

The association of lymph node involvement with lenfovascular invasion, perineural invasion and peritumoral lymphocytic reaction in surgically treated colon cancer patients

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Abstract

Aim: The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) cancer staging system is the strongest prognostic parameter for colorectal cancer. However, additional markers are needed to improve clinical decision making. The aim of this study was to investigate the effects of lenfovascular invasion (LVI), perineural invasion (PNI) and peritumoral lymphocytic reaction (PLR) on lymph node involvement in surgically treated colon cancer patients.

Materials and Methods: The historical records of patients having undergone colon cancer surgery in the Department of General Surgery were evaluated. In addition to demographic data and pathological TNM staging, parameters including tumor location, type, differentiation, LVI, PNI, PLR and tumor growth pattern were recorded and analyzed. $p < 0.05$ was considered as statistically significant.

Results: The study group of 71 patients consisted of 39 (54.9%) men and 32 (45.1%) women with a mean age of 65.1 ± 12.3 (range: 39-89) years. Tumors were located in the ascending colon in 18 (25.4%) patients, in the transverse colon in 3 (4.2%), in the descending colon in 8 (11.2%) and in the sigmoid colon in 42 (59.2%) patients. According to the postoperative histopathological examinations LVI was detected in 65 (91.6%) cases whereas PNI was found in 14 (19.7%) cases. PLR was detected in 69 (97.2%) cases that was mild in 53 (74.6%) and moderate in 16 (22.6%) cases. The incidence of PNI was significantly higher in stage N2 cases ($p = 0.001$). On the other hand, no significant differences were found among N stage groups regarding LVI or PLR ($p = 0.409$ and $p = 0.441$, respectively). Although it was detected that LVI and PLR were present concomitantly in 63 (88.7%) cases, no significant differences were detected between mild, moderate or negative PLR with respect to LVI positivity ($p = 0.748$).

Conclusion: PNI was associated with increased lymph node involvement. Larger prospective randomized controlled studies are needed to be conducted in order to establish additional prognostic parameters in colon cancer surgery.

Keywords: Colonic neoplasms; general surgery; lymph nodes; metastasis; pathology

INTRODUCTION

Colorectal carcinoma is the most common malignancy of the gastrointestinal tract and the third most lethal cancer. The incidence is similar in both genders and aging is a dominant risk factor for colorectal cancer, thus, more than 90% of cases diagnosed are older than the age of 50 (1).

In colorectal cancer surgery, survival is significantly affected by the presence and degrees of local invasion, lymph

node involvement and distant metastasis. Lenfovascular invasion, perineural invasion and peritumoral lymphocytic reaction are important histopathological features that have been shown to predict tumor cell biology and progression in colorectal cancer (2). The American Joint Committee on Cancer (AJCC) adopted lenfovascular invasion, peritumoral lymphocytic reaction and perineural invasion as prognostic factors and recommended their categorization in all pathology reports (3). The tumor

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stage reflected by the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) cancer staging system is currently considered the strongest prognostic parameter in patients with colorectal cancer. However, additional histopathological markers are needed to improve clinical decision making (4).

The aim of this study was to investigate the effects of lenfovascular invasion, perineural invasion and peritumoral lymphocytic reaction on lymph node involvement as well as their relationships with each other in surgically treated colon cancer patients.

MATERIALS and METHODS

The historical records of patients having undergone colon cancer surgery in the Department of General Surgery between 2008 and 2012 were evaluated. Approval for this study was obtained from the Institutional Review Board Ethics Committee, and signed informed consent forms were obtained from all patients.

Standard oncological colon cancer resection with complete mesocolic excision was performed on all patients included in the study. Cases with recurrent colorectal surgery, inoperable cases without tumor resection, rectal cancer cases, patients receiving neoadjuvant treatment, and cases with less than 12 lymph nodes removed were excluded from the study.

In addition to the demographic data regarding age and gender in the patients' hospital records, all surgical specimens obtained were examined by the same pathology team postoperatively. In addition to pathological staging according to the AJCC TNM system, parameters including tumor location, tumor type, tumor differentiation, lenfovascular invasion, perineural invasion, peritumoral lymphocytic reaction and tumor growth pattern were recorded and evaluated.

