logistic regression and the number of removed lymph nodes of the indicated independent variables was examined (Table 3). The probability of inadequate lymph node dissection was found to be 1.59 times higher in male patients but this was not significant (p=0.072). The probability of inadequate lymph node dissection was 2.79 times [95% confidence interval (CI): 1.55-5.04] higher in tumors of the left colon than the right colon (p<0.001). The risk of inadequate lymph node assessment was higher in patients who did not have lymphovascular invasion (OR: 1.77) but this was not significant (p=0.053).

As a result of univariate analysis a number of variables were identified for inclusion in the multivariate logistic regression model. These variables included gender, location, tumor size, T-group, lymphovascular invasion and surgical margin. In the Enter model, there was a multiple connection problem between the T-group and the surgical margin. As a result of the stepwise model, the surgical border variable was not included in the model, whereas the T-group variable was included in the model. In the last model, the effect of gender, location, tumor size (≥5/<5 cm) and T-group (3 + 4/1 + 2) variables were significant.

Discussion

Lymph node metastasis alone is the most important prognostic factor in colon cancer.[17] The 5-year survival rate is over 75% in patients without metastatic lymph nodes but decreases below 30% in patients with lymph node invasion.[18] Therefore, in order to perform accurate staging of colon cancer according to AJCC TNM classification, it is necessary to thoroughly examine the surgical specimen and determine the status of lymph node metastasis.

In many studies, it has been shown that total survival and disease-free survival rates are directly proportional with the number of removed lymph nodes.[19,20] However, it has been reported that regional lymph node dissection is affected by many factors.[14] Currently, the rate of adequate lymph node dissection (≥12 lymph nodes) in colon cancer was reported to be 70%.[2,19]

The proportion of patients who underwent inadequate lymph node dissection in our cohort was 21.9%, which is similar to the literature. However, in contrast to earlier studies, we could not find a correlation between lymph node dissection and patient age in colon cancer patients. Studies have reported that fewer lymph nodes are dissected in elderly patients whichmay be associated with the decrease in immunological and inflammatory reactions to cancer tissues in elderly patients.[10,21]

Table 1. Demographic characteristics of patients

Variables	n (%)	Variables	n (%)
Age (year)		**N**	
<65	204 (52.6)	0	165 (42.5)
≥65	184 (47.4)	1	90 (23.2)
Gender		2	48 (12.4)
Male	232 (59.8)	X	85 (21.9)
Female	156 (40.2)	**TNM stage**	
BMI (kg/m²)		Stage I	42 (10.8)
<25	74 (33.9)	Stage II	180 (46.4)
≥25	144 (66.1)	Stage III	166 (42.8)
Lymph node		Lymphovasculer invasion	
<12	85 (21.9)	No	278 (71.6)
≥12	303 (78.1)	Yes	110 (28.4)
Preoperative CEA		Extranodal involvement	
<5	108 (27.8)	No	365 (94.1)
≥5	42 (10.8)	Yes	23 (5.9)
n/a	238 (61.4)	Free tumor nodule	
Elective/emergency		No	337 (86.9)
Elective	278 (71.6)	Yes	51 (13.1)
Emergency	110 (28.4)	Perineural invasion	
Localisation		No	327 (84.3)
Left	253 (65.2)	Yes	61 (15.7)
Right	135 (34.8)	Mucinous component	
Tumor size (cm)		No	341 (87.9)
<5	219 (56.4)	Yes	47 (12.1)
≥5	169 (43.6)		
Differentiation			
Well	58 (14.9)		
Moderate	283 (72.9)		
Poor	24 (6.3)		
Undefined	23 (5.9)		
Histopathology			
Adenocarsinom	364 (93.8)		
Mucinous carsinom	21 (5.4)		
Signet-ring carsinom	3 (0.8)		
T			
1	14 (3.6)		
2	39 (10.1)		
3	253 (65.2)		
4	82 (21.1)		

