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Factors Associated with the Lack of Adjuvant Chemotherapy Following Curative Surgery for Stage II and III Colon Cancer: A Korean National Cohort Study

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Abstract. *Background: To evaluate factors associated with the lack of adjuvant chemotherapy after curative surgery in patients with stage II and III colon cancer based on national population-based data. Patients and Methods: A total of 8,412 patients diagnosed with stage II or III disease who underwent curative resection were included. Results: Adjuvant chemotherapy was not administered in 3,057 cases (36.34%). Factors associated with the lack of chemotherapy were older age [hazard ratio (HR)=1.50 in patients 65-74 years and 5.23 in patients ≥75 years of age], female sex (HR=1.15), tumor-node-metastasis (TNM) stage II (HR=4.28), emergency surgery (HR=1.45), American Society of Anesthesiologists (ASA) score of 3 or higher (HR=1.62), fewer than 12 lymph nodes examined (HR=1.19), a greater quantity of transfusion (HR=1.08), and hospital type (tertiary referral center) (HR=1.62). Conclusion: Patient-related (older age, female sex, and ASA score of 3 or higher) and treatment-related factors (TNM stage II, emergency surgery, fewer than 12 lymph nodes examined, a greater quantity of transfusion, and hospital type) influenced the lack of adjuvant chemotherapy. Given that the use of adjuvant chemotherapy improves overall survival, physicians should make an effort to increase the proportion of patients receiving chemotherapy after surgery.*

Complete surgical resection is the gold-standard treatment for localized colon cancer. After removal of the tumor, adjuvant chemotherapy is performed to destroy undetectable occult micrometastases, thereby minimizing the risk of recurrence and metastasis (1). Although it is difficult to estimate the survival benefits of adjuvant chemotherapy, chemotherapy with fluorouracil prolonged survival by 5% in patients with node-positive colon cancer in a meta-analysis (2). In stage III colon cancer, modern cytotoxic chemotherapy including oxaliplatin can reduce the risk of recurrence by approximately 30% or the risk of death by 22-32% (3).

The current National Comprehensive Cancer Network guidelines recommend adjuvant chemotherapy for stage II and III colon cancer following curative surgery (4); however, not all patients receive adjuvant chemotherapy. In the United States, only 67% of patients with stage III colon cancer received adjuvant chemotherapy after colectomy based on data from 2013 (5). The receipt of chemotherapy depends on the patient's age, ethnicity, comorbid disease, marital and socioeconomic status, and the presence of postoperative complications (6).

To date, the reasons for the lack of adjuvant chemotherapy have not been extensively investigated using a national population-based cohort study. Since 2011, the Korean Health Insurance Review and Assessment Service (HIRA, Seoul, Korea) has collected treatment data for all new patients with colon cancer to monitor the cancer treatment process and improve the quality of colon cancer care. Using the Korean population-based cohort, we investigated factors associated with the lack of adjuvant chemotherapy after curative surgery in patients with stage II and III colon cancer.

Patients and Methods

Patients. This was a retrospective study using national population-based cohort data and was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (7). All clinical investigations were conducted following the principles expressed in the Declaration of Helsinki. This analysis was approved and participants' informed consent was waived by the Ethics Review Committee of the HIRA (Seoul, South Korea) and the Institutional Review Board of Wonju Severance Christian Hospital (YWMR-15-5-041).

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Key Words: Colonic neoplasms, adjuvant chemotherapy, survival, mortality.

Table I. *Details of hospital treatment data collected.*

1	Presence of a specialized cancer care team
2	Record of preoperative pain score
3	Record of preoperative family history
4	Whether to perform appropriate preoperative examinations (serum carcinoembryonic antigen (CEA), abdomino-pelvic computed tomography scan, upper gastrointestinal endoscopy, colonoscopy, and pelvic magnetic resonance imaging for rectal cancer)
5	Surgical record for completeness of tumor resection (R0, R1, or R2)
6	Whether to perform follow-up serum CEA within 3 months after surgery
7	Quality of pathological records
8	Whether to examine an adequate number of lymph nodes (more than 12 nodes)
9	Quality of medical records with regard to cancer treatment
10	Ostomy education
11	Whether not to perform adjuvant chemotherapy in stage I disease
12	Commencement of adjuvant chemotherapy within 8 weeks after surgery
13	Education on the adjuvant chemotherapy plan
14	Use of a flow sheet to record the schedule and dose of adjuvant chemotherapy
15	Whether to perform recommended chemotherapy regimens according to the colorectal cancer treatment guidelines
16	Use of antiemetics during chemotherapy
17	Whether to perform postoperative radiation therapy for rectal cancer
18	Whether to perform preoperative concurrent chemoradiation therapy for rectal cancer
19	Length of hospital stay after surgery
20	Surgical treatment cost
21	In-hospital mortality after surgery