Statistical Analysis

Statistical analysis was performed using NCSS (Number Cruncher Statistics System) 2007 and PASS 2008 Statistical Software (Utah, USA) program. Besides descriptive statistical methods (mean, standard deviation, frequency, rate), the Kruskal-Wallis test was used to compare quantitative data, and the Mann-Whitney U test was used for two-group comparisons. The Pearson's chi-squared test and Fisher's exact test were used to compare qualitative data. $p < 0.05$ was considered as statistically significant.

RESULTS

The study group of 71 patients consisted of 39 (54.9%) men and 32 (45.1%) women with a mean age of 65.1 ± 12.3 (range: 39-89) years. Tumors were located in the ascending colon in 18 (25.4%) patients, in the transverse colon in 3 (4.2%), in the descending colon in 8 (11.2%) and in the sigmoid colon in 42 (59.2%) patients (Table 1).

According to the AJCC TNM staging system, none of the patients were in the T1 stage while 19 (26.8%) patients were in the T2 stage, 46 (64.8%) in the T3 stage and 6

(8.5%) patients were in the T4 stage. On the other hand, 42 (59.2%) patients were free of nodal involvement whereas 20 (28.2%) patients were in the N1 stage and 9 (12.7%) patients were in the N2 stage. Additionally, one (1.4%) patient in the study group was detected to harbour distant metastasis (Table 1).

Table 1. The distribution of demographic, pathologic and surgical parameters among the patients of the study group

Surgically treated colon cancer patients (n=71)		
	Mean	SD
Age	65.1	12.3
	n	%
Gender		
Male	39	54.9
Female	32	45.1
Tumor location		
Ascending colon	18	25.4
Transverse colon	3	4.2
Descending colon	8	11.2
Sigmoid colon	42	59.2
AJCC TNM Stage		
T1	0	0.0
T2	19	26.8
T3	46	64.8
T4	6	8.5
N0	42	59.2
N1	20	28.2
N2	9	12.7
M0	70	98.6
M1	1	1.4
Differentiation		
Well	10	14.1
Moderate	52	73.2
Poor	9	12.7
Lenfovascular invasion		
Negative	6	8.5
Positive	65	91.6
Perineural invasion		
Negative	57	80.3
Positive	14	19.7
Peritumoral lymphocytic reaction		
Mild	53	74.6
Moderate	16	22.6
Negative	2	2.8
Tumor growth pattern		
Infiltrative	31	43.7
Polypoid	8	11.3
Ulcerative	2	2.8
Ulcerative-infiltrative	1	1.4
Ulcerative-polypoid	29	40.9

n: Number of patients; SD: Standard deviation; AJCC: American Joint Committee on Cancer

Postoperative histopathological examination results revealed adenocarcinoma in all patients 10 (14.1%) of which were well differentiated while 52 (73.2%) were moderately differentiated and 9 (12.7%) were poorly differentiated. Lenfovascular invasion was detected in 65 (91.6%) cases whereas perineural invasion was found in 14 (19.7%) cases. Peritumoral lymphocytic reaction was detected in 69 (97.2%) cases that was mild in 53 (74.6%) and moderate in 16 (22.6%) cases. Examinations of tumor growth patterns revealed infiltrative growth pattern in 31 (43.7%) cases, polypoid in 8 (11.3%), ulcerative in 2 (2.8%), ulcerative-infiltrative in 1 (1.4%) and ulcerative-polypoid pattern in 29 (40.9%) cases (Table 1).

The rates of stage N0 and stage N1 cases were significantly higher in the moderately differentiated adenocarcinoma group, while the rate of stage N2 was significantly higher in the poorly differentiated adenocarcinoma group ($p=0.049$). The incidence of N0 stage was significantly higher in the patients at stage T2, the incidence of N1 stage was significantly higher in the patients at stage T3, and the incidence of N2 stage was significantly higher in the patients at stage T4 ($p=0.002$). The single one patient at stage M1 did not possess nodal involvement (Table 2).

