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ORIGINAL ARTICLE – OPEN ACCESS

The Impact of Lymphovascular Invasion on Recurrence-Free Survival in Patients with High-Risk Stage II Colorectal Cancer Treated with Adjuvant Therapy

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ABSTRACT

Objective: Lymphovascular invasion (LVI) may affect disease recurrence after operation for colorectal cancer (CRC). Whether LVI is an exact prognostic variable remains uncertain. This research aimed to investigate the relationship between clinicopathologic factors, disease-free survival (DFS), and overall survival (OS) in patients with high-risk stage II colon cancer who underwent adjuvant treatments, focusing on LVI.

Materials and Methods: This study retrospectively investigated 173 patients who underwent operation for stage II tumors from September 2000 and December 2013. All patients received postoperative adjuvant therapy. The distinction among factors was calculated by a chi-square test. Survival probabilities were predicted with the Kaplan–Meier method, and group comparisons were applied with the log-rank test. Furthermore, univariate and multivariate cox regression analysis were used to determine the most substantial risk elements.

Results: LVI was identified in 26 of 173 patients (15%) and was significantly related with positive perineural invasion (PNI) ($p<0.001$). There were no considerable differences among LVI and other clinicopathologic factors. LVI-positive patients had significantly lower DFS than LVI negative patients, with a hazard ratio of 2.83 (95% CI 1.24–6.48). The five-year survival rate of the LVI-positive group was substantially lower than for those who were LVI negative ($p=0.004$).

Conclusion: In this research, LVI was a meaningful prognostic variable for DFS, but not for OS. This study revealed a prognostic value of LVI for DFS in patients with high-risk stage II tumor who underwent adjuvant treatments.

Keywords: Early-stage colon cancer, disease-free survival, lymphovascular invasion, chemotherapy

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INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent neoplasm worldwide, and its incidence has increased in recent years (1). The actual treatment for CRC is a curative resection of the primary cancer. After the primary treatment, adjuvant therapy generally is administered to patients to exterminate malignant cells that may have disseminated (2).

The five-year lifespan rate in patients with stage II malignant colorectal tumors who underwent curative surgery is between 75 and 80% (3). Despite its surrounding controversy, chemotherapy for stage II cancer is recommended for patients who have some clinicopathologic features including bowel obstruction and perforation, T4 tumor; low number of lymph nodes evaluated a high-grade tumor, positive lymphovascular invasion (LVI), or PVI, which has been linked to a high possibility of recurrence in patients with stage II CRC (4, 5). The importance of these clinicopathologic features has not been adequately assessed in high-risk early-stage CRC treated with adjuvant therapy. In this research, we intended to investigate the value of clinical determinants of recurrent survival in early-stage tumor in patients who underwent adjuvant therapy.

MATERIALS and METHODS

We retrospectively explored patients who had been diagnosed with primary CRC and had completed all phases of their primary treatment for the disease between September 2000 and December 2013. The research was approved by the Erciyes University Medical School ethics committee (No: 2018/593).

Demographics and clinicopathologic data, including age, sex, adjuvant chemotherapy, cancer location, vascular invasion, perineural invasion (PNI), primary tumor size, tumor differentiation, preoperative colonic obstruction/perforation, the total count of lymph nodes examined, and year of surgery were provided from chart reviews of patients with CRC from one oncology center in Turkey.

The inclusion requirements for this study were histologically approved CRC, undergone curative operation for stage II CRC,18 years of age or older, and had adjuvant treatment administered. Patients with lymph node metastases, neoad-

juvant chemoradiation for a locally advanced rectal tumor, distant metastases, or T1/T2 tumor were excluded from the cohort study.

Curative resection was considered in the case that no obvious residual cancer stayed in the operating bed, and the distal and proximal excision margins were negative in terms of tumor invasion. Two pathologists built pathologic examination on all radical colorectal excision material. After the last pathologic analysis, CRC was staged in accordance with the American Joint Committee on Cancer (AJCC). Excision samples were appraised for lymph node involvement, depth of tumor attack, LVI, PNI, and histological type. Follow-up evaluations comprised carcinoembryonic antigen (CEA) assay, physical examination and history, routine blood tests, and visualization every three months for the first two years, every six months from the third to the fifth year, and annually thereafter. When the patient had symptoms associated with carcinoma relapse, further imaging assessments were performed. The locations and number of cases of relapse were detected according to scanning results of the disease with positron emission tomography and computerized tomography (PET/CT), ultrasound, colonoscopy, and CT. Tumor relapse was described as radiographic proof; doubtful scanning results were followed by a biopsy of the suspected lesion and graded as a disease relapse after pathological approval.

