Research Article

Predictive Factor for Lymph Node Metastasis in Non-Metastatic Colorectal Adenocarcinomas

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Abstract

Objectives: To evaluate the predictive factors of lymph node involvement in non-metastatic colorectal adenocarcinomas (nmCRC).

Methods: A total of 453 patients diagnosed with nmCRC were analyzed regarding T stage, lymphovascular invasion status, tumor grade and proposed risk score (RS), determined by the combination of these three factors for lymph node metastasis.

Results: The median age was 62 (25-90 years), M/F ratio was 1.4:1 and majority of the patients had tumors localized on the left colon (70.6%). The number of excised lymph nodes was ≥12 in 77% of the cases. The postoperative pathological assessments revealed that 57.2% of patie,nts had N0 disease, 29.1% had N1 disease, and 13.7% had N2 disease. The T stages (p=0.007), grade (p<0.001), lymphovascular invasion (p=0.002), RS (p<0.001), and number of excised lymph nodes (p=0.029) were significantly different between N0, N1, and N2 patients. Higher RS was associated with lymph node metastasis (p<0.001).

Conclusion: The risk score may predict lymph node metastasis in patients with nmCRC and if validated may be helpful in the decision-making of adjuvant chemotherapy, especially in the elderly and patients with inadequate lymph node dissection.

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Colorectal cancer (CRC) is the third most common cancer worldwide.[1, 2] According to current guidelines, curative treatment in CRC includes surgery, and application of postoperative adjuvant radiotherapy and chemotherapy, which administered according to the disease stage and tumor location.[3, 4]

The TNM staging system of the American Joint Committee on Cancer (AJCC) is based on the tumor size, lymph node, and metastatic assessment of the malignancies, and being used worldwide to predict prognosis and survival of cancer patients. For colorectal cancer, the TNM system classifies patients as stage III if there is lymph node metastasis without distant metastasis. The T stage is not considered for this stage shift, regardless of its contribution of clinical outcomes, such as early T stages with lymph node positivity might have better outcomes than lymph node negative patients.[5, 6] As a consequence, primary criteria for determination of stage shift and indication for adjuvant treatment after potentially curative resection in nmCRC is the lymph node invasion.[7, 8]

The expected 5-year survival in node-positive disease is approximately 30%-60%, whereas this is 70%-80% in node-negative disease. Nevertheless, 20%-30% of disease recurrence might be observed even in surgically completely resected and initially node-negative patients, which has been presumed to be associated with occult lymph node disease.[9] There are several factors related to underassessment of lymph nodes in CRC, such as patient age, incomplete excision of lymph nodes.[10-12] According to the current evidence, the International Union Against Cancer (IUAC) and the AJCC suggest that a minimum of 12 lymph nodes should be evaluated for an adequate assessment for disease staging.[13, 14] Nevertheless, identification of predictive factors for lymph node metastasis may guide clinicians for a complete clinical assessment of CRC patients, particularly in non-metastatic settings.

Based on the current literature on lymph node assessment in CRC, we aimed to evaluate the predictive factors associated with lymph node invasion in nmCRC.

Methods

The study was conducted in a retrospective cross-sectional plan. Study reporting was done following the STROBE guidelines.[15] The study protocol was approved by the Local Ethics Committee at Ankara University Medical Faculty (IRB number: 3/1; Date: 15 August 2016).

