Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Recurrence-Free Survival Outcomes Based on Novel Classification Combining Lymphovascular Invasion, Perineural Invasion, and T4 Status in Stage II–III Colon Cancer

Jae Hyun Kang[1], Il Tae Son[2], Byung Chun Kim[3], Jun Ho Park[4], Jeong Yeon Kim[1], Jong Wan Kim[1]

[1]Department of Surgery, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong-si, Gyeonggi, 445-170, Republic of Korea; [2]Department of Surgery, Hallym Sacred Heart Hospital, Hallym University College of Medicine, Anyang, 445-907, Republic of Korea; [3]Department of Surgery, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, 150-950, Republic of Korea; [4]Department of Surgery, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, 134-701, Republic of Korea

Correspondence: Jong Wan Kim, Department of Surgery, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 40, Sukwoo-Dong, Hwaseong-Si, Gyeonggi-Do, 445-170, Republic of Korea, Tel +82 31-8086-2430, Fax +82 31-8086-2709, Email kjw0153@hanmail.net

Background: T4 tumor, lymphovascular invasion (LVI) and perineural invasion (PNI) are regarded as one of risk factors and associated with poor outcomes in colorectal cancer. The relationship between these three combined risk factors and the prognosis for colon cancer is not yet clear. The purpose of this study was to evaluate the prognostic value of combining the risk factors T4 tumor, LVI, and PNI in stage II–III colon cancer.

Methods: Between January 2011 and December 2019, we retrospectively reviewed the medical records of patients who underwent curative resection for stage II–III colon cancer at four Hallym University-affiliated hospitals. These patients are categorized into three groups based on T4, LVI and PNI: no-risk group (no risk factors), low-risk group (one risk factor), and high-risk group (two or more risk factors).

Results: Of 1684 patients, the incidence of no-, low-, and high-risk group were 49.3%, 32.6%, 18.0%, respectively. The median follow-up period was 48.9 months, and the 5-year recurrence-free survival (RFS) rate decreased from 78.5% to 58.7% as the number of risk factors increased ($P < 0.001$). Cox's proportional hazard regression models showed that T4 ($P < 0.001$), LVI ($P = 0.043$), and PNI ($P = 0.018$) were independent prognostic factors for poor RFS. In subgroup analysis in stage II colon cancer, patients with one or more risk factors showed the better 5-year RFS rate when they received adjuvant chemotherapy than in those who did not ($P < 0.001$). Poor/mucinous differentiation, obstruction, and lymph-node positivity were independent predictors in the high risk group.

Conclusion: The present study showed the histological combination of LVI, PNI, and T4 indicates a poor prognosis for RFS in patients with stage II–III colon cancer. Therefore, patients with one of these risk factors should be considered for chemotherapy and have close follow-up.

Keywords: colon cancer, T4 tumor, lymphovascular invasion, perineural invasion

Introduction

Colon cancer is one of the most common cancers and the fifth leading cause of cancer-related mortality.[1] The extent of the disease is important in the treatment and prognosis of colorectal cancer (CRC), and is based on the American Joint Committee on Cancer (AJCC) staging. This classification includes several histopathological features, such as the depth of tumor invasion (T), lymph-node metastasis (N), and the presence of metastatic disease (M).[2] However, the TNM classification is insufficient to predict the prognosis of colorectal cancer because patients with the same TNM stage may experience different survival and recurrence.[3,4]

Several risk factors for a poor prognosis have been defined: T4 tumor, perforation, obstruction, high-grade tumor, lymphovascular invasion (LVI) or perineural invasion (PNI), positive resection margin, and fewer than 12 lymph nodes

Received: 18 January 2022
Accepted: 21 May 2022
Published: 20 June 2022

examined.[5–9] Several international guidelines, including those of the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network, and the European Society for Medical Oncology, recommend adjuvant chemotherapy for stage II patients with these risk factors.[5,8,9] However, there is no conclusive evidence supporting the effectiveness of adjuvant chemotherapy in this patient group. Moreover, several conflicting results have been reported about the benefits of adjuvant chemotherapy, even among high-risk patients.[10,11]

In recent years, several studies have reported the prognostic value of some risk factors in various stages of CRC when they are combined.[6,12–17] Huh et al categorized patients with stage II/III CRC into four groups based on their LVI and PNI status. The authors concluded that LVI+/PNI+ patients had the lowest overall survival (OS) ($P < 0.001$) and disease-free survival (DFS) ($P < 0.001$) compared with the other three groups (LVI−/PNI−, LVI+/PNI−, and LVI−/PNI+).[16] Kim et al divided patients with stage I CRC into two groups (risk vs no risk) depending on the presence of risk factors, such as LVI, PNI, or tumor budding. They showed a worse 5-year DFS rate in the risk group than in the no-risk group ($P = 0.025$).[12] Although previous studies have combined and analyzed different risk factors in several stages of CRC for different endpoints, they have consistently shown the significant effects of these risk features on the oncological outcomes. However, few studies have evaluated the prognosis of stage II–III colon cancer by combining LVI, PNI, and T4.

The purpose of this study was to evaluate the prognostic value of combining the risk factors T4 tumor, LVI, and PNI in assessing patients with stage II–III colon cancer. We also performed a subgroup analysis of patients with stage II colon cancer to assess the potential survival benefit of adjuvant chemotherapy in the presence of these risk factors.