BMI: Body mass index, CEA: Carcinoembryonic antigen

Table 2. The statistical numerical variables

Variables	n	Median (min; max)	Mean ± SD
Age	388	63.5 (24; 91)	62.93±11.72
BMI	218	26.63 (16.51; 45.2)	27.3±4.64
Preoperative CEA	150	2.4 (0.1; 247)	10.06±29.35
Size (cm)	388	4.5 (0; 19)	4.86±2.31
LN	388	17 (0; 116)	19.56±11.79
LN positive	388	0.0 (0.0; 22.0)	1.36±2.70
Surgical margin (cm)	388	5 (0.2; 40)	6.21±4.86

SD: Standart deviation, min: Minimum, max: Maximum, BMI: Body mass index, CEA: Carcinoembryonic antigen

As previously reported, male sex was found to be associated with inadequate lymph node dissection in our study, but this relationship remains unclear. Larger and deeper-penetrating (T3-4) tumors were associated with a greater number of lymph nodes dissected by the surgeon. This may be the result of more antigenic immune and inflammatory responses increasing the number and size of regional lymph nodes.[10,22] As a result, lymph nodes were more easily identifiable for pathological examination. In our study, tumors in the left colon were associated with inadequate lymph node dissection, as many studies have reported, and this may be due to the surgeon avoiding a high anterior resection for distal sigmoid and rectosigmoid located neoplasms.[23] Additionally, the vascular anatomy of the right colon and associated neoplasms allows the removal of an extended bowel segment and wider mesentery.[15] Also, microsatellite instability, which is an essential pathway in tumor biology, is detected in 20-25% of right colon neoplasms, and this results in an increased propensity for metastatic locoregional lymph nodes.[24]

Close surgical margin is more common in sigmoid and rectosigmoid resections, and it is also associated with low numbers of lymph nodes being dissected.[25] In our study, the relationship between the close surgical margin and low lymph node number was found to be statistically significant in univariate analysis but not significant in multivariate analysis.

Tekkis et al.[21] reported that tumor differentiation was associated with the number of removed lymph nodes, so that poorly differentiated tumors had more lymph nodes removed compared with well or moderate differentiation neoplasms. We did not find any correlation between tumor differentiation and the number of lymph nodes removed.

Lymphovascular invasion, extranodal involvement, perineural involvement and free tumor nodule are indicators of tumor aggression. In a limited number of studies, their relationship with the number of removed lymph nodes could not be demonstrated. Gelos et al.[26], in a retrospective study of 341 patients, showed that the presence of lymphovascular invasion did not correlate with the number of removed lymph nodes and this is in agreement with our findings.

Although some studies have reported low numbers of lymph node being removed in patients with a high body mass index (BMI)[27], the effect of BMI on the number of removed lymph nodes is still unclear. In our cohort there was no relationship between the number of lymph nodes removed in low-weight and normal-weight patients (BMI <25 kg/m^2) and overweight and obese patients (BMI >25 kg/m^2).

The number of lymph nodes removed depends on different factors, including quality of surgical specimen, pathological examination, and characteristics of the patient and neoplasm. The limitation of our study was that more than 10 surgeons treated patients and different pathologists examined specimens. However, our hospital can be considered as a high-volume centre where approximately 100 colorectal cancer surgeries are performed annually. Moreover, some studies reported that higher hospital volume, more experienced surgeons and pathologists improve the quality of lymph node evaluation.[28] However, some other studies indicated that there was no statistical relationship between them.[29] Elferink et al.[30] reported that increased workload and, in particular that the pathologists could not perform a more detailed examination, so that there was an indirect relationship between the number of lymph nodes removed and the hospital volume.