Two different chemotherapeutic protocols were applied: (a) 5-fluorouracil (5-FU) and calcium folinate (six cycles of monthly bolus intravenous calcium folinate 20 mg/ m^2/day, days 1–5 and 5-FU 400–425 mg/ m^2/day, days 1–5); and (b) capecitabine regimen: orally at a dosage of 1000 mg/m^2 twice daily on days 1–14 of a three-week period. Adjuvant radiotherapy comprise 45–50. 4 Gy in 25–28 fractions performed on the pelvis, using a four-field box method.

Statistical Analysis

The Shapiro–Wilk test was used; and histograms and q-q plots were plotted to detect the datum normality. Fisher exact test or Pearson chi-square test was performed for factors. Frequencies and percentages were used for categorical variables. Survival probabilities were predicted with the Kaplan–Meier method, and group comparisons were applied with the log-rank test. Furthermore, univariate and multivariate cox regression analysis were used to determine the most substantial risk elements. The cumulative sum of the Schoenfeld residuals was used to assess proportional hazards assumption. Significant variables at $p<0.25$ on univariate analysis were taken into multiple model, and forward stepwise selection was performed usage likelihood ratio statistic at $p<0.10$ stringency level. Hazard ratios were also given with 95% confidence intervals. The calibration of the model was identified using the Hosmer–Lemeshow goodness-of-fit test. The TURCOSA (Turcosa Analytics Ltd. Co., Turkey, https://turcosa.com.tr/) statistical software was used for statistical analysis. A p value less than 5% was considered as statistically significant.

RESULTS

LVI was identified in 26 of the 173 patients (15%) and was significantly related with PNI ($p<0.001$). However, there were no meaningful distinctions in terms of preoperative colonic obstruction or perforation, count of lymph nodes retrieved, age, gender, differentiation, location, and preoperative serum CEA level (Table 1).

Table 1. Comparison between LVI and the clinicopathologic variables of patients with stage II colorectal cancer

Characteristic	LVI (-) (n=147)		LVI (+) (n=26)		p
	n	%	n	%	
Age					
60 years≥	49	66.7	12	46.2	0.206
60 years<	98	33.3	14	53.8	
Sex					
Male	75	51	16	61.5	0.396
Female	72	49	10	38.5	
Tumor location					
Colon	112	76.2	17	65.4	0.327
Rectum	35	23.8	9	34.6	
Nuclear grade					
Well	52	35.4	13	50	
Moderate	68	46.3	13	50	0.100
Poor	16	10.9	0	0	
Not available	11	7.5	0	0	
No. of lymph nodes retrieved					
<12	69	46.9	13	50	0.833
≥12	78	53.1	13	50	
Perineural invasion					
Yes	132	89.8	13	50	<0.001
No	15	10.2	13	50	
Depth of tumor invasion					
pT3	51	34.7	14	53.8	0.063
pT4	96	65.3	12	46.2	
Perforation					
Yes	8	5.4	3	11.5	0.217
No	139	94.6	23	88.5	
Obstruction					
Yes	33	22.4	5	19.2	0.803
No	114	77.6	21	80.8	
Preoperative CEA, ng/mL					
<5	82	55.8	15	57.7	
≥5	9	6.1	0	0	0.426
Not available	56	38.1	11	42.3	

LVI: Lymphovascular invasion; CEA: Carcinoembryonic antigen

The global test or the Schoenfeld residuals resulted as $\chi^2=1.81$, $p=0.875$. Based on this result, it can be stated that the proportional hazard assumption is met. None of the univariate results were significant to predict the OS, while only LVI was found to be significant (OR=2.83(95% CI 1.24–6.48), $p<0.05$) to predict the DFS of patients (Table 2). Thus, a multiple model was created to estimate the DFS by using only the LVI variable. The Hosmer–Lemeshow test resulted as $\chi^2=10.31$, $p=0.066$. This result

Table 2. Univariate cox regression analysis of variables for OS and DFS

Variables	OS HR (95% CI)	DFS HR (95% CI)
Age, years (60≥, 60<)	1.11 (0.38–3.27)	2.00 (0.94–4.27)
Gender (Male/Female)	1.69 (0.60–4.76)	0.92 (0.43–1.97)
Location (Colon/Rectum)	1.69 (0.57–4.94)	2.31 (0.93–4.45)
No. of lymph nodes retrieved (<12, ≥12)	1.17 (0.41–3.38)	0.53 (0.24–1.19)
Depth of tumor invasion (pT3/ pT4)	1.55 (0.49–4.87)	0.54 (0.25–1.15)
Perineural invasion (Yes)	0.91 (0.20–4.06)	0.95 (0.33–2.75)
Perforation (Yes)	1.23 (0.16–9.52)	1.18 (0.28–5.02)
Obstruction (Yes)	0.27 (0.03–2.10)	0.44 (0.13–1.46)
LVI (Yes)	1.83 (0.51–6.50)	2.83 (1.24–6.48)*

