RESEARCH ARTICLE

Factors Associated With Poor Lymph Node Dissection of Colon Neoplasms

Kolon Kanseri Cerrahisinde Yetersiz Lenf Nodu Çıkarılması ile İlişkili Risk Faktörleri

Ⓘ **Mustafa Taner Bostancı**[1], Ⓘ **Ibrahim Yilmaz**[1], Ⓘ **Mehmet Saydam**[1], Ⓘ **Ahmet Seki**[1], Ⓘ **Pervin Demir**[2], Ⓘ **Gökşen İnanç İmamoğlu**[3], Ⓘ **Aysun Gökçe**[4]

[1]General Surgery University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital
[2]Biostatistics University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital
[3]Medical Oncology University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital
[4]Pathology University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital

ABSTRACT

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

Method: Retrospectively, patients' hospital records who underwent surgery due to stage 1-3 colon neoplasms between January 2009 and December 2017 were evaluated. Univariate and multivariate analyzes were performed to evaluate the clinical and pathological risk factors of poor lymph node dissection.

Results: Stage 1-3 total of 388 colon neoplasm patients were included in the study, and <12 lymph nodes were dissected in 21,9% of the patients. Left colon localization, large tumours, 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 localization, large-sized tumors and deep penetrating tumours were found to be independent markers for poor lymph node dissection by multivariate analysis.

Conclusion: Adequate lymph node dissection for colon neoplasm patients has prognostic significance. Male patients, pT stage advanced neoplasms, and left colon tumors had an increased risk of poor lymph node dissection; therefore, lymph node dissection should be appropriately done for 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.

Yöntemler. 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

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 contains; complete tumour resection with involved bowel segment and its mesentery with drained lymph nodes dissection.

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

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

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

Institutional guidelines; 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 patients.[13-15] Several factors have been shown to influence the number of lymph nodes removed such as; patient and surgeons and pathological evaluation related factors which some of them could not be optimized.[14-15]

In this study, we aimed to determine the clinicopathological factors affecting inadequate lymph node dissection in patients with curative resection of colon neoplasms.

Methods

This study is a retrospective single-centre study comprised of colon cancer patients who underwent emergency and elective surgery between January 2009 and December 2017 in our hospital. Rectal neoplasms, synchronous colon neoplasms, colon neoplasms of familial polyposis, metastatic diseases, palliative surgery patients, and patients whose histopathology other than adenocarcinoma were excluded from the study. Eventually, a total of 388 stage 1-3 colon cancer patients were evaluated in this study.

Preoperative laboratory analysis, colonoscopy, imaging procedures (chest radiography and computed tomography) were performed in all elective surgery patients. The local Ethics Committee of XXX Training and Research Hospital approved the study (Date:25.12.2017, No: 44 / 24). The written patient consent was not obtained because of the retrospective natüre 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 (HE) stained sections of all lymph nodes were examined microscopically. If mucin constitutes >50% of tumour volume histopathologically, the tumour was defined as mucinous carcinoma. Vascular invasion was defined as; the presence of tumour cells along the venous endothelial surface, thrombosis of the venous lumen with tumour cells or destruction of the venous wall by tumour cells. The extraneural appearance of tumour cells was defined as "perineural invasion. In all pathology reports, tumour 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 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.

The neoplasms were pathologically classified according to the 8th AJCC TNM classification and <12 removed lymph nodes were evaluated in the inadequate dissection group.[16]

Statistical Analysis

Shapiro-Wilk test was used to determine the numerical variables of the normal distribution, and numerical variables were demonstrated as mean ± standard deviation, median (minimum; maximum) and categorical variables as number (percentage).

The univariate logistic regression model calculated the effect of independent variables on the 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 0.10.95% confidence intervals were determined for the Odds Ratio (OR) value obtained by logistic regression.