Between January 1, 2011 and December 31, 2012, a total of 8,412 patients with colon cancer who underwent curative resection and were diagnosed with stage II or III disease were included based on HIRA data obtained from all hospitals registered in the Korean HIRA. The inclusion criteria were histologically proven colonic adenocarcinoma and age older than 18 years. Exclusion criteria included stage I or IV disease, incomplete tumor removal (R2, macroscopic residual disease) or palliative non-resectional surgery, and rectal cancer.

Data source. In 2011, the Korean HIRA launched a project termed 'Monitoring and Evaluation of the Quality of Colon Cancer Care'. The HIRA collected hospital treatment data to improve the quality of colon cancer care at the national level. The diseases evaluated were colon and rectal adenocarcinoma, such as C18 (malignant neoplasm of the colon), C19 (malignant neoplasm of the rectosigmoid junction), and C20 (malignant neoplasm of the rectum), based on the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 version (8). All hospitals in South Korea requesting reimbursement for colorectal cancer care have been mandated to submit 21 detailed items of treatment data on newly diagnosed patients older than 18 years of age. These 21 items submitted in detail are listed in Table I.

Study objective. The primary objective was to identify factors associated with the lack of adjuvant chemotherapy after curative surgery in patients with stage II and III colon cancer. The secondary objective was to evaluate the overall survival rates according to the use of adjuvant chemotherapy and prognostic factors for survival using Cox proportional hazard modeling.

Recommendation for adjuvant chemotherapy. The Korean government agency (HIRA) and the Korean Clinical Practice Guidelines for Colon and Rectal Cancer (v.1.0) recommend that all colon cancer patients with stage II or III disease receive adjuvant chemotherapy after curative resection (9, 10). The chemotherapeutic agents included fluoropyrimidine (fluorouracil with folinic acid, capecitabine) alone or in combination with oxaliplatin (FOLFOX). High-risk features for recurrences were defined when patients had T4 tumors, histological grade 3, peritumoral lymphovascular invasion, intestinal obstruction at presentation, T3 lesions with perforation or inadequate, indeterminate, or positive resection margins, or perineural invasion. In stage II disease, patients with high-risk features were recommended to receive a FOLFOX regimen.

Patients were followed-up until death or August 31, 2015. The date of death was collected from the National Health Insurance Service System (Seoul, Korea). The median follow-up period was 1,264 days (mean±standard deviation: 11,95.2±335.08 days).

Variables. In South Korea, the current National Health Insurance System covers all nationals, and the National Health Security System comprises two categories, health insurance and medical aid, based on economic status. The presence of comorbidity was defined when a patient had one of any medical condition presented in the Charlson comorbidity index (11). The quantity of blood transfusion was quantified as units received during the postoperative period in the hospital.

Statistical analysis. All statistical analyses were performed using MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Categorical variables are presented as frequencies and percentages and were analyzed by the chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as the means and standard deviations and were analyzed by the two-sample *t*-test.

Firstly, factors associated with the lack of chemotherapy were identified by univariable logistic regression analysis, and variables

Table II. *Factors associated with the lack of adjuvant chemotherapy in patients with stage II and III colon cancer (n=8,412).*

