Original Article

Prognostic Value of Lymphovascular and Perineural Invasion in Colon Cancer

Kolon Kanserinde Lenfovasküler ve Perinöral İnvazyonun Prognostik Önemi

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ABSTRACT

Aim: Colon cancer is one of the most common types of malignant tumours in the world. Colon cancer ranks fourth among cancer-related deaths. Lymphovascular invasion (LVI) is the tumour involvement of small lymphatic or blood (typically venous) vessels while perineural invasion (PNI) is the growth of the tumour in, around, and along the nerves and nerve sheaths. In our study, we investigated the effects of LVI and PNI on prognosis, tumour stages, and lymph node metastasis in colon cancer patients.

Methods; The data of patients, who underwent colon cancer surgery in our clinic in the period between February 2013 and January 2020, were analyzed retrospectively. The surgery and pathology reports, demographic characteristics, and overall survival of the patients were examined.

Results: A total of 248 patients were operated due to colon cancer. LVI and PNI were present in 120 (48.3%) and 105 (41.9%) patients, respectively. The relationship of the grade, of the presence of positive lymph nodes, LVI, and PNI, and of the T- and N-stages with the survival were statistically significant with the following p-values of 0.028, <0.001, <0.001, <0.001, 0.005, and <0.001, respectively. When the relationship of LVI and PNI with other factors was examined, it was shown that there was a statistically significant relationship in both groups in terms of T and N stage, metastatic lymph node and survival time. (p <0.001)

Conclusion: Because the presence of LVI and PNI is a determinant of prognosis and lymph node metastasis especially in early-stage patients; we think that close follow-up of patients with LVI and PNI and the evaluation of such patients by a multidisciplinary council for the administration of adjuvant therapy, may affect prognosis favourably.

Key Words: Colon Cancer; Lymphovascular invasion; Perineural invasion

ÖZET

Amaç: Kolon kanseri tüm dünyada en sık görülen maligniteler arasındadır. Kansere bağlı ölüm nedenleri arasında 4. sıradadır. Lenfovasküler invazyon (LVI), küçük lenfatik veya kan (tipik olarak venöz) damarların tümör tarafından tutulması iken perinöral invazyon (PNI) ise sinirlerin ve sinir kılıflarının içinde, çevresinde ve boyunca tümörün büyümesidir. Çalışmamızda LVI ve PNI'nın kolon kanserli hastalarda prognoz, tümör evresi ve lenf nodu metastazına etkisi araştırdık.

Yöntem: Şubat 2013-Ocak 2020 tarihleri arasında kliniğimizde kolon kanseri nedeniyle opere edilen hastaların verileri retrospektif olarak inceledi. Hastaların ameliyat ve patoloji raporları, demografik özellikleri, genel sağkalımları incelendi.

Bulgular: 248 hasta kolon kanseri nedeniyle opere edildi. 120 hastada LVI, 105 (41.9%) PNI hastada vardı. Grade, lenf nodu pozitifliği, LVI, PNI, T ve N evrelerinin sağkalımla ilişkisi istatistiksel olarak anlamlı bulunmuş olup sırasıyla p değerleri: 0.028, <0.001, <0.001, <0.001, 0.005 ve <0.001'dir. LVI ve PNI'nin diğer faktörlerle ilişkisi incelendiğinde, T ve N evresi, metastatik lenf nodu ve sağkalım süresi açısından her iki grupta da istatistiksel olarak anlamlı bir ilişki olduğu gösterilmiştir. (p <0,001)

Sonuç: LVI ve PNI varlığı özellikle erken evre hastalarda prognozun, lenf nodu metastazının bir belirleyici olmasından dolayı; LVI ve PNI pozitif olan hastaların yakın izlemin, adjuvan tedavi için multidisipliner konseyde değerlendirilmenin prognoza olumlu etkilerinin olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Kolon Kanseri, Lenfovasküler invazyon, Perinöral invazyon