Statistical Analyzes

Statistical analyzes and calculations were performed using IBM SPSS Statistics21.0 (IBM Corp. Released in 2012. IBM SPSS Statistics for Windows, Version21.0. Armonk, NY:IBM Corp.) 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 and according to the inclusion criteria 388 of 761 (50.98%) stage 1-3 colon cancer patients underwent curative surgery (Figure 1).

Demographic characteristics of patients were listed in Table 1. 204 patients (52.6%) were younger than 65 years, and 232 (59.8%) were male. Adequate lymph node dissection (≥ 12) was 303 (78.1%) and inadequate (< 12) was 85 (21.9%). The statistical numerical variables were listed in Table 2.

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; however, this difference was not statistically significant ($p = 0.072$). The probability of inadequate LN dissection of the left colon was 2.79 times (95% CI: 1.55-5.04) higher than the right colon ($p < 0.001$). The risk of inadequate LNs was higher in patients who did not have lymphovascular invasion (OR = 1.77) but not statistically significant ($p = 0.053$).

As a result of univariate analysis; multivariate logistic regression model (backward method) was established with variables with significance level below 0.25 (gender, localization, tumour 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, 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 (F / M), localization (right / left), tumor size ($\geq 5 / < 5$) 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 the 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 have a direct proportion with the number of removed lymph nodes.[19-20] However, it was reported that regional lymph node dissection had been affected by many factors.[14] Nowadays; adequate lymph node dissection (LNs ≥ 12) rates in colon cancer was reported as still at 70% levels.[12-19]

The rate of patients who underwent inadequate lymph node dissection was 21,9% (85/388), similar to literature in our study. Unlike literature, we could not find a correlation between lymph node dissection and patient age in colon cancer patients. Studies reporting that fewer number of lymph node dissections in elderly patients associated with the decrease of immunological and inflammatory reactions to cancer tissue in elderly patients.[10-21]

Following the literature, in our study, male sex was found to be associated with inadequate lymph node dissection, but this relationship remains unclear. We concluded that big-sized and deeper penetrating (T3-4) tumours were associated with more lymph node dissection by the surgeon who seemed to be the result of more antigenic immune and
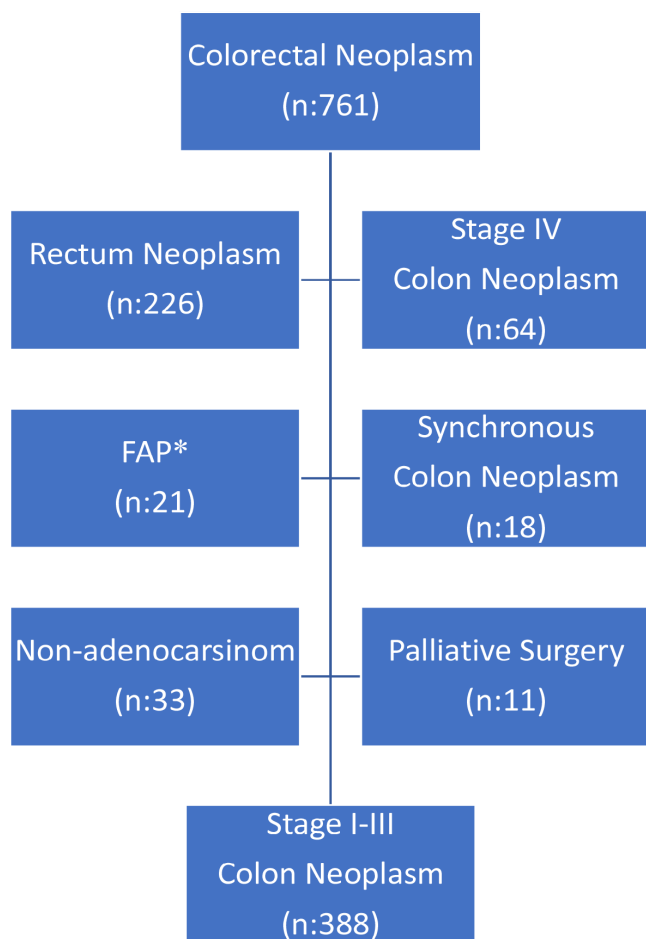