Variable	Univariate analysis			Multivariate analysis	
	Chemotherapy (N=5,355)	No chemotherapy (N=3,057)	*p*-Value	OR (95%CI)	*p*-Value
Age (years)					
Mean±SD	62.90±11.13	70.88±11.70	<0.0001	NA	
Age subgroups (years)					
<65	2,804 (52.36%)	830 (27.15%)	<0.0001	1	<0.0001
65-74	1,749 (32.66%)	860 (28.13%)		1.50 (1.32-1.70)	
≥75	802 (14.98%)	1,367 (44.72%)		5.23 (4.57-5.99)	
Gender					
Male	3,187 (59.51%)	1,638 (53.58%)	<0.0001	1	0.0082
Female	2168 (40.49%)	1,419 (46.42%)		1.15 (1.04-1.28)	
Health security system					
National health insurance	5,024 (93.82%)	2,777 (90.84%)	<0.0001	1	0.067
Medical aid	331 (6.18%)	280 (9.16%)		1.20 (0.99-1.47)	
TNM					
II	2,022 (37.76%)	2,087 (68.27%)	<0.0001	4.28 (3.85-4.77)	<0.0001
III	3,333 (62.24%)	970 (31.73%)		1	
ASA score					
1,2	4,656 (88.91%)	2,250 (75.76%)	<0.0001	1	<0.0001
3,4	581 (11.09%)	720 (24.24%)		1.62 (1.41-1.87)	
Emergency					
Yes	355 (6.64%)	381 (12.5%)	<0.0001	1.45 (1.18-1.80)	0.0006
No	4,993 (93.36%)	2,668 (87.5%)		1	
Lymph nodes retrieved (number)					
<12	491 (9.41%)	370 (12.82%)	<0.0001	1.19 (1.01-1.41)	0.0406
≥12	4,728 (90.59%)	2,515 (87.18%)		1	
Comorbidity					
+	3,902 (72.87%)	2,417 (79.06%)	<0.0001	1.00 (0.88-1.14)	0.9787
Transfusion (units)					
Mean±SD	0.05±0.59	0.31±4.35	0.001	1.08 (1.03-1.14)	0.0033
Hospital type					
Tertiary referral hospital	4,952 (92.47%)	2,909 (95.16%)	<0.0001	1.62 (1.26-2.08)	0.0002
General hospital (≥100 beds)	402 (7.51%)	148 (4.84%)		1	
District hospital (<100 beds)	1 (0.02%)	0 (0%)		NA	
Chemotherapy regimen					
Fluoropyrimidine-based	2296 (42.88%)	0 (%)	–	NA	
Oxaliplatin-based	3,059 (57.12%)	0 (%)			

OR, Odds ratio; CI, confidence interval; NA, not applicable; SD, standard deviation; TNM, tumor-node-metastasis; ASA, American Society of Anesthesiologists.

with a *p*-value of less than 0.05 were utilized for multivariate analysis. Multivariate logistic regression analysis was then performed by the forward stepwise selection of variables. Survival and prognostic factor analyses were performed by the Kaplan–Meier method with log-rank tests and the Cox proportional hazards model. A *p*-value of less than 0.05 was considered statistically significant.

Results

Factors associated with the lack of adjuvant chemotherapy. Among 8,412 patients with stage II (n=4,109) or III (n=4,303) disease, adjuvant chemotherapy was not administered in 3,057 cases (36.34%). Among 5,355 patients with adjuvant chemotherapy, the chemotherapy agents included fluoropyrimidine (n=2,296, 42.88%) and oxaliplatin (n=3,059, 57.12%).

Based on the multivariate analysis, the factors associated with the lack of chemotherapy were older age [hazard ratio (HR)=1.50 in patients 65-74 years and 5.23 in patients ≥75 years of age, $p<0.0001$], female sex (HR=1.15, $p=0.0082$), tumor-node-metastasis (TNM) stage II (HR=4.28, $p<0.0001$), American Society of Anesthesiologists (ASA) score of 3 or higher (HR=1.62, $p<0.0001$), emergency surgery (HR=1.45, $p=0.0006$), fewer than 12 lymph nodes examined (HR=1.19, $p=0.0406$), a greater quantity of transfusion (HR=1.08, $p=0.0033$), and hospital type (tertiary referral center) (HR=1.62, $p=0.0002$) (Table II).

Table III. *Overall survival rates in patients with stage II and III colon cancer according to the receipt of adjuvant chemotherapy (N=8,412).*

Chemotherapy	Parameter	Baseline	1-Year	2-Year	3-Year	4-Year	*p*-Value
Yes	Number at risk	5,355	5,235	5,012	4,208	1,115	<0.0001
	Proportion surviving	100%	97.76%	93.59%	89.37%	85.64%	
No	Number at risk	3,057	2,683	2,469	2,046	491	
	Proportion surviving	100%	87.77%	80.77%	75.52%	70.6%	

*By log-rank test.