Introduction

Colon cancer is one of the most common types of malignant tumours in the world. Colon cancer ranks fourth among cancer-related deaths [1]. Despite the advances in treatment and technology, recurrences and metastasis continue to reduce patient survival [2]. The lymphatic system is the main route of metastasis in colon cancer as in many types of cancer. The status of lymph nodes is used to determine the stage of the disease, predict prognosis and select treatment modalities [3]. While surgical treatment is often curative for stage 1-2 colon cancers [4], adjuvant chemotherapy is recommended for stage 3-4 colon cancer [5-7]. Lymphovascular invasion (LVI) is the tumour involvement of small lymphatic or blood (typically venous) vessels while perineural invasion (PNI) is the growth of the tumour in, around, and along the nerves and nerve sheaths [8,9]. Recent advances in histopathological analysis techniques have suggested that histopathological factors such as LVI and PNI are unfavourable prognostic characteristics and may be harbingers of lymph node metastasis in early-stage colon cancers [6] thus, such findings can help identify patients at risk, who will benefit from adjuvant chemotherapy [10]. National Comprehensive Cancer Network (NCCN) guidelines described several additional factors such as LVI and PNI to identify stage II colorectal cancer patients with a high risk for metastasis [7]. In our study, we investigated the effects of LVI and PNI on prognosis, tumour stages, and lymph node metastasis in colon cancer patients.

Material-Method

The data of patients, who underwent colon cancer surgery in the period between February 2013 and January 2020, were analyzed retrospectively. All patients underwent standard surgical therapy. Patients; who were younger than 18 years old, who had distant metastases, who underwent additional visceral organ resection (resection of the liver, pancreas, colon, or small intestine), who had a cancer diagnosis other than adenocarcinoma, who had recurrences, who were operated due to emergency conditions, or who previously underwent surgery due to other types of cancer, were excluded from the study. The study included 248 patients. The surgery and pathology reports, demographic characteristics, and overall survival of the patients were examined. Electronic radiological examination records of chest radiograms, computed tomography, ultrasound, endoultrasound, magnetic resonance imaging, and PET-CT were examined retrospectively. Tumours were categorised based on location as the right colon, transverse colon, and left colon tumours. The 8th edition of the Union for International Cancer Control TNM classification system was used for staging [11]. PNI was defined as the presence of tumour cells in the perineural sheath involving at least 1/3 of the nerve's circumference [9]. LVI was defined as the involvement of the lymphatic or vascular channels by the tumour [12]. The patients were followed at 3-month intervals for 2 years, at 6-month intervals for the next 3 years, and annually thereafter.

Statistical Analysis

SPSS 25.0 software was used in the analysis of the data. For descriptive analysis, quantitative variables mean ± standard deviation and median (minimum-maximum), and qualitative variables were presented as number of patients (percentage). The mean distributions of the quantitative data were tested with the Shapiro-Wilk test and histogram curves. In terms of the quantitative variable, the difference between the categories of the qualitative variable with two categories was examined using the Mann-Whitney U test for those who provided normal distribution assumptions and those who did not provide the Student-t-test. The Chi-squared test was used to evaluate the relationship between two qualitative variables. The statistical significance level was accepted as 0.05.

Results

A total of 248 patients were operated due to colon cancer. Open surgery and laparoscopic surgery were performed on 24 (9.6%) and 224

Table 1. Descriptive characteristics

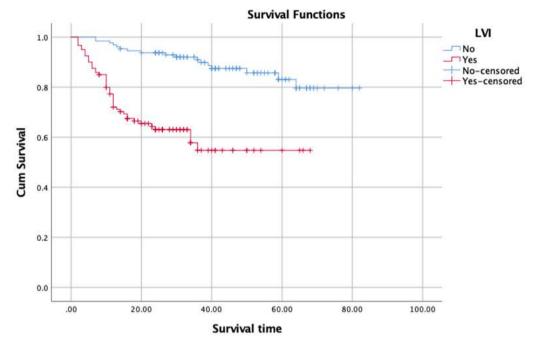| Variables		
Age	Mean±SD	58.23±13.22
Survival time	Mean±SD	33.6±19.4
Gender, n(%)	Male	143 (57.7)
	Female	105 (42.3)
Location, n(%)	Right	81 (32.7)
	Transvers	5 (2.0)
	Left	162 (65.3)
Operation, n(%)	Laparoscopic	224 (90.3)
	Open	24 (9.6)
Grade, n(%)	1	20 (8.1)
	2	176 (71.0)
	3	41 (16.5)
	4	11 (4.4)
Mortality, n(%)	Yes	186 (75.0)
	No	62 (25.0)
T stage, n(%)	1	31 (12.5)
	2	36 (14.5)
	3	130 (52.4)
	4	51 (20.6)
N stage, n(%)	0	136 (54.8)
	1	76 (30.6)
	2	34 (13.7)
	3	2 (0.8)