A total of 536 patients diagnosed with colorectal cancer between January 2010 and December 2016 were evaluated retrospectively for inclusion to the study. After exclusion of those patients, remaining 453 patients were included in the analyses (Fig. 1).
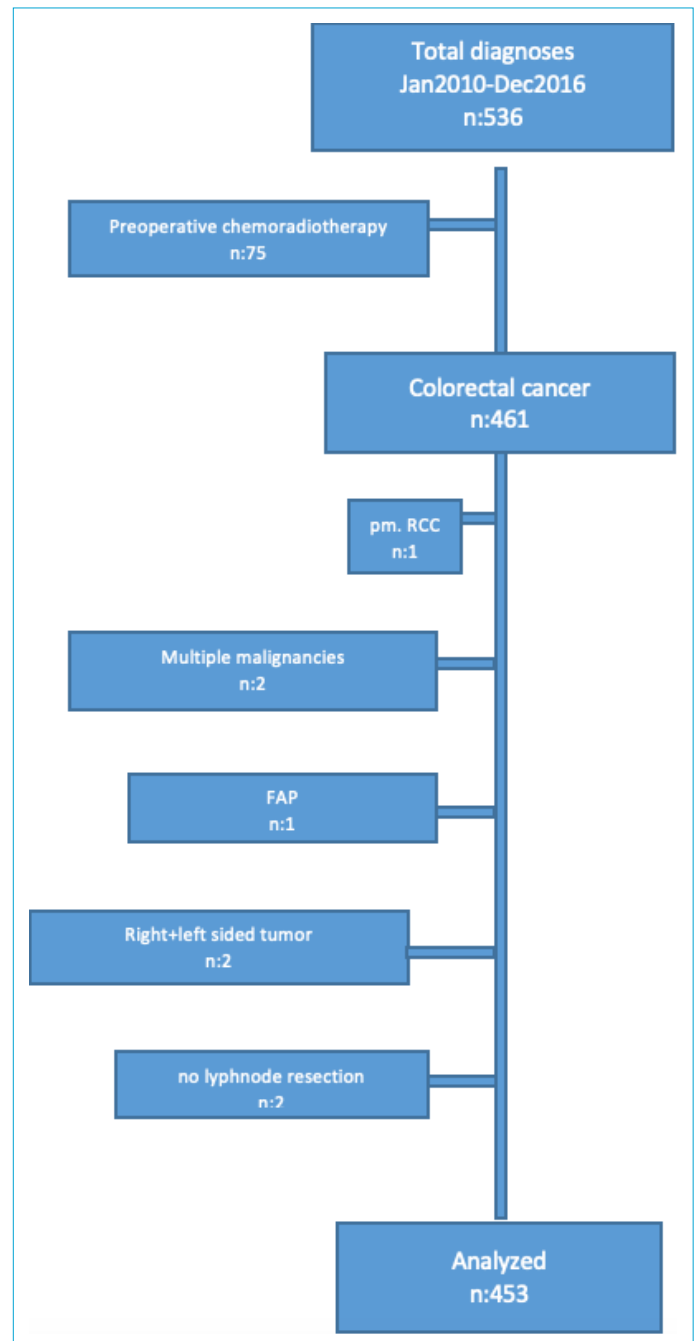

Figure 1. Study flow diagram.

The potential factors for predicting lymph node metastasis were determined as T stage, lymphovascular invasion status, localization of the primary tumor. Also, the correlations of postoperative pathological lymph node positivity with sex, age, T stage, tumor grade, lymphovascular invasion, primary localization of the tumor, preoperative CEA and CA19-9 levels were evaluated. Moreover, a risk score based on the tumor grade (1 point for Grade 1, 2 points for Grade 2 and 3 points for Grade 3), T stage (0 points for T0, 1 point for T1, 2 points for T2, 3 points for T3 and 4 points for

T4 tumor), and lymphovascular invasion (0 points for negative, 1 point for positive invasion) was calculated as a candidate predictive factor for lymph node involvement. This risk score ranged between 0 to 8, and classified as low-risk (0-3 points), moderate-risk (4-5 points) and high-risk (6-8 points).

Statistical Analysis

Numerical variables were presented as a median and minimum-maximum range, and categorical variables were presented as frequency and percent. The differences between more than two independent groups were analyzed by ANOVA test and chi-square test for numerical, and categorical variables, respectively. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 17 software) (IBM Inc., Armonk, NY, USA).

Results

A total of 453 patients with CRC were included in the final analyses. Median age of the patients was 62 years (25-90 years), and M/F ratio was 1.4:1 in the study group. Majority of the patients had tumors localized on the left colon (70.6%). The number of excised lymph nodes was ≥12 in 77% of the cases. The postoperative pathological assessments revealed that 57.2% of patients had N0 disease, 29.1% had N1 disease, and 13.7% had N2 disease. General characteristics of patients and the laboratory analyses were summarized in Table 1.