Overall survival rates according to the use of adjuvant chemotherapy. The 1-year overall survival rates were 97.76% and 87.77% in the chemotherapy and no chemotherapy groups, respectively. The 3-year overall survival rates were 89.37% and 75.52% in the chemotherapy and no chemotherapy groups, respectively ($p<0.001$) (Figure 1, Table III).

Prognostic factors for survival using Cox proportional hazard modeling. Adverse prognostic factors for overall survival included the lack of adjuvant chemotherapy (HR=1.93, $p<0.0001$), older age (HR=1.83 in patients 65-74 years and 3.08 in patients ≥75 years of age, $p<0.0001$), TNM stage III (HR=2.45, $p<0.0001$), ASA score of 3 or higher (HR=1.79, $p<0.0001$), emergency surgery (HR=2.36, $p<0.0001$), fewer lymph nodes examined (HR=1.43, $p<0.0001$), and a greater quantity of transfusion (HR=1.03, $p<0.0001$) (Table IV).

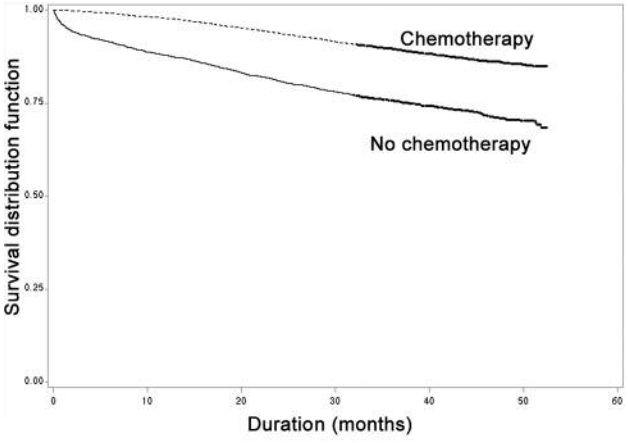

Figure 1. *Overall survival rates in patients with stage II and III colon cancer according to the receipt of adjuvant chemotherapy (N=8,412).*

Discussion

This study shows that a significant proportion (36.34%) of patients with stage II and III disease do not receive adjuvant chemotherapy after curative surgery. In population-based studies, rates of adjuvant chemotherapy ranged from 41% to 93.9% (Table V) (12-28). The major finding of this study is that factors affecting the lack of chemotherapy were older age, female sex, TNM stage II, emergency surgery, ASA score of 3 or higher, fewer than 12 lymph nodes examined, a greater quantity of transfusion, and hospital type (tertiary referral center). Survival analysis confirmed that the lack of chemotherapy was associated with unfavorable overall survival, which indicates that increased administration of adjuvant chemotherapy could improve the outcomes of colon cancer care.

Diverse factors are associated with no receipt of adjuvant chemotherapy. Older age is a well-known risk factor for the lack of adjuvant chemotherapy (12-16, 18-26, 28). We also observed that the lack of chemotherapy was associated with increasing age based on age subgroup analysis. Chronological aging is related to diminished physiological reserve and high susceptibility to comorbidities. Thus, with elderly patients, the patient, physician, or both tend to be discouraged from using adjuvant chemotherapy (15, 29). Four population-based studies focusing on elderly patients aged 65-79 years (14), 66-99 years (15), or over 65 years (19, 21) showed rates of chemotherapy that ranged from 41% to 63%. In this series, 53.4% of patients aged 65 years or older received chemotherapy.

Female sex has been reported as a significant factor for the lack of adjuvant chemotherapy (14, 16, 23, 24, 28), as reported in the current study. However, in a study by Lin *et al.* (25), male sex was a risk factor for the lack of chemotherapy. The underlying mechanism in the role of sex has not been elucidated; however, Oliver *et al.* suggested that in female patients, fragile condition or poor economic status may preclude physicians' willingness to perform chemotherapy (23).