Methods

We retrospectively reviewed the medical records of patients who had undergone curative resection for stage II–III colon cancer at four Hallym University-affiliated hospitals (Kangnam Sacred Heart Hospital, Kangdong Sacred Heart Hospital, Hallym Sacred Heart Hospital, and Dongtan Sacred Heart Hospital) between January 2011 and December 2019. The study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB 2021–09-005). Because the study was a retrospective cohort study, the data were anonymous and informed consent was not required. Patients with recurrent disease, stage IV cancer, familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or incomplete records of LVI and PNI were excluded from the study. Patients who had undergone palliative surgery, including stoma construction or bypass surgery, or who had only undergone local resection were also excluded.

LVI was defined by the presence of tumor cells or tumor cell thrombi within the endothelium-lined space or the destruction of a lymphovascular wall by tumor cells.[18] PNI was defined as the presence of tumor cells within the perineural space or the infiltration of tumor cells into the endoneurium.[19] The tumor stage was defined according to the 8th edition of the AJCC TNM staging system.[20] Based on a pathological examination, postoperative adjuvant chemotherapy was considered for patients with stage II and III disease. The chemotherapy regimen was determined at a multidisciplinary team conference that considered the patient's health status and compliance and the physician's preference. Four anticancer drug regimens were predominantly used: (1) 5-fluorouracil (FU) and leucovorin (FL; 6 cycles of monthly bolus intravenous 5-FU 400–425 mg/m^2/d, days 1 to 5 and leucovorin 20 mg/m^2/d, days 1 to 5; (2) oxaliplatin + 5-FU + leucovorin (FOLFOX; 12 cycles of oxaliplatin 85 mg/m^2 on day 1 and leucovorin 200 mg/m^2 as a 2 h infusion on day 1, 5-FU 400 mg/m^2 as a bolus, and 600 mg/m^2 22 h infusion on days 1 and 2 bimonthly; (3) irinotecan + 5-FU + leucovorin (FOLFIRI; 12 cycles of irinotecan 180 mg/m^2 on day 1 and leucovorin 400 mg/m^2 as a 2 h infusion on day 1, 5-FU 400 mg/m^2 as a bolus, and a 600 mg/m^2 22 h infusion on days 1 and 2 bimonthly); (4) capecitabine (8 cycles of 1250 mg/m^2 twice daily for 14 days, followed by 7 days rest at the conclusion of each cycle). Adjuvant chemotherapy was started within 4–6 weeks of surgery and administered for about 6 months.

The patients were categorized into three groups according to their risk factors, including T4 tumor, LVI and PNI: no-risk group (no risk factors), low-risk group (one risk factor), and high-risk group (two or more risk factors). In the subgroup analysis of patients with stage II colon cancer, the patients were divided into two groups based on the presence of risk factors: no-risk group (no risk factors) and risk group (one or more risk factors).

The patients were followed-up with physical examinations and measurements of serum carcinoembryonic antigen and cancer antigen 19–9 concentrations every 3–6 months for the first 2 years, and every 6 months thereafter until 5 years.

Chest and abdominopelvic computed tomography scans were repeated every 6 months until 5 years. Colonoscopy was performed after 1 year and then biennially during the follow-up period. The long-term oncological outcomes were evaluated in terms of recurrence-free survival (RFS), defined as the time between cancer-related surgery and disease recurrence or death from any cause.

The primary endpoint was the RFS rate at 5 years after surgery according to the risk group in patients with stage II–III colon cancer. The secondary endpoint was the potential benefit of adjuvant chemotherapy in patients with stage II colon cancer based on the presence of risk factors.

Statistical Analysis

Categorical variables were analyzed with a χ^2 test, and are presented as numbers and percentages of patients. Continuous variables were analyzed with one-way analysis of variance and least significant difference multiple comparisons, and are presented as means and stand deviations. Logistic regression models were used to evaluate the independent predictors of RFS in the high-risk group. The confounding factors selected for the multivariable analysis were those previously reported to have an association with high-risk patients.[12,13,16] RFS was calculated with the Kaplan–Meier method and compared with the Log rank test. Cox's proportional hazards regression models were used to identify the prognostic factors for RFS. These factors included age (≥70 years), sex (male), American Society of Anesthesiologists physical status score (ASA; ≥3), number of comorbidities (≥3), histological grade (poor/undifferentiated), obstruction, T stage (T4), presence of lymph-node metastasis, LVI, and PNI.

All statistical analyses were performed with SPSS version 26.0 (SPSS Inc., Chicago, IL). P values of <0.05 were considered statistically significant.

Results

During the study period, a total of 1890 patients underwent surgery for colon cancer. We excluded 12 patients with FAP and HNPCC, 30 patients with stage 0 disease, 437 patients with stage I disease, 123 patients with stage IV disease, 21 patients with incomplete records of LVI and PNI, and 20 patients with recurrence. After excluding these 643 patients, 1247 patients were included in the study. The clinicopathological characteristics of the patients are summarized in Table 1. The patients included 703 men (56.4%) and 544 women (43.6%), with a median age of 67.3 years (range, 26–89 years).