Table 1. General characteristics of the patients

	Median	Range
Age (years)	62	25-90
CEA	3.08	0.20 – 999
CA19-9	10.9	0.60 – 2111
	N	**%**
Sex		
Female	191	42.2
Male	262	57.8
Tumor localization		
Left colon	320	70.6
Right colon	133	29.4
Lymph node involvement		
N0	259	57.2
N1	132	29.1
N2	62	13.7
Excised lymph node count		
<12	104	23.0
≥12	348	77.0

The comparisons of demographic and clinical factors according to the N stage revealed that distributions of T stages (p=0.007), grade (p<0.001), lymphovascular invasion (p=0.002), lymph node risk score (p<0.001), and number of excised lymph nodes (p=0.029) were significantly different between N0, N1, and N2 categories (Table 2). Subsequent analyses revealed that patients with initial preoperative CEA levels higher than 3-fold of upper limit of normal values had more lymph node involvement (p=0.046). High RS was found to be associated with lymph node metastasis. (p<0.001) and the risk of lymph node metastasis increased as with higher RS.

Discussion

In this study, calculated risk score was associated with lymph node metastasis in patients with nmCRC.

Currently, the prognosis, survival, and more importantly treatment decisions of CRC patients is primarily based on the TNM classification of the AJCC. The major prognostic factor in the TNM for treatment decision is lymph node involvement [8]. In this study, we evaluated the potential predictive factors for lymph node invasion in a large sample of non-metastatic CRC patients. Our results revealed that T stage, grade, and lymphovascular invasion were associated with the LN involvement. Also, the risk score as a pivot item that based on these parameters were found to be correlated with the lymph node involvement. We herein suggest that utilization of this risk score in non-metastatic colorectal cancer patients may be beneficial for determining high-risk patients for lymph node invasion.

For adequate lymph node dissection in patients undergoing colon surgery, at least 12 lymph nodes must be removed. However, patients' age is the leading factor determining lymph node dissection in the literature. Meyer et al. [10] suggested that same surgical procedure on a younger patient will typically result in a larger number of lymph nodes to be examined pathologically, which will provide a more accurate assessment of lymph node metastasis. Similarly, several other researchers showed that increased age results with decreased number of lymph nodes excised and evaluated.[16, 17] This is a crucially important issue, because adequate evaluation of lymph node status is the key element to determine the accurate disease stage in CRC. According to our results, 77% of the cases had more than 12 lymph nodes excised. Moreover, N stage was found to be more advanced if the patient was older than 61.5 years, and the difference of N stage distribution in those was statistically significantly different from the patients younger than 61.5 years-old. These results suggest that those parameters should be taken into consideration in patient management.

Table 2. Comparisons of demographic and clinical factors between N stages

	N0 n (%)	N1 n (%)	N2 n (%)	P
Sex				0.86
Female	107 (41.3)	56 (42.4)	28 (45.1)	
Male	152 (58.7)	76 (57.6)	34 (54.9)	
T stage				0.007
T1	6 (2.4)	1 (0.7)	-	
T2	31 (12.0)	10 (7.5)	2 (0.3)	
T3	189 (73.6)	91 (69.0)	43 (69.3)	
T4	31 (12.0)	30 (22.8)	17 (27.4)	
Grade				<0.001
Well-differentiated	21 (8.2)	5 (3.7)	1 (1.6)	
Moderately-differentiated	185 (71.4)	84 (63.6)	30 (48.4)	
Poor-differentiated	36 (13.8)	33 (25.1)	26 (42.0)	
Unknown	17 (6.6)	10 (7.6)	5 (8.0)	
Lymphovascular invasion				0.002
LVI (-)	57 (43.8)	20 (28.5)	9 (20.5)	
LVI (+)	73 (56.2)	50 (71.5)	35 (79.5)	
Tumor localization				0.51
Left colon	185 (71.4)	95 (71.9)	40 (64.5)	
Right colon	74 (28.6)	37 (28.1)	22 (35.5)	
Age				0.04
<61.5 years	123 (51.3)	47 (35.6)	32 (51.6)	
>61.5 years	136 (48.7)	85 (64.4)	30 (48.4)	
Risk score				<0.001
Low risk	4 (3.2)	-	-	
Moderate risk	58 (44.9)	19 (27.5)	5 (12.5)	
High risk	67 (51.9)	50 (72,5)	35 (87.5)	
Excised lymph node count				0.029
<12	69 (26.7)	28 (21.2)	7 (11.2)	
≥12	189 (73.3)	104 (78.8)	55 (88.8)	