Colorectal Neoplasm (n:761)

Rectum Neoplasm (n:226)

Stage IV Colon Neoplasm (n:64)

FAP* (n:21)

Synchronous Colon Neoplasm (n:18)

Non-adenocarsinom (n:33)

Palliative Surgery (n:11)

Stage I-III Colon Neoplasm (n:388)

Figure 1. Selection of colorectal neoplasm patients' criterias (*Familial Adenomatous Polyposis)

Table 1. Demographic characteristics of patients

inflammatory responses
increasing the number

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)		

lymph nodes removed compared with well or moderate differentiation neoplasms.[21] We did not find any correlation between tumour differentiation and the number of lymph nodes removed.

Lymphovascular invasion, extranodal involvement, perineural involvement and free tumour nodule are indicators of tumour aggression. In a limited number of studies, their relationship with the number of removed lymph nodes could not be demonstrated. Gelos et al., in a retrospective study of 341 patients, showed that the presence of lymphovascular invasion did not correlate with the number of removed lymph nodes [26]; also we could not find a correlation between them.

Although some studies indicated that low number of lymph node removed in patients with a high BMI score [27], the effect of BMI on the number of removed lymph nodes is still unclear. We could not find a statistically significant relationship between the number of lymph nodes removed between low-weight and normal-weight patients (BMI <25 kg / m2) and overweight, obese patients (BMI> 25 kg / m2). The number of lymph nodes removed depends on different factors like; quality of surgical specimen, pathological examination, patient and neoplasm characteristics.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 hospital volume, the experience of the surgeon and the performance of the pathologist improve the quality of lymph node evaluation.[28] However, some other studies indicated that there was no statistical relationship between the.[29] Elferink et al. reported that the increased workload and in particular the pathologists could not perform a more detailed examination and that there was an indirect relationship between the number of lymph nodes removed and the hospital volume.[30]

Conclusion

Adequate lymph node removal in colon surgery has prognostic significance for the patient, and this has been achieved in most of the curative resections in our hospital. There is an increased risk for inadequate lymph node dissection in male patients, in patients with left colon tumours, and patients with not local advanced tumours, therefore we concluded with our study that surgeons should be more careful in lymph node dissection in such patients.

References

1. Nelson H, Petrelli N, Carlin A et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93: 583–596.

2. Huh JW, Kim CH, Kim HR, et al. Factors predicting oncologic outcomes in patients with fewer than 12 lymph nodes retrieved after curative resection for colon cancer. J Surg Oncol 2012; 105(2): 125-9.

3. Namm J, Ng M, Roy-Chowdhury S, et al. Quantitating the impact of stage migration on staging accuracy in colorectal cancer. J Am Coll Surg 2008; 207: 882-887.

4. Tsai HL, Yeh YS, Yu FJ, et al. Predicting factors of postoperative relapse in T2-4N0M0 colorectal cancer patients via harvesting a minimum of 12 lymph nodes. Int J Colorectal Dis 2009; 24(2): 177-83.

5. Shanmugam C, Hines RB, Jhala NC, et al. Evaluation of lymph node numbers for the adequate staging of Stage II and III colon cancer. J Hematol Oncol 2011; 4: 25.

6. Iachetta F, Reggiani BL, Marcheselli L, et al. Lymph node evaluation in stage IIA colorectal cancer and its impact on patient prognosis: a population-based study. Acta Oncol 2013; 52(8): 1682–90.

7. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. J Clin Oncol 2009; 27(36): 6166–71.

8. Shia J, Wang H, Nash GM, et al. Lymph node staging in colorectal cancer: revisiting the benchmark of at least 12 lymph nodes in R0 resection. J Am Coll Surg 2012; 214(3): 348–55.