Table 2. The comparison of N stages with respect to tumor differentiation, T and M stages

Postoperative Pathological Examination	N stage			p
	N0 n=42 n (%)	N1 n=20 n (%)	N2 n=9 n (%)	
Differentiation				
Well	6 (14.3%)	3 (15%)	1 (11.1%)	
Moderate	33 (78.6%)	15 (75.0%)	4 (44.4%)	0.049
Poor	3 (7.1%)	2 (10%)	4 (44.4%)	
T stage				
T2	17 (40.5%)	2 (10%)	0 (0.0%)	
T3	23 (54.8%)	17 (85.0%)	6 (66.7%)	0.002
T4	2 (4.8%)	1 (5.0%)	3 (33.3%)	
M stage				
M0	41 (97.6%)	20 (100.0%)	9 (100%)	
M1	1 (2.4%)	0 (0.0%)	0 (0.0%)	N/A

n: Number of patients. N/A: Not applicable

Perineural invasion was detected in 4 (9.5%) patients in stage N0, 4 (20%) in stage N1 and 6 (66.7%) patients in stage N2. It was found that the perineural invasion rate increased directly proportional to the increase in N stages as the incidence of this parameter was significantly higher in stage N2 cases ($p=0.001$). On the other hand, no significant differences were found among N stage groups regarding lenfovascular invasion or peritumoral lymphocytic reaction ($p=0.409$ and $p=0.441$, respectively) (Table 3).

When the association between lenfovascular invasions with peritumoral lymphocytic reaction was analyzed, it

was detected that lenfovascular invasion and peritumoral lymphocytic reaction were present concomitantly in 63 (88.7%) cases. However, no significant differences were detected between mild, moderate or negative peritumoral lymphocytic reaction with respect to lenfovascular invasion positivity ($p=0.748$) (Table 4).

Table 3. The distribution of perineural invasion, lenfovascular invasion and peritumoral lymphocytic reaction among N stages

Postoperative Pathological Examination	N stage			p
	N0 n=42 n (%)	N1 n=20 n (%)	N2 n=9 n (%)	
Perineural invasion	4 (9.5%)	4 (20.0%)	6 (66.7%)	0.001
Lenfovascular invasion	37 (88.1%)	19 (95.0%)	9 (100%)	0.409
Peritumoral lymphocytic reaction				
Mild	33 (78.5%)	13 (65.0%)	7 (77.8%)	
Moderate	7 (16.7%)	7 (35.0%)	2 (22.2%)	0.441
Negative	2 (4.8%)	0 (0.0%)	0 (0.0%)	

n: Number of patients

Table 4. The association between lenfovascular invasion and peritumoral lymphocytic reaction

Postoperative Pathological Examination	Lymphovascular invasion		p
	Positive n=65 n (%)	Negative n=6 n (%)	
Peritumoral lymphocytic reaction			
Moderate	14 (21.5%)	2 (33.3%)	
Mild	49 (75.4%)	4 (66.7%)	0.748
Negative	2 (3.1%)	0 (0.0%)	

n: Number of patients

DISCUSSION

The principle of colon cancer surgery is to remove the primary tumor along with its lenfovascular supply. It is necessary to harvest a minimum of 12 lymph nodes for adequate staging (1). Currently, the AJCC TNM staging is the most important predictive and prognostic factor in colon cancer (4).

Potter JD et al. reported that colon cancer was observed at the similar frequency in both genders, but rectal cancers were two times more common in men compared to women in their study (5). Fietkau et al. showed that the frequency of colon cancer increases with increasing age (6). In our study group of patients, 54.9% were men and 45.1% were women with a mean age of 65.1 ± 12.3 years.

Wray CM et al. found that the tumors were localized in the right colon in 48%, in the transverse colon in 10%, in the descending colon in 10% and in the sigmoid colon in 32%

of the patients in their study (7). In our study, tumors were located in the ascending colon in 25.4%, in the transverse colon in 4.2%, in the descending colon in 11.2% and in the sigmoid colon in 59.2% of the patients.