Of these patients, 612 (49.0%) and 635 (50.9%) had stage II and III disease, respectively. The cohorts were 192 (15.4%) patients with T4 disease, 551 (44.1%) patients who were LVI positive, and 319 (25.0%) patients who were PNI positive. Of the 1247 patients enrolled, 771 (61.9%) received postoperative adjuvant chemotherapy. The proportion of patients receiving chemotherapy was higher in the stage IIII group than in the stage II group (76.8% vs 46.6%, respectively, P < 0.001). Of the four anticancer regimens, the most commonly used was FOLFOX (60.3%), followed by FL (22.3%), capecitabine (8.2%), and FOLFIRI (5.3%).

Using the risk grouping criteria, 470 (37.7%), 485 (38.9%), and 292 (23.4%) patients were referred to the no-, low-, and high-risk groups, respectively. The risk factors sex, ASA ≥ 3, TNM stage, T stage, N stage, histologic grade, and number of harvested lymph nodes ≥ 12 differed significantly among the three groups (Table 2). The proportion of patients receiving chemotherapy was greatest in the high-risk group (high-risk: 71.1%; low-risk: 69.2%, no risk: 48.7%, P < 0.001).

Over a median follow-up period of 48.9 months (range, 2–108 months), the 5-year RFS rate worsened as the number of independent prognostic factors increased (no-risk group, 78.5%; low-risk group, 65.5%; high-risk group, 58.7%; P < 0.001; Figure 1A). When the risk groups were divided according to pathological stages II and III, the 5-year RFS of the high-risk group was still significantly lower than those of the other groups (Figure 1B, stage II: no-risk group, 82.5%; low-risk group, 76.2%; high-risk group, 55.5%; P < 0.001) (Figure 1C; stage III: no-risk group, 76.0%; low-risk group, 59.9%; high-risk group, 57.0%; P < 0.001).

We evaluated the risk factors for RFS in patients with stage II–III colon cancer (Table 3). Cox's proportional hazards regression models showed that age ≥ 70 years ($P < 0.001$), ASA ≥ 3 (P < 0.001), T4 ($P < 0.001$), LVI (P = 0.043), PNI (P = 0.018), obstruction (P = 0.035), and lymph-node metastasis (P < 0.001) were independent prognostic factors for poor RFS.

Table 1 Patient Characteristics (n = 1247)

	No (%)
Age (years)	67.3 (26–89)
Gender	
Male	703 (56.4)
Female	544 (43.6)
CEA	13.0 (42.0)
ASA	
I	122 (9.8)
II	715 (57.3)
III	377 (30.2)
IV/V	33 (2.7)
Comorbidities	807 (64.7)
Location of tumor	
Right colon	586 (46.9)
Left colon	661 (53.0)
TNM stage	
II	612 (49.0)
III	635 (50.9)
Histologic grade	
Well	280 (22.5)
Moderate	878 (70.4)
Poor/undifferentiated	89 (7.1)
Obstruction	306 (24.5)
T4	192 (15.4)
LVI	551 (44.1)
PNI	319 (25.0)
Adjuvant chemotherapy	771 (61.9)
5FU-LV	172 (22.3)
FOLFOX	463 (60.3)
FORFIRI	41 (5.3)
Capecitabine	76 (8.2)
Others	19 (1.5)

Note: Data are presented as the number of patients (%) or median (range) unless otherwise stated.
Abbreviations: No, number; CEA, Carcinoembryonic Antigen; ASA, American Society of Anesthesiologists; LVI, Lymphovascular invasion; PNI, Perineural invasion.

We performed a subgroup analysis to evaluate the effect of adjuvant chemotherapy on the prognosis of stage II colon cancer in the presence of risk factors (Figure 2). The 5-year RFS was similar in the stage II group and the stage II with no risk factors group, regardless of the administration of adjuvant chemotherapy (Figure 2A: stage II: 75% (chemotherapy (-)) vs 79.4% (chemotherapy (+)); P = 0.338; Figure 2B; stage II with no risk: 80.5% (chemotherapy (-)) vs 86.3% (chemotherapy (+)); P = 0.232). However, in the risk group, the 5-year RFS rate was significantly better in patients who received adjuvant chemotherapy (75.2%) than in those who did not (59.5%) (P < 0.001; Figure 2C).

Given the significant effects of T4, LVI, and PNI on RFS, we used univariable and multivariable analyses to identify the factors associated with the high risk group (Table 4). In the univariable analysis, poor/undifferentiated (P = 0.041), obstruction (P = 0.003), and lymph-node positivity (P < 0.001) were independent predictors of the risk group (Table 4). In the multivariable analysis, poor/undifferentiated (P = 0.044), obstruction (P = 0.004), and lymph-node positivity (P < 0.001) were significantly associated with the risk group (Table 4).