*Only variable remained in the multiple model. CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; DFS: Disease-free survival

revealed the appropriateness of the built multiple Cox regression model to predict the DFS of the patients. The five-year survival rate of LVI-positive patients was significantly lower than of those who were LVI negative (p=0.004) (Fig. 1).

DISCUSSION

We analyzed the data of 173 patients with stage II CRC who underwent adjuvant chemotherapy and displayed a five-year recurrence rate of 14.5%. A large part of relapse was revealed after the first two years of operation.

In some studies, different clinicopathologic features, such as T4 tumor, low count lymph node evaluation, high-grade tumor, male gender, bowel obstruction, presence of LVI or PNI, and high preoperative CEA, have been linked to a high possibility of death and recurrence (6–17).

We detected the frequency of vascular invasion to be 15%, which is within the interval detected by previous studies (16, 18). Invasion by malignant cells, including into the venous and lymphatic pathways, may show that malignant cells have spread throughout the body, and may be used as a prognostic tool for recurrence prediction (11). Tsai et al. found that LVI was a substantial prognostic tool for survival and recurrence (11). However, another study advised that vascular invasion is not a substantial prognostic tool in patients with stage II CRC (19). In contrast, a retrospective study asserted that vascular invasion might be handy in determining which patients with stage II CRC might benefit from adjuvant therapy (20). Despite all patients having received adjuvant treatment, our result demonstrated that vascular invasion was a prognostic factor of the DFS rate. These results were contrary to some studies, which show that differences may be due to the different number of patients, the retrospective state of the analysis performed, and differential features of patients between studies. Additionally, these consequences can be clarified by the fact that these patient groups may have different molecular changes, such as allelic loss of chromosome 18q, microsatellite instability, and secretion of thymidylate synthase by tumor.

Several studies have indicated that patients with few total lymph nodes retrieved during surgery received a poorer prognosis than those who had high amount of total nodes examined (12, 21).