Grene F et al. stated that more than 80% of adenocarcinomas showed moderate differentiation, and the risk of lymph node metastasis was 81% in poorly differentiated tumors, while it was 30% in well differentiated tumors in their study (8). In the present study, postoperative histopathological examination results revealed adenocarcinoma in all patients 14.1% of which were well differentiated while 73.2% were moderately differentiated and 12.7% were poorly differentiated as the rate of stage N2 was significantly higher in the poorly differentiated adenocarcinoma group revealing that poor differentiation was associated with increased lymph node involvement ($p < 0.05$).

Jimenez-anula J et al. reported that infiltrating tumor type was significantly related with disease-free interval and this growth pattern was an independent prognostic factor of survival in colorectal cancer (9). Examinations of tumor growth patterns in our series revealed infiltrative growth pattern in 43.7% of the cases, polypoid in 11.3%, ulcerative in 2.8%, ulcerative-infiltrative in 1.4% and ulcerative-polypoid pattern in 40.9% of the cases.

Studies on postoperative pathological examinations of colorectal cancer mention the concepts of skip metastasis and related stage migration (Will Rogers phenomenon) as a result of distant metastasis development without the presence of lymph node involvement (10). There was only one patient that possessed distant metastasis (stage M1) in our study group who was at stage N0. We consider that skip metastasis and related stage migration were observed in this patient.

The incidence of lenfovascular invasion was reported to vary between 10-89.5%, whereas the incidence of perineural invasion was reported to be 14.1% in different colon cancer series (2,4). In the present study, lenfovascular invasion was detected in 91.6% of the cases whereas perineural invasion was found in 19.7% of the cases reflecting slightly increased values probably because of the reason that the patients in our study group were had presented in advanced stages of their diseases.

Huh JW et al. found that the rates of lenfovascular and perineural invasion were significantly higher in lymph node-positive patients in their study of 224 patients. In this study, the mean follow-up period was 49 months. Lymph node metastasis was the strongest predictive factor affecting survival in colorectal cancer. Lenfovascular invasion ($p < 0.001$) and perineural invasion ($p = 0.004$) were independent predictive factors for lymph node metastasis (11). In our study, it was found that the incidence of stage N2 was significantly higher in the perineural invasion group, and perineural invasion was associated with increased lymph node involvement ($p < 0.05$). On the other hand, no statistically significant result could be reached regarding the comparison of lenfovascular invasion with N stages ($p > 0.05$).

In their study of 226 patients, Xu FY et al. reported six independent negative prognostic factors in colorectal cancer as advanced age, advanced TNM stage, rapid tumor growth (rapid tumor budding), perineural invasion, insufficient peritumoral lymphocytic reaction and urine glucose level (12). Ogino S et al. found that increased lymphocytic reaction was associated with better overall survival in colorectal cancer in their study of 843 patients ($p < 0.003$). In this study, peritumoral lymphocytic reaction was found to be associated with better prognosis independently of the clinical, pathological and molecular characteristics and number of lymph nodes (13). In our study, peritumoral lymphocytic reaction was detected to be mild in 74.6% and moderate in 22.6% of the cases revealing no statistically significant differences with respect to N stages ($p > 0.05$).

To the best of our knowledge, there is no study revealing the relationship between lenfovascular invasion and peritumoral lymphocytic reaction. Although the frequency of concurrent peritumoral lymphocytic reaction and lenfovascular invasion were found to be high (88.7%) in our study group, no statistically significant difference was observed when these two parameters were compared ($p > 0.05$).

CONCLUSION

In the present study, the rate of stage N2 was higher in the perineural invasion group revealing that perineural invasion was associated with increased lymph node involvement. However, no significant differences were found among N stage groups regarding lenfovascular invasion or peritumoral lymphocytic reaction. Although an association between lenfovascular invasion and lymph node involvement could not be detected, the coexistence of peritumoral lymphocytic reaction and lenfovascular invasion was found to be high in our study group. In the light of these data, further randomized, prospective studies with larger number of patients are needed to be conducted in order to establish the prognostic values of these parameters in colon cancer surgery.

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