Table 2 Comparison of Clinicopathologic Features According to the Risk Grouping

	No Risk (n = 470)	Low Risk (n = 485)	High Risk (n = 292)	*P*
Age ≧ 70 (years)	222 (47.2)	220 (45.4)	114 (39.0)	0.034
Male	192 (40.9)	209 (43.1)	143 (49.0)	0.033
ASA ≧ 3	192 (36.2)	168 (34.1)	50 (22.3)	0.003
Comorbidities ≧ 3	62 (13.2)	51 (10.5)	21 (7.2)	0.009
TNM stage				< 0.001
II	366 (68.9)	193 (39.2)	53 (23.7)	
III	165 (31.1)	299 (60.8)	171 (76.3)	
T stage				< 0.001
1	15 (2.8)	11 (2.3)	1 (0.3)	
2	13 (2.4)	24 (4.9)	5 (1.7)	
3	442 (83.2)	389 (80.2)	155 (53.1)	
4	0 (0)	61 (12.6)	131 (44.9)	
N stage				< 0.001
0	322 (68.5)	219 (45.2)	66 (22.6)	
1	126 (26.8)	177 (36.5)	108 (37.0)	
2/3	22 (4.7)	88 (18.1)	118 (40.4)	
Histologic grade				0.037
Well/Moderate	442 (94.2)	453 (93.4)	263 (90.1)	
Poor/Undifferentiated	27 (5.8)	32 (6.6)	29 (9.9)	
No of harvested LN ≧ 12	442 (94.0)	461 (95.4)	286 (97.9)	0.013
Adjuvant chemotherapy	229 (48.7)	335 (69.2)	207 (71.1)	< 0.001

Note: Data are presented as the number of patients (%).
Abbreviations: ASA, American Society of Anesthesiologists; No, number; LN, Lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion.

Discussion

We analyzed the prognostic impact of a grading system combining LVI, PNI, and T4 tumor status. RFS was lower in the high-risk group of patients with stage II–III colon cancer than in the no- and low-risk groups, and the result was the same when the patients were divided into stage II and III. In a subgroup analysis, adjuvant chemotherapy improved the RFS of patients with stage II disease and at least one risk factor.

In the present study, the rate of LVI was 44.1%, which is similar to the rates (12.4–50%) reported in previous studies.[13,16,18,21,22] Although Artac et al suggested that LVI is not an independent risk factor for DFS in patients with stage II colon cancer,[7] several studies have shown that LVI is an unfavorable prognostic factor for survival in patients with CRC.[18,21] In a recent systematic review, LVI was significantly associated with a poor prognosis in terms of overall survival (OS; hazard ratio [HR], 2.15; 95% confidence interval [CI], 1.72–2.68; $P < 0.01$) and DFS (HR, 1.73; 95% CI, 1.50–1.99; $P < 0.01$).[23] Although 12 lymph nodes or more must be harvested to accurately assess the status of lymph-node metastasis, it is not always possible to access this number of nodes in all colorectal surgery. Because LVI is related to the degree of lymph-node metastasis and staging,[18,21] it could be used as a supplementary factor to optimize the accuracy of staging.

The rate of PNI was 25.0% in the present study, which is consistent with the rates of 14.8–30.9% in previous studies.[16,22,24,25] Although the mechanisms by which PNI is associated with tumor progression through the nerves are poorly understood, Jobling et al suggested that the infiltration of nerve fibers stimulates cancer cell growth and dissemination by releasing neurotransmitters, and that cancer cells also secrete neurotrophic factors that promote the outgrowth of nerves in solid tumors.[26] These mechanisms could explain why PNI is an unfavorable prognostic factor in CRC patients. Liebig et al reported that the 5-year OS and DFS were much higher in patients with PNI-negative tumors than in patients with PNI-positive tumors (OS: 72% vs 25%, respectively; $P < 0.001$; DFS: 65% vs 16%, respectively; $P < 0.001$). In a subgroup analysis, stage II PNI-positive patients had a poorer DFS than stage III patients (29% vs 56%, respectively, $P = 0.002$).[24]