SD: standard deviation

(90.3%) patients, respectively. Of the study patients, 105 (42.3%) were women and 143 (57.7%) were men. The mean ± standard deviation and median (minimum-maximum) values of the patients' age were 61.50 ± 12.98 and 62.00 (22.00-93.00) years, respectively. The tumour was located in the right colon in 81 (32.7%) patients; in the transverse colon in 5 (2.0%) patients, and in the left colon in 162 (65.3%) patients. The T-stage of the tumour was T_1 in 31 (12.5%) patients, T_2 in 36 (14.5%) patients, T_3 in 130 (52.4%) patients, and T_4 in 51 (20.6%) patients. The distribution of the patients by the N-stages revealed 136 (54.8%) patients in N_0, 76 (30.6%) patients in N_1, 34 (13.7%) patients in N_2, and 2 (0.8%) patients in N_3. The mean number of resected lymph nodes was 17.78 ± 9.72 and the mean number of the metastatic lymph nodes was 2.02 ± 3.87. Patient characteristics are shown in Table 1.
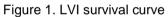
LVI and PNI were present in 120 (48.3%) and 105 (41.9%) patients, respectively. As for the overall survival, 186 (75.0%) patients survived and 62 (25.0%) patients died out of 248 patients. The mean survival time was 33.6 (2-82) months. The relationship of the grade, of the presence of positive lymph nodes, LVI, and PNI, and of the T and N stages with the survival were statistically significant with the following p-values of 0.028, <0.001, <0.001, <0.001, 0.005, and <0.001, respectively. The results of the Kaplan-Meier analysis were shown in Table 2 (Figure 1-2).

The ratio of the number of metastatic lymph nodes to the total number of the lymph nodes in patients was evaluated as the lymph node ratio. The mean value of the lymph node ratio was 0.11 ± 0.20. The values of the lymph node ratios were classified under 4 categories as Rosenberg et al. described [13]. The lymph node ratio categories were as follows: Category 1 included ratios in the range of 0.01-0.17, category 2 included ratios in the range of 0.18-0.41, category 3 included ratios in the range of 0.42-0.69, and category 4 included ratios of ≥0.70. There were 186 patients in category 1, 38 in category 2, and 12 patients in each of the categories 3 and 4. There were no statistically significant correlations between lymph node ratios and survival (p=0.477). When the relationship of LVI and PNI with other factors was examined, no statistically significant relationships were found with age or gender with p-values of 0.232 and 0.321 for LVI and 0.742 and 0.681 for PNI, respectively. Both LVI and PNI were statistically significantly related to the categorical variables of the tumour grade and the T and N stages. Of the qualitative variables, the relationships of the survival time and metastatic lymph nodes with LVI and PNI were statistically significant. The relationships of LVI and PNI with the investigated factors are shown in Table 3.

Discussion
LVI and PNI are the two major histopathological features that were shown to predict tumour biology and progression in colorectal cancers [14]. In the 1970s, LVI was
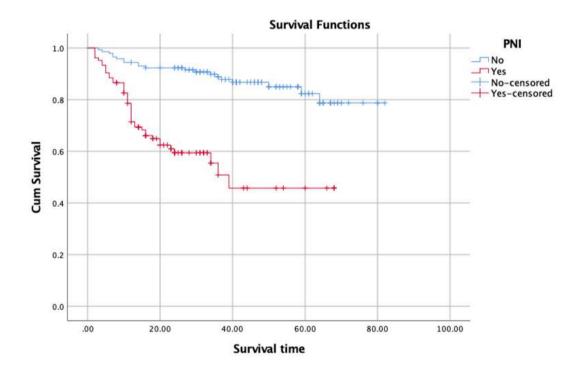
Figure 1. LVI survival curve