In this study, TNM stage II was associated with a lack of chemotherapy. In the literature, advanced tumor stage, in terms of a greater number of positive lymph nodes (12, 15, 21, 24, 25) or TNM III stage (23) compared to TNM II stage, has been associated with the more frequent use of adjuvant

Table IV. *Prognostic factors for overall survival in patients with stage II and III colon cancer (n=8,412).*

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Adjuvant chemotherapy				
Yes	1	<0.0001	1	<0.0001
No	2.4 (2.17-2.66)		1.93 (1.71-2.18)	
Age subgroups (years)				
<65	1	<0.0001	1	<0.0001
65-74	2.01 (1.74-2.32)		1.83 (1.57-2.13)	
≥75	4.66 (4.09-5.30)		3.08 (2.65-3.58)	
Gender				
Male	1.01 (0.91-1.12)	0.8261	NA	
Female	1			
Health security system				
National health insurance	1	<0.0001	1	0.1405
Medical aid	1.64 (1.40-1.93)		1.15 (0.96-1.37)	
TNM				
II	1	<0.0001	1	<0.0001
III	1.84 (1.66-2.05)		2.45 (2.18-2.75)	
Emergency				
Yes	3.42 (3.02-3.88)	<0.0001	2.36 (2.02-2.74)	<0.0001
No	1		1	
ASA score				
1,2	1	<0.0001	1	<0.0001
3,4	2.98 (2.68-3.33)		1.79 (1.58-2.03)	
Lymph nodes retrieved (number)				
<12	1.77 (1.54-2.04)	<0.0001	1.43 (1.24-1.66)	<0.0001
≥12	1		1	
Comorbidity				
+ *vs.* −	1.28 (1.13-1.45)	0.0001	0.98 (0.86-1.12)	0.7795
Transfusion (units)	1.03 (1.03-1.04)	<0.0001	1.03 (1.02-1.04)	<0.0001

HR, Hazard ratio; CI, confidence interval; NA, not applicable; TNM, tumor-node-metastasis; ASA, American Society of Anesthesiologists.

chemotherapy. This finding might be explained by the need for increased oncological consultation (15) or physicians' recommendation for more aggressive treatment for more advanced tumors.

In this study, an ASA score of 3 or higher was associated with a lack of chemotherapy. The ASA score is a six-category physical status classification system reflecting preoperative functional status, and patients with an ASA score of 1 (healthy), 2 (mild systemic), or 3 (severe systemic disease) are candidates for elective colon cancer resection. The functional status of patients with cancer is important before considering the use of chemotherapy, and the Eastern Cooperative Oncology Group score or Karnofsky score are also used to determine a patient's performance status. However, few studies have focused on the relation between functional status and the receipt of adjuvant chemotherapy (22, 29). Another study showed that poor performance status was associated with the underuse of palliative chemotherapy in patients with stage IV disease (10). The patient's functional status is also influenced by comorbidity, which is related to the receipt of chemotherapy (12-18, 20, 21, 23, 25, 26, 28). A greater Charlson comorbidity score has been associated with a lower rate of chemotherapy use (12-16, 18, 20, 21, 23, 25, 26, 28), and Gross *et al*. (17) observed that the presence of congestive heart failure, chronic obstructive pulmonary disease, or diabetes was associated with the lack of adjuvant chemotherapy. Unlike the ASA score, comorbidity was not a significant predictor for chemotherapy use in our study.

Complicated postoperative recovery in terms of severe surgical complications (22), reoperation (22, 24), or prolonged hospital stay (13, 24) has been shown to increase the lack of chemotherapy. Although we were unable to obtain data regarding postoperative complications in this study, emergency surgery, fewer than 12 lymph nodes examined, and a greater quantity of transfusion were associated with the lack of chemotherapy. We speculate that these factors are surgical treatment-related. Indeed, emergency surgery is more likely to cause postoperative complications (30) or low lymph node yield (31), and

Table V. *Population-based cohort studies regarding the administration of adjuvant chemotherapy for colon cancer.*