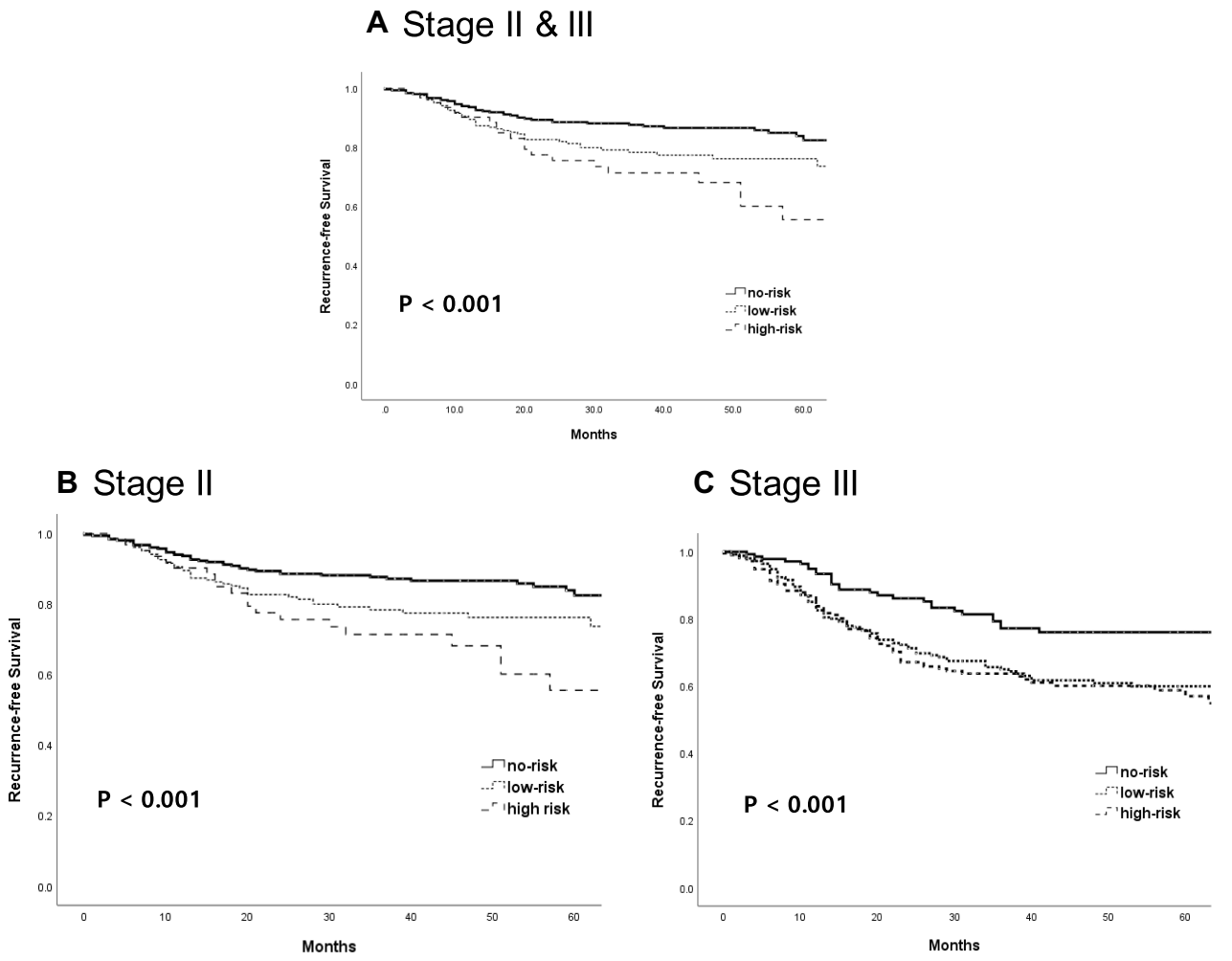

Figure 1 Comparison of 5-year recurrence-free survival according to the risk grouping and TNM stage in patients with stage II–III (**A**) no-risk group, 78.5%; low-risk group, 65.5%; high-risk group, 58.7%, P < 0.001), in patients with stage II (**B**) no-risk group, 82.54%; low-risk group, 76.2%; high-risk group, 55.5%; P < 0.001), in patients with stage III (**C**) no-risk group, 76.0%; low-risk group, 59.9%; high-risk group, 57.0%; P < 0.001).

As a tumor gradually grows, the extent and depth of its invasion increase, causing obstruction and ultimately perforation. Zhou et al reported that as a tumor invades more deeply to stages T3 and T4, PNI lesions are distributed in the submucosa, muscular propria, and subserosa (rs = 0.410, P < 0.001).[15] A review of the National Cancer Database of colon cancer revealed that as the pathological T stage increased, the incidence of LVI positivity and PNI positivity increased.[14] These results indicate that a more deeply invasive tumor is associated with a more aggressive tumor. Therefore, in this study we combined the depth of the tumor (T4) with other risk factors, such as LVI and PNI, in our analysis.

Previous studies have stratified several risk factors for CRC and analyzed the prognostic value of this classification.[12–16,22] Moreover, several studies have combined T4, LVI, and PNI in their analyses and estimated the effects of the combinations on survival outcomes.[6,17] Those studies showed that only T4 tumors or combinations involving T4 tumors and other risk factors (T4 & <12 lymph nodes, T4 & poorly/undifferentiated tumor, T4 & LVI, T4 & obstruction) predicted a survival benefit from adjuvant therapy. Unlike previous studies that only evaluated T4 tumors among several factors, the present study shows that LVI (HR 1.123, P = 0.043), PNI (HR 1.363, P = 0.018), and T4 tumor (HR 1.770, P < 0.001) are all associated with poor RFS in patients with colon cancer. The 5-year RFS rate also decreased significantly from the no-risk group (78.5%) to the high-risk group (58.7%; P < 0.001). These results were similar when we divided the patients into stage II (no-risk group, 82.5%; low-risk group, 76.2%; high-risk group, 55.5%; P < 0.001) and stage III (no-risk group, 76.0%; low-risk group, 59.9%; high-risk group, 57.0%; P < 0.001) groups. Previous studies have been limited to patients with stage II colon cancer, whereas the present study included both stages II and III.