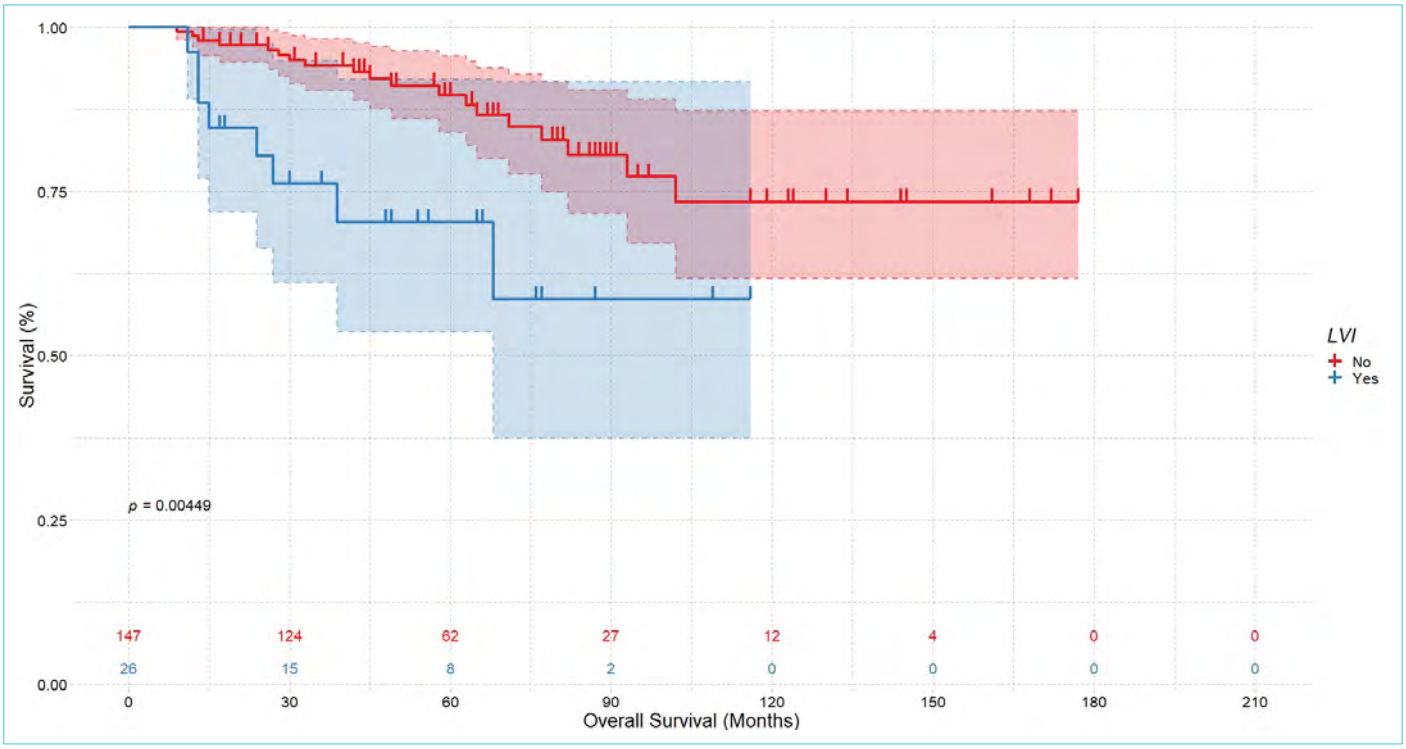

Figure 1. Kaplan–Meier curves of survival based on lymphovascular invasion status. The survival rate of LVI-positive patients was significantly lower than of those who were LVI negative

Removing more lymph nodes can ensure better staging or apronounced host immunologic reaction (7, 22, 23). The AJCC has proposed an evaluation of 12 or more lymph nodes for exact staging (24). Our study found that recovering more lymph nodes was not related to higher rates of DFS and overall survival (OS) in patients with stage II CRC who underwent adjuvant chemotherapy.

The identified frequency of PNI ranges from 9% to 30% in patients with stage II tumor. Nevertheless, its prognostic importance is still uncertain (6, 7, 11, 14). This study found PNI in 16.2% of patients, which was not significant for DFS and OS in patients with stage II colon cancer who received adjuvant therapy.

A few reports demonstrated that the depth of cancer penetration was a vital prognostic tool for survival and recurrence in patients with CRC after curative operation (11, 25). In our report, the depth of invasion was not meaningful for DFS and OS in this group of patients.

Important researches have examined the subject of adjuvant therapy for patients with early-stage colorectal tumor. A pooled analysis of adjuvant chemotherapy studies compared adjuvant chemotherapy to surgery only for patients with stage II resected colon tumors. It detected a 17% reduction in the relative risk of disease relapse in this group, though 1% improvement was detected in overall lifespan, which was not statistically significant (26).

Clinical trials show that patients who receive adjuvant chemotherapy have an absolute improvement in the five-year survival rate of 2%–4%. With respect to substantial guidelines, certain pathologic and clinical prognostic elements, including intestinal perforation, obstruction, fewer than 12 nodes analyzed, T4 tumor, poor differentiation, LVI, and PNI can detect the smaller number of patients with stage II of the disease who have an elevated risk for recurrence and who could benefit from adjuvant therapy. In this study, these factors, excluding LVI, were not significant for DFS in high-risk patients with CRC. This status can be explained by means of the treatment of all patients with adjuvant therapy.

A restriction of this study is that the sample was relatively minor, which restricts the interpretation of the results. The chemotherapeutic regimens were not homogeneous. This study did not contain any molecular markers of the neoplasms, including microsatellite instability status, which is an encouraging molecular tool with both predictive and prognostic importance for chemosensitivity. Lastly, the median follow-up duration for this study was 49 months, and recurrences may occur in some patients after this time.

In conclusion, findings of the study detected that LVI was the solely prognostic tool for DFS, and not for OS, in patients with high-risk stage II malignant neoplasm who underwent adjuvant therapy. With knowledge of colon cancer, biology has detected probable molecular tools to risk-stratify patients with early-stage colon cancer. An evaluation of both molecular markers and pathological factors can lead to a more accurate determination of high-risk patients who may benefit from adjuvant chemotherapy. Nevertheless, these findings need to be proved by the means of larger prospective clinical trials.

Ethics Committee Approval: The research was approved by the Erciyes University Medical School ethics committee (No: 2018/593).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Designed the study: OB. Collected the data: STF, ED, MI. Analyzed the data: GEZ. Wrote the paper: OB, KD, MO. All authors have read and approved the final manuscript.

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