Conclusion

Adequate lymph node removal in colon surgery has prognostic significance for the patient, and this was achieved in most of the curative resections in this study. There is an

Table 3. Univariate and multiple logistic regression model results

Variables	LNs group ≥12 n (%)	LNs group <12 n (%)	Univariate analysis Crude OR (95% CI)	Univariate analysis p	Multivariate analysis* Adjusted OR (95% CI)	Multivariate analysis* p
Gender				0.072		0.042
Female	129 (82.7)	27 (17.3)	1.00		1.00	
Male	174 (75.0)	58 (25.0)	1.59 (0.96-2.65)		1.74 (1.02-2.95)	
Age				0.678		
<65	161 (78.9)	43 (21.1)	1.00			
≥65	142 (77.2)	42 (22.8)	1.11 (0.68-1.79)			
BMI				0.367		
<25 kg/m^2	60 (81.1)	14 (18.9)	1.00			
≥25 kg/m^2	109 (75.7)	35 (24.3)	1.38 (0.69-2.76)			
Preoperative CEA				0.695		
≥5	31 (73.8)	11 (26.2)	1.00			
<5	83 (76.9)	25 (23.1)	0.85 (0.37-1.93)			
Elective/emergency				0.765		
Elective	216 (77.7)	62 (22.3)	1.00			
Emergency	87 (79.1)	23 (20.9)	0.92 (0.54-1.58)			
Localisation				<0.001		0.006
Right	119 (88.1)	16 (11.9)	1.00		1.00	
Left	184 (72.7)	69 (27.3)	2.79 (1.55-5.04)		2.34 (1.27-4.32)	
Tumor Size				0.001		0.008
≥5	146 (86.4)	23 (13.6)	1.00		1.00	
<5	157 (71.7)	62 (28.3)	2.51 (1.48-4.25)		2.10 (1.21-3.64)	
Differentiation				0.388		
Poor+undefined	39 (83.0)	8 (17.0)	1.00			
Well+moderate	264 (77.4)	77 (22.6)	1.42 (0.64-3.17)			
T				0.008		0.024
3+4	269 (80.3)	66 (19.7)	1.00		1.00	
1+2	34 (64.2)	19 (35.8)	2.28 (1.22-4.25)		2.10 (1.10-4.00)	
Lymphovasculer invasion				0.053		
Yes	93 (84.5)	17 (15.5)	1.00			
No	210 (75.5)	68 (24.5)	1.77 (0.99-3.18)			
Extranodal Involvement				0.289		
Yes	20 (87.0)	3 (13.0)	1.00			
No	283 (77.5)	82 (22.5)	1.93 (0.56-6.66)			
Free tumor nodule				0.764		
Yes	39 (76.5)	12 (23.5)	1.00			
No	264 (78.3)	73 (21.7)	0.90 (0.45-1.80)			
Perineural invasion				0.646		
Yes	49 (80.3)	12 (19.7)	1.00			
No	254 (77.7)	73 (22.3)	1.17 (0.59-2.32)			
Surgical margin				0.020		
≥5	175 (82.5)	37 (17.5)	1.00			
<5	128 (72.7)	48 (27.3)	1.77 (1.09-2.88)			

OR: Odds ratio, CI: Confidence interval/ *Backward Wald model accurate classification rate= 78.6%, Exp (constant)= 0.060

increased risk for inadequate lymph node dissection in male patients, in patients with left colon tumors, and in patients without locally advanced tumors. Therefore, lymph node dissection should be undertaken particularly meticulously in these patients.

Ethics

Ethics Committee Approval: The local Ethics Committee of University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study (date: 25.12.2017, no: 44/24).

Informed Consent: Written patient consent was not obtained because of the retrospective nature of the study.

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Authorship Contributions

Surgical and Medical Practices: M.T.B., İ.Y., Concept: M.T.B., İ.Y., Design: M.T.B., İ.Y., Data Collection or Processing: M.S., A.S., P.D., G.İ.İ., A.G., Analysis or Interpretation: P.D., Literature Search: M.S., A.S., G.İ.İ., A.G., Writing: M.T.B., İ.Y.

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