Table 3 Univariate and Multivariate Analysis of Recurrence-Free Survival

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ≧ 70 (years)	1.675 (1.336–2.101)	<0.001	1.592 (1.237–2.049)	< 0.001
Male	1.179 (0.940–1.478)	0.155	1.025 (0.811–1.296)	0.833
ASA ≧ 3	1.751 (1.393–2.203)	<0.001	1.627 (1.264–2.095)	< 0.001
Comorbidities ≧ 3	1.212 (0.848–1.731)	0.292	1.034 (0.710–1.505)	0.863
Poor/Undifferentiated	1.390 (0.942–2.051)	0.097	1.135 (0.762–1.693)	0.533
T4	2.061 (1.579–2.689)	<0.001	1.770 (1.339–2.340)	< 0.001
LVI	1.648 (1.308–2.076)	<0.001	1.123 (1.013–1.578)	0.043
PNI	1.664 (1.309–2.114)	<0.001	1.363 (1.055–1.760)	0.018
Obstruction	1.501 (1.173–1.922)	0.001	1.312 (1.019–1.689)	0.035
LN metastasis	1.879 (1.484–2.381)	<0.001	1.683 (1.304–2.171)	< 0.001

Abbreviations: OR, Odd Ratio; CI, Confidence interval; ASA, American Society of Anesthesiologists; LVI, Lymphovascular invasion; PNI, Perineural invasion; LN, lymph node.

There have been several conflicting reports of the benefits of adjuvant chemotherapy, even among patients with one more risk factors in stage II colon cancer. Yun et al reported that chemotherapy improved the survival of patients with T3N0M0 colon cancer without known risk factors (5-year OS: 85.4% in the surgery-only group vs 94.2% in

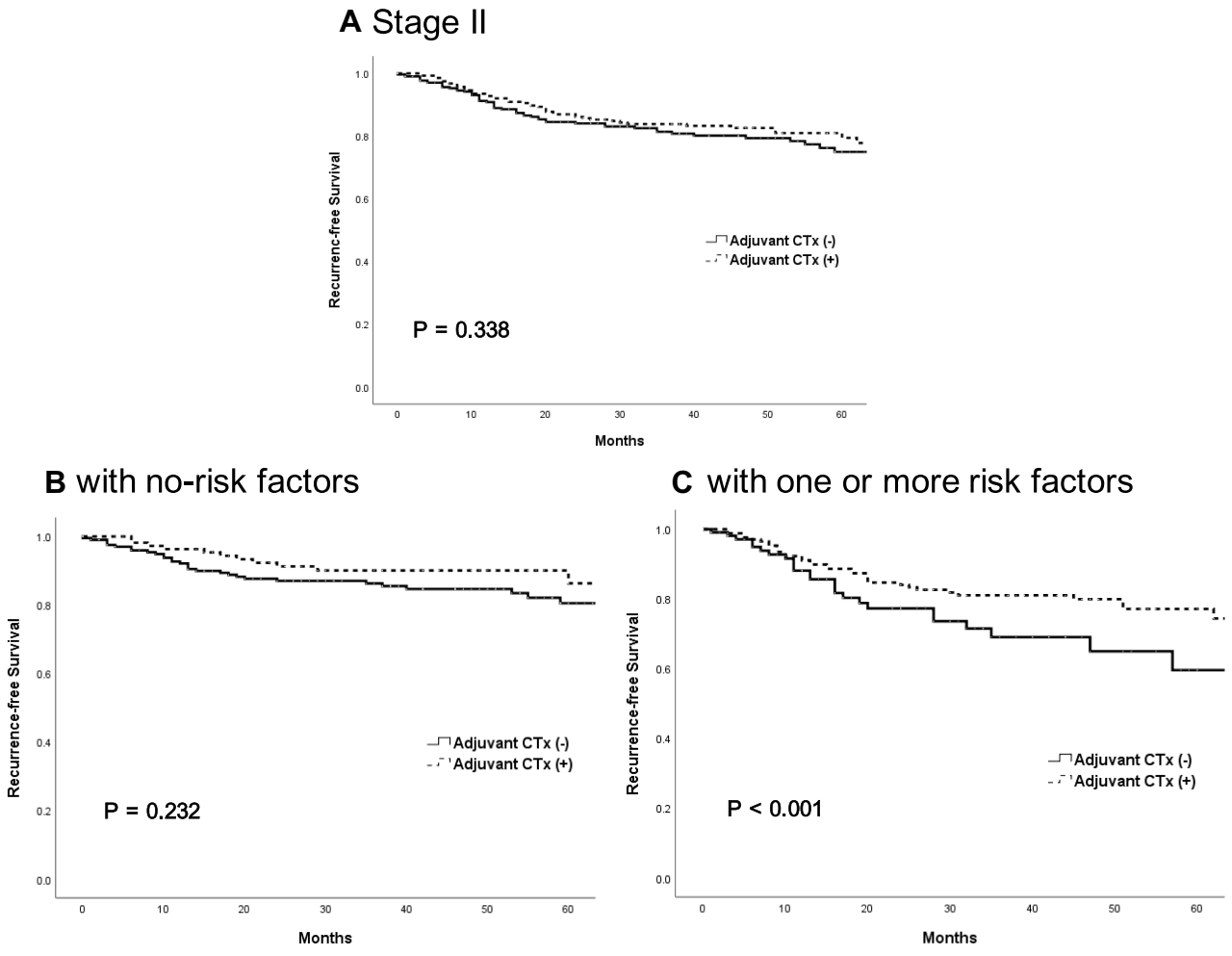

Figure 2 Comparison of 5-year recurrence-free survival in patients with stage II according to the presence of risk factors and chemotherapy (**A**) stage II: 75% (chemotherapy (-)) vs 79.4% (chemotherapy (+)); P = 0.338), (**B**) stage II with no risk factor: 80.5% (chemotherapy (-)) vs 86.3% (chemotherapy (+)); P = 0.232), (**C**) stage II with one or more risk factors; 59.5% chemotherapy (-) vs 75.2% (chemotherapy (+)); P < 0.001).