Efforts to define novel and clinically applicable risk factors and indicators in malignancies are ongoing efforts and subject to many clinical trials. For our particular study, we have evaluated the prognostic value of lymph node risk score that based on the T stage, grade and lymphovascular invasion yielded statistically significant results to define lymph node metastasis in early-stage CRC patients. A similar effort has been performed by Kong et al.,[18] who have evaluated the weighing of T stage in TNM for patient staging to overcome survival bias, which has been defined as the better survival in node-positive but T stage-early patients. Authors suggested that the so-called T-plus staging system reflects the significance of the T stage in colorectal cancer and abandons the rigid classification according to lymph node status. In our study, we have observed that advanced T stage is more associated with node-positive disease, but some patients were node-positive despite early T stage. When our results were combined with the outcomes of Kong et al. [18], we can postulate that T stage should also be considered during patient staging, even if the lymph nodes were negative.

The most important limitation of the study is that it is retrospective. Due to its retrospective nature, it is not exempt from drawbacks. Furthermore, it is not known how the treatment decision according to the recommended risk score will affect oncological outcomes.

Conclusion

According to this study, RS may be a useful tool in predicting lymph node metastasis. If validated by large-scale prospective studies, it may be helpful in the decision-making of adjuvant treatment, especially in elderly patients who have undergone insufficient lymph node dissection.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. Cancer Epidemiol Biomarkers Prev 2009;18:1688–94.

2. Eser S, Chang J, Charalambous H, Silverman B, Demetriou A, Yakut C, et al. Incidence patterns of colorectal cancers in four countries of the Middle East Cancer Consortium (Cyprus, Jordan, Israel, and İzmir, Turkey) compared with those in the United States Surveillance, Epidemiology, and End Results Program. Turk J Gastroenterol 2018;29:36–44.

3. Benson AB, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, et al. Colon Cancer, Version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:370–98.

4. Yazilitas D, Özdemir N, Yazıcı O, Hocazade C, Demirci NS, Zengin N. The clinical and pathological features affecting the time of relapse in patients with early stage colorectal cancer. J Cancer Res Ther 2016;12:1257–60.

5. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart A. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. J Clin Oncol 2010;28:256–63.

6. Kim MJ, Jeong SY, Choi SJ, Ryoo SB, Park JW, Park KJ, et al. Survival paradox between stage IIB/C (T4N0) and stage IIIA (T1-2N1) colon cancer. Ann Surg Oncol 2015;22:505–12.

7. Isik A, Peker K, Firat D, Yilmaz B, Sayar I, Idiz O, et al. Importance of metastatic lymph node ratio in non-metastatic, lymph node-invaded colon cancer: a clinical trial. Med Sci Monit 2014;20:1369–75.

8. King PM, Blazeby JM, Ewings P, Longman RJ, Kipling RM, Franks PJ, et al. The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. Colorectal Dis 2006;8:506–13.

9. Ong MLH, Schofield JB. Assessment of lymph node involvement in colorectal cancer. World J Gastrointest Surg 2016;8:179–92.

10. Meyer JE, Cohen SJ, Ruth KJ, Sigurdson ER, Hall MJ. Young age increases risk of lymph node positivity in early-stage rectal cancer. J Natl Cancer Inst 2016;108:djv284.

11. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65–71.

12. Wong JH, Bowles BJ, Bueno R, Shimizu D. Impact of the number of negative nodes on disease-free survival in colorectal cancer patients. Dis Colon Rectum 2002;45:1341–48.

13. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005;97:219–25.

14. Sobin LH, Greene FL. TNM classification: clarification of number of regional lymph nodes for pN0. Cancer 2001;92:452.

15. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. PLoS Med 2007;4:1623–7.

16. Ostadi MA, Harnish JL, Stegienko S, Urbach DR. Factors affecting the number of lymph nodes retrieved in colorectal cancer specimens. Surg Endosc 2007;21:2142–6.

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

18. Kong X, Li J, Cai Y, Tian Y, Chi S, Tong D, et al. A modified TNM staging system for non-metastatic colorectal cancer based on nomogram analysis of SEER database. BMC Cancer 2018;18:50.