Figure 2. PNI survival curve

Table 2. Kaplan Meier analysis results

Variables		1 year (%)	3 years (%)	5 years (%)	Life Time Mean±SD	p-value
General		95.2	87.9	81.6	33.6±19.4	-
LVI	No	93.7	92.0	87.5	44.26±17.41	<0.001
	Yes	90.0	77.3	65.4	22.37±14.64	
Grade	1	89.5	89.5	67.1	45.21±19.74	0.028
	2	93.2	85.0	82.5	34.69±19.00	
	3	82.9	57.5	57.5	26.60±18.75	
	4	72.7	54.5	54.5	22.54±17.73	
Lymph node positivity	No	94.0	87.9	84.6	42.01±18.12	<0.001
	Yes	90.4	74.1	68.2	23.86±16.22	
PNI	No	92.3	90.7	87.8	42.59±17.64	<0.001
	Yes	88.5	71.4	62.4	21.44±14.80	
T stage	1	100.0	96.2	88.8	48.03±15.17	0.005
	2	88.9	75.6	75.6	36.19±18.70	
	3	89.2	75.6	68.1	34.67±19.76	
	4	76.4	63.6	63.6	20.60±13.21	
N stage	0	91.2	80.4	75.5	40.08±19.34	<0.001
	1	86.8	72.4	64.3	29.25±17.11	
	2	72.3	68.3	-	19.23±13.55	
	3	0	-	-	11.00±1.41	
Lymph node ratio	0.01-0.17	88.7	77.5	72.5	35.09±20.20	0.477
	0.18-.41	84.2	73.1	53.2	30.05±15.52	
	0.42-0.69	83.3	72.9	54.7	26.58±21.29	
	≥0.70	83.3	83.3	83.3	30.16±15.58	

SD: standard deviation

for the first time associated with poor prognosis in colorectal cancers with blood vessel involvement. In 1989, Minsky et al. described LVI as an independent prognostic factor [15]. In the same years, PNI was defined as the invasion of the nerves around the tumour and was identified as a poor prognostic factor in many cancer types such as the cancers of the colon, pancreas, and prostate [16]. In the 2000s, the American Joint Committee on Cancer (AJCC) identified LVI and PNI as adverse prognostic factors and recommended that they should be addressed every time in pathology reports [17]. We evaluate the status of LVI and PNI of all our patients in our clinic and in every tumour board.

Despite some previous studies arguing about LVI and PNI contrarily, unfavourable prognostic effects of LVI and PNI have been shown in many studies [18-20]. The study by Al-Sukhni et al. reported LVI and PNI rates of 26.3% and 11.1% at all stages, respectively. [21] However, the ratios reported for LVI (33%) and PNI (15-22%) vary in the literature [22,23]. In the same study; the positivity of LVI and PNI was associated with advanced T stages, high tumour grade, a high number of lymph node metastases, and distant metastases. Similarly, Huh et al. found that; in T1 and T2 tumours, the positivity of LVI and PNI was statistically significantly associated with the depth of tumour invasion [24]. In our study; the rates of LVI and PNI were 48.3%