Table 4 Univariate and Multivariate Analysis of Predicting Factor for the High Risk Group

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ≧ 70 (years)	0.607 (0.355–1.037)	0.065	0.671 (0.384–1.171)	0.160
Male	0.968 (0.580–1.615)	0.900	0.956 (0.559–1.634)	0.868
Poor/Undifferentiated	2.329 (1.109–4.890)	0.041	2.197 (1.022–4.726)	0.044
Obstruction	2.269 (1.350–3.813)	0.003	2.182 (1.287–3.699)	0.004
Presence of LN (+)	3.879 (2.085–7.216)	<0.001	3.729 (1.995–6.970)	< 0.001

Abbreviations: OR, Odd Ratio; CI, Confidence interval; LN, lymph node.

surgery and chemotherapy group, P = 0.029).[27] A Surveillance, Epidemiology, and End Results (SEER)–Medicare database study reported that adjuvant chemotherapy conferred no survival benefit in patients with stage II colon cancer and poor prognostic features, with either right-sided cancer (HR, 0.97; 95% CI, 0.87–1.09; P = 0.64) or left-sided cancer (HR 0.97, 95% CI 0.84–1.12, P = 0.68).[10] However, the ASCO guideline recommends that adjuvant chemotherapy be considered in stage II patients with risk factors, including T4 tumor, perforation, poor differentiation, or inadequate harvested lymph nodes.[5] In a California Cancer Registry-based study of 5160 patients with stage II colon cancer, the authors reported that the greatest survival benefit conferred by adjuvant chemotherapy was in patients with T4 tumors or when T4 tumors were combined with other high-risk features, such as <12 lymph nodes, high tumor grade, or LVI.[17] Kumar et al reported that adjuvant chemotherapy use among high-risk patients improved OS (HR, 0.65; P = 0.001), RFS (HR, 0.76; P = 0.05), and disease-specific survival (DSS; HR, 0.73; P = 0.05), whereas chemotherapy use in low-risk patients reduced RFS (HR, 2.18; P = 0.05) and DSS (HR, 3.01; P = 0.03).[6] In the present study, adjuvant chemotherapy in patients with stage II colon cancer had no benefit in those without risk factors (P = 0.232), but significantly improved RFS in patients with risk factors (P = 0.037).

There were several limitations to our study. First, because the study was retrospective, there may have been an inherent selection bias. Moreover, genetic information, including microsatellite instability, and BRAF, KRAS, and NRAS status, was not adequately recorded in the records accessed. Therefore, we could not include genetic information in the analysis. Second, although the study was conducted at four hospitals and included a larger number of patients than previous studies,[12,15,16,22] the relatively small number of patients was insufficient to evaluate other risk factors, including perforation, obstruction, and poor differentiation. Finally, because this was a multicenter study, there may have been discrepancies in the pathological evaluation of LVI and PNI among the four hospitals. However, the rates of LVI and PNI positivity were consistent with the rates in previous studies. In a future study, the lack of universal definitions for LVI and PNI will be addressed and the effect of risk factors on rectal cancer will be studied.

Despite these limitations, we believe that this study provides valuable information about RFS in patients with stage II–III colon cancer in terms of the risk factors present. The present study consistently demonstrates that the combination of LVI, PNI, and T4 (the high-risk group) was associated with poor RFS in patients with stage II–III colon cancer when analyzed together (Figure 1A) or separately (stag II, Figure 1B; stage III, Figure 1C). Moreover, stage II patients with at least one risk factor showed significantly improved RFS when adjuvant chemotherapy was administered. We believe that these results will help clinicians in deciding whether to use adjuvant chemotherapy in patients with high-risk stage II colon cancer.

Conclusion

This study suggests that the histological combination of LVI, PNI, and T4 indicates a poor prognosis for RFS in patients with stage II–III colon cancer. The presence of these risk factors should be taken into account when deciding whether to administer adjuvant chemotherapy to patients with stage II colon cancer.

Ethics Approval and Informed Consent

The study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB 2021-09-005). This study was conducted in accordance with the declaration of Helsinki. As this study was a retrospective cohort study, the data was anonymous and informed consent was not required.