9. Chen HH, Chakravarty KD, Wang JY, et al. Pathological examination of 12 regional lymph nodes and long-term survival in stages I-III colon cancer patients: an analysis of 2,056 consecutive patients in NE. Reftwo branches of the same institution. Int J Color Dis 2010; 25(11): 1333–41.

10. Tsai HL, Huang CW, Yeh YS, et al. Factors affecting the number of lymph nodes harvested and the impact of examining a minimum of 12 lymph nodes in stage I-III colorectal cancer patients: a retrospective single-institution cohort study of 1167 consecutive patients. BMC Surg 2016; 16: 17.

11. American Joint Committee on Cancer. Cancer staging manual 5th ed.: Springer; 1997: 83-91.

12. Bilimoria KY, Bentrem DJ, Stewart AK, et al. Lymph node evaluation as a colon cancer quality measure: a national hospital report card. J Natl Cancer Inst. 2008; 100(18): 1310–7.

13. Nelson H, Petrelli N, Carlin A, Couture J, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93(8): 583–96.

14. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005; 41: 272–9.

15. Nathan H, Shore AD, Anders RA, et al. Variation in lymph node assessment after colon cancer resection: patient, surgeon, pathologist, or hospital? J Gastrointest Surg 2011; 15: 471–9.

16. Jessup JM, Goldberg RM, Asare EA, et al. AJCC cancer staging manual. 8th edition. New York: Springer-Verlag 2017: 251–74.

17. Brunicardi FC, Andersen DK, Billiar TR, et al. Schwartz's principles of surgery. 10th ed. New York: McGraw-Hill Education; 2015: 1175-1241.

18. Le Voyer TE, Sigurdson ER, Hanlon AL et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of Intergroup Trial INT-0089. J Clin Oncol 2003; 21: 2912–2919.

19. Aan de Stegge WB, van Leeuwen BL, Elferink MA, et al. The Evaluation of More Lymph Nodes in Colon Cancer Is Associated with Improved Survival in Patients of All Ages. PLoS One 2016; 11(5): e0155608.

20. Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al. Lymph node evaluation and survival after curative resection of colon cancer: Systematic review. J Natl Cancer Inst 2007; 99: 433–441.

21. Tekkis P, Smith JJ, Heriot AG, et al. A national study on lymph node retrieval in resectional surgery for colorectal cancer. Dis Colon Rectum 2006; 49: 1673–83.

22. Baxter NN, Virnig DJ, Rothenberger DA, et al. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005; 97: 219–25.

23. Morikawa T, Tanaka N, Kuchiba A et al. Predictors of lymph node count in colorectal cancer resections: data from US nationwide prospective cohort studies. Arch Surg 2012; 147: 715–23.

24. Søreide K, Nedrebø BS, Søreide JA, et al. Lymph node harvest in colon cancer: influence of microsatellite instability and proximal tumor location. World J Surg 2009; 33: 2695–703.

25. Morikawa T, Tanaka N, Kuchiba A et al. Predictors of lymph node count in colorectal cancer resections: data from US nationwide prospective cohort studies. Arch Surg 2012; 147: 715–23.

26. Gelos M, Gelhaus J, Mehnert P, et al. Factors influencing lymph node harvest in colorectal surgery. Int J Colorectal Dis 2008; 23: 53-59.

27. Kuo YH, Lee KF, Chin CC, et al. Does body mass index impact the number of LNs harvested and influence long-term survival rate in patients with stage III colon cancer? Int J Colorectal Dis 2012; 27: 1625-1635.

28. Evans MD, Barton K, Rees A, et al. The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival for patients with Dukes' stage B disease. Colorectal Dis 2008; 10(2):157–64.

29. Bilchik AJ, DiNome M, Saha S, et al. Prospective multicenter trial of staging adequacy in colon cancer: preliminary results. Arch Surg 2006; 141(6):527–33.

30. Elferink MA, Wouters MW, Krijnen P, et al. Disparities in quality of care for colon cancer between hospitals in the Netherlands. Eur J Surg Oncol 2010; 36(Suppl 1): S64–73.