Table 3. Association of LVI and PNI with clinicopathological features

Variables		LVI			PNI		
		Yes (n=120)	No (n=128)	p value	Yes (n=120)	No (n=128)	P
Grade(%)	1	1 (0.8)	19 (14.8)	<0.001c	2 (1.9)	18 (12.6)	<0.001c
	2	77 (64.1)	99 (77.30)		68 (65.4)	107 (74.8)	
	3	32 (26.6)	9 (7.1)		26 (25.0)	15 (10.5)	
	4	10 (8.5)	1 (8.8)		8 (7.7)	3 (2.1)	
Survival time	Mean±SD	22,37±14,64	44,26±17,41	<0.001a	21,44±14,80	42,59±17,64	<0.001a
Lymph node ratio	Mean±SD	0.13±0.20	0.10±0.19	0.421b	0.13±0.21	0.10±0.19	0.276b
T stage, n(%)	T1	3 (2.5)	28 (21.9)	<0.001c	2 (1.9)	28 (19.6)	<0.001c
	T2	18 (15.0)	18 (14.1)		13 (12.5)	23 (16.1)	
	T3	59 (49.2)	71 (55.5)		58 (55.8)	72 (50.3)	
	T4	40 (33.3)	11 (8.6)		31 (29.8)	20 (14.0)	
N stage, n(%)	N0	45 (37.5)	91 (71.1)	<0.001c	45 (30.8)	103 (72.0)	<0.001c
	N1	46 (38.3)	30 (23.4)		46 (41.3)	33 (23.1)	
	N2	27 (22.5)	7 (5.5)		45 (26.0)	7 (4.9)	
	N3	2 (1.7)	0 (0)		46 (1.9)	0 (0)	
Metastatic lymph node	Mean±SD	3.55±4.98	0.58±1.27	<0.001a	2.17±5.05	0.59±1.61	<0.001a

a.   Mann Withney U b. Student t c. Ki-kare

and 41.9% at all stages, respectively. We demonstrated in our study that the posivity of LVI and PNI was statistically significantly associated with both the tumour invasion depth (p<0.001, p<0.001) and high histological grades (p<0.001, p<0.001).

One of the most important prognostic factors in colorectal cancers is the presence of lymph node metastases [3,25]. Many studies have been conducted so far to predict the emergence of lymph node metastases [26,27]. Huh et al. found LVI and PNI as the only factors that could be used to predict lymph node metastases [24]. In the same study, it was shown that the presence of PNI increased the presence of lymph node positivity by 10 times. In our study, the effects of the presence of LVI and PNI on lymph node metastasis were found to be statistically significant (p<0.001, p<0.001). We found that the presence of LVI and PNI increased the likelihood of lymph node metastasis 3 and 5 times, respectively.

There is still no consensus in the literature, especially for early-stage (stage 1-2) patients, about whether such patients should receive adjuvant chemotherapy [28,29]. Studies are available showing that adjuvant chemo-therapy increases survival and decreases mortality in Stage 2 patients with high-risk factors [30,31]. According to the NCCN guidelines; poorly differentiated histology, LVI, bowel obstruction, resection of less than 12 lymph nodes, PNI, tumour or colon perforation, and close, vague, or positive surgical margins can be considered as high-risk factors for colon cancer. We think that the statistically significant relationship of the presence of LVI and PNI with the tumour grade, lymph node metastasis, and tumour invasion depth found in our study may effectively help identify high-risk patients and make treatment decisions, especially in stage-2 patients in whom the administration of adjuvant chemotherapy remains to be controversial. In our clinical practise, we recommend adjuvant chemotherapy especially in stage-2 patients, whose histological features are unfavourable and who have LVI and PNI.

As for the overall survival, Lim et. al showed that 5-year overall survival and 5-year

disease-free survival were statistically significantly reduced in patients with LVI [32]. In another study; the effect of LVI on survival could not be shown but PNI was found to reduce the overall survival significantly [20]. In our study; we found out that the presence of LVI and PNI statistically significantly reduced the one-year, three-year, and five-year survival (p<0.001, p=0,001).

Many molecular markers other than LVI and PNI have recently been investigated for prognostic value in colon cancers but the results are controversial [33,34]. Micro-satellite instability, allelic loss, tumour expression mechanisms, and molecular markers such as MLH, MSH, and PMS are insufficient to predict the prognosis and disease course. The use of such markers in clinical practise continues to be studied [35-37].

The retrospective study design, the absence of potential prognostic factors such as microsatellite instability and lympho-plasmacytic infiltration in the pathology report of some patients, and the lack of evaluation of clinical factors including comorbidities, operative times, the administration of perioperative transfusion, and postoperative complications are the limitations of this study.

In conclusion, several factors exist affecting prognosis in colorectal cancers. Because the presence of LVI and PNI is a determinant of prognosis and lymph node metastasis especially in early-stage patients; we think that close follow-up of patients with LVI and PNI and the evaluation of such patients by a multidisciplinary council for the administration of adjuvant therapy, may affect prognosis favourably.

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