Author (Ref)	Year	Data source	N	Chemotherapy receipt (%)	Stage	Significant factors
Schrag *et al*. (12)	2001	SEER	6,262	55%	III	Age, race, no. of positive lymph nodes, comorbidity, year of diagnosis
Baldwin *et al*. (13)	2005	SEER	5,294	59.8%	III	Age, race, comorbidity, married, surgical length of stay, rehospitalization, region
Lemmens *et al*. (14)	2005	Netherlands	577*	41%	III	Sex, socioeconomic status, comorbidity, year of diagnosis
Luo *et al*. (15)	2006	SEER	7,569*	58.5%	III	Age, race, marital status, year of diagnosis, no. of positive lymph nodes, comorbidity
McGory *et al*. (16)	2006	CA	13,231	48%	III	Age, sex, race, insurance, comorbidity, poverty, college education
Gross *et al*. (17)	2007	SEER	5,330	60.3%	III	Comorbidities (CHF, COPD, diabetes)
Cress *et al*. (18)	2009	SEER	973	67%	III	Residence (state, education level, non-working class neighborhood), age, comorbidity, marital status
Davidoff *et al*. (19)	2009	SEER	7,176*	51.7%	III	Race
Winget *et al*. (20)	2010	Canada	618	63%	III	Age, comorbidity
Hsieh *et al*. (21)	2013	SEER	13,608*	56%	III	Age, race, socioeconomic status, marital status, intestinal obstruction, no. of positive lymph nodes, comorbidity, diagnosis year
Merkow *et al*. (22)	2013	ACS-NSQIP	2,368	63.2%	III	Age, ASA, functional status, body mass index, income, serious complication, organ space SSI, prolonged ventilation, reintubation, pneumonia, VTE, renal failure, sepsis/shock, return to operating room
Oliver *et al*. (23)	2013	AL	1,182	93.9%	II & III	Age, sex, stage III, comorbidity
van der Geest *et al*. (24)	2013	Netherlands	606	60%	III	Age, sex, tumor stage, reoperation, prolonged postoperative hospital stay
Lin *et al*. (25)	2015	NCDB	34,694	75.7%	III	Age, sex, travel distance, race, insurance, facility type, comorbidity, no. of positive lymph nodes, tumor grade, region (univariate)
Murphy *et al*. (26)	2015	SEER	1,849	65.4%	III	Age, race/ethnicity, comorbidity, year of diagnosis
Murphy *et al*. (27)	2015	SEER	1,219	64.6%	III	Race/ethnicity
Upadhyay *et al*. (28)	2015	NCDB	207,718	62%	III	Age, sex, race/ethnicity, treatment facility, year of treatment, insurance, education, income, comorbidity, distance to facility (univariate)
Current study	2016	Korean HIRA	8,412	63.7%	II & III	Age, sex, TNM stage, ASA, emergency surgery, lymph nodes examined, transfusion, hospital type

SEER, Surveillance Epidemiology and End Results-Medicare; CA, California Cancer Registry, California Discharge Records, 2000 census; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; SSI, surgical site infection; VTE, venous thromboembolism; AL, Alabama; NCDB, National Cancer Data Base; HIRA, Health Insurance Review and Assessment Service; TNM, tumor-node-metastasis; ASA, American Society of Anesthesiologists. *Elderly patients only.

complicated postoperative recovery is linked to a greater quantity of transfusion (32).

In this study, treatment in a tertiary referral center was associated with a lack of chemotherapy. This finding might be due to the rather small study sample of the general hospital group compared to those of the tertiary center and that patients with more severe conditions are more likely to be treated in a tertiary center. In contrast to our results, an academic center (28) and the facility of the National Cancer Institute program (25) showed increased rates of chemotherapy among patients at a tertiary referral center.

In the literature, other factors such as race/ethnicity (12, 13, 15, 16, 19, 21, 25-28), marital status (13, 15, 18, 21), residence (13, 18, 25, 28), education (16, 28), insurance (16, 25, 28) and year of diagnosis (12, 14, 15, 21, 26, 28) have been reported to be significant risk factors for the lack of chemotherapy.

This study was limited by its retrospective design. In addition, data on short-term surgical outcomes, such as postoperative complications and severity, and data for stage II disease in high-risk patients, were not available. However, this study has some strengths. The study cohort included a significant quantity of Korean population data and was based on highly credible data collected by a government health service agency. The study was also performed in a recent period and with current chemotherapeutic agents based on the current chemotherapy guidelines for colon cancer.

In summary, patient-related (older age, female, and ASA score of 3 or higher) and treatment-related factors (TNM stage II, emergency surgery, fewer than 12 lymph nodes examined, a greater quantity of transfusion, and hospital type) influenced the lack of adjuvant chemotherapy based on this national population-based cohort study. Given that the use of adjuvant chemotherapy improves overall survival, physicians should make efforts to increase the proportion of patients receiving chemotherapy after surgery.

Conflicts of Interest

Each Author confirms that they have no commercial associations that might pose a conflict of interest in connection with this article.

Competing Interests

The Authors have no competing interests to declare.

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