Funding

No funding was received for conducting this study.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2021;71:7–33. doi:10.3322/caac.21654
2. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474. doi:10.1245/s10434-010-0985-4
3. McLeod HL, Murray GI. Tumour markers of prognosis in colorectal cancer. *Br J Cancer*. 1999;79(2):191–203. doi:10.1038/sj.bjc.6690033
4. Lyall MS, Dundas SR, Curran S, Murray GI. Profiling markers of prognosis in colorectal cancer. *Clin Cancer Res*. 2006;12:1184–1191. doi:10.1158/1078-0432.CCR-05-1864
5. Benson AB 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol*. 2004;22:3408–3419. doi:10.1200/JCO.2004.05.063
6. Kumar A, Kennecke HF, Renouf DJ, et al. (2015) Adjuvant chemotherapy use and outcomes of patients with high-risk versus low-risk stage II colon cancer. *Cancer*. 2015;121(121):527–534. doi:10.1002/cncr.29072
7. Artac M, Turhal NS, Kocer M, et al. Do high-risk features support the use of adjuvant chemotherapy in stage II colon cancer? A Turkish Oncology Group study. *Tumori*. 2014;100(2):143–148. doi:10.1177/030089161410000205
8. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;24(Suppl 6):vi64–vi72. doi:10.1093/annonc/mdt354
9. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2017;15(3):370–398. doi:10.6004/jnccn.2017.0036
10. Weiss JM, Schumacher J, Allen GO, et al. Adjuvant chemotherapy for stage II right-sided and left-sided colon cancer: analysis of SEER-medicare data. *Ann Surg Oncol*. 2014;21(6):1781–1791. doi:10.1245/s10434-014-3631-8
11. Booth CM, Nanji S, Wei X, et al. Adjuvant chemotherapy for stage II colon cancer: practice patterns and effectiveness in the general population. *Clin Oncol*. 2017;29(1):e29–e38. doi:10.1016/j.clon.2016.09.001
12. Kim S, Huh JW, Lee WY, et al. Lymphovascular invasion, perineural invasion, and tumor budding are prognostic factors for stage I colon cancer recurrence. *Int J Colorectal Dis*. 2020;35(5):881–885. doi:10.1007/s00384-020-03548-4
13. Huh JW, Lee WY, Shin JK, et al. A novel histologic grading system based on lymphovascular invasion, perineural invasion, and tumor budding in colorectal cancer. *J Cancer Res Clin Oncol*. 2019;145(2):471–477. doi:10.1007/s00432-018-2804-4
14. Skancke M, Arnott SM, Amdur RL, Siegel RS, Obias VJ, Umapathi BA. Lymphovascular invasion and perineural invasion negatively impact overall survival for stage II adenocarcinoma of the colon. *Dis Colon Rectum*. 2019;62(2):181–188. doi:10.1097/DCR.0000000000001258
15. Zhou Y, Wang H, Gong H, Cao M, Zhang G, Wang Y. Clinical significance of perineural invasion in stages II and III colorectal cancer. *Pathol Res Pract*. 2019;211:839–844. doi:10.1016/j.prp.2015.09.001
16. Huh JW, Lee JH, Kim HR, Kim YJ. Prognostic significance of lymphovascular or perineural invasion in patients with locally advanced colorectal cancer. *Am J Surg*. 2013;206(5):758–763. doi:10.1016/j.amjsurg.2013.02.010
17. Babcock BD, Aljehani MA, Jabo B, et al. High-risk stage II colon cancer: not all risks are created equal. *Ann Surg Oncol*. 2018;25(7):1980–1985. doi:10.1245/s10434-018-6484-8
18. Lim SB, Yu CS, Jang SJ, Kim TW, Kim JH, Kim JC. Prognostic significance of lymphovascular invasion in sporadic colorectal cancer. *Dis Colon Rectum*. 2010;53:377–384. doi:10.1007/DCR.0b013e3181cf8ae5
19. Batsakis JG. Nerves and neurotropic carcinomas. *Ann Otol Rhinol Laryngol*. 1985;94:426–427.
20. Weiser MR. AJCC 8th edition: colorectal cancer. *Ann Surg Oncol*. 2018;25(6):1454–1455. doi:10.1245/s10434-018-6462-1
21. Akagi Y, Adachi Y, Ohchi T, Kinugasa T, Shirouzu K. Prognostic impact of lymphatic invasion of colorectal cancer: a single-center analysis of 1616 patients over 24 years. *Anticancer Res*. 2013;33:2965–2970.
22. Tsai HL, Cheng KI, Lu CY, et al. Prognostic significance of depth of invasion, vascular invasion and numbers of lymph node retrievals in combination for patients with stage II colorectal cancer undergoing radical resection. *J Surg Oncol*. 2008;97:383–387. doi:10.1002/jso.20942
23. Yuan H, Dong Q, Zheng B, Hu X, Xu JB, Tu S. Lymphovascular invasion is a high risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. *Oncotarget*. 2017;8:46565–46579. doi:10.18632/oncotarget.15425
24. Liebig C, Ayala G, Wilks J, Berger DH, Albo D. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol*. 2009;27:5131–5137. doi:10.1200/JCO.2009.22.4949
25. Al-Sukhni E, Attwood K, Gabriel EM, LeVea CM, Kanehira K, Nurkin SJ. Lymphovascular and perineural invasion are associated with poor prognostic features and outcomes in colorectal cancer: a retrospective cohort study. *Int J Surg*. 2017;37:42–49. doi:10.1016/j.ijsu.2016.08.528

26. Jobling P, Pundavela J, Oliveira SM, Roselli S, Walker MM, Hondermarck H. Nerve-cancer cell cross-talk: a novel promoter of tumor progression. *Cancer Res*. 2015;75:1777–1781. doi:10.1158/0008-5472.CAN-14-3180
27. Yun HR, Kim HC, Lee WY, Cho YB, Yun SH, Chun HK. The necessity of chemotherapy in T3N0M0 colon cancer without risk factors. *Am J Surg*. 2009;198:354–358. doi:10.1016/j.amjsurg.2008.09.027