Original Study

Predictive Nomogram for Recurrence of Stage I Colorectal Cancer After Curative Resection

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Abstract

In a study that aimed to develop a predictive nomogram for postoperative recurrence in stage I colorectal cancer (CRC), a predictive nomogram was developed with a total of 1538 stage I CRC patients and internally validated. This nomogram will assist physicians to more accurately identify high-risk patients who need more active surveillance and will help ensure more efficient disease management.

Background: Patients with stage I colorectal cancer (CRC) have excellent prognosis after curative surgery. However, approximately 5% to 10% of patients experience recurrence and have a poor prognosis. Because the incidence of stage I CRC is increasing with active screening programs worldwide, a more accurate and easy-to-use predictive tool for recurrence is becoming more important. This study aimed to develop a predictive nomogram for recurrence in stage I CRC. **Patients and Methods:** A total of 1538 patients who underwent curative surgery for stage I CRC were enrolled. Predictive factors for recurrence were determined by multivariate Cox regression model and were used to develop a predictive nomogram. This model was internally validated, and performance was evaluated through calibration plots. **Results:** The cumulative recurrence rate at 5 years after surgery for stage I CRC was 5.3%. In multivariate Cox analysis, independent predictors of recurrence were tumor location at rectum, pT2 stage, and presence of lymphovascular invasion. The 5-year recurrence rate was significantly different depending on the number of risk factors (0.7% for 0, 5.8% for 1, and 9.7% for $\geq$ 2 risk factors). On this basis, a nomogram for recurrence-free survival was developed and internally validated. The concordance index of the nomogram was 0.71, and the performance was acceptable. **Conclusion:** We developed and internally validated a nomogram that can predict postoperative recurrence in stage I CRC patients. This nomogram may be used to more accurately stratify the risk of recurrence and to perform personalized postoperative surveillance in stage I CRC patients.

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Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy and leading cause of cancer-related death worldwide. It is expected that CRC incidence will increase to 160% by 2030, with an estimated 2.1 million new cases and 1.1 million deaths annually.[1-3]

More than 20% of CRC patients are initially diagnosed with stage I disease, and surgical resection is the treatment of choice for this stage.[4-8] In stage I CRC, adjuvant therapy has not been recommended because surgery is curative in most cases, and regular follow-ups are routinely performed to detect and treat any recurrence as early as possible.[8-10] The prognosis of stage I CRC is excellent, with a 5-year overall survival of more than 90%.[11] However, approximately 5% to 10% of stage I CRC patients still experience recurrence after surgery, and prognosis is poor in such cases.[2,4]

Because the patient population with stage I CRC is expected to greatly increase as a result of advanced screening programs

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worldwide, disease recurrence after surgical resection is becoming an increasingly important clinical issue.[6,7] Therefore, it is necessary to more precisely stratify the risk of recurrence in individual patients and to implement a personalized surveillance program for patients with stage I CRC.

We therefore aimed to identify clinicopathologic factors associated with recurrence and to generate a simple and precise nomogram for predicting postsurgical recurrence in stage I CRC.

Materials and Methods

Patient Selection

This study investigated stage I CRC patients who underwent curative surgical resection at 2 tertiary-care hospitals in Korea, Severance Hospital (Seoul, Korea) and CHA Bundang Medical Center (Seongnam, Korea), between 2005 and 2014. Of the 1692 stage I CRC patients, a total of 1538 patients were enrolled and underwent final analysis after excluding patients who underwent perioperative chemo- or radiotherapy, and patients with multiple primary cancers. All patients were carefully evaluated and reviewed on the basis of their institutional electronic medical records. Clinicopathologic features such as sex, age, location of primary tumor, histology, tumor, node, and metastasis stage, presence of lymphovascular invasion (LVI), presence of perineural invasion (PNI), maximal size of primary tumor, carcinoembryonic antigen levels at diagnosis, and clinical outcomes were analyzed thoroughly. Classification and staging of cancer were performed according to the American Joint Committee on Cancer, 7th edition, guidelines. All patients underwent regular follow-up every 3 months for the first 2 years after surgery, and every 6 months thereafter until 5 years after surgery.

Statistical Analysis and Nomogram Development

SPSS 20.0 (IBM SPSS, Chicago, IL) was used for statistical analysis. The Student t test and the chi-square test were used for analysis of variables. Recurrence-free survival (RFS) was defined as the interval between time of surgery to recurrence, death, or last follow-up. Overall survival was defined as the interval between time of surgery and death or last follow-up. Survival plots were constructed on the basis of the Kaplan-Meier method and were compared by log-rank tests. Statistical significance was defined as $P < .05$. A nomogram for predicting recurrence of stage I CRC was created with the statistically significant variables and evaluated using concordance index (c index) and calibration plots. The specific scores of each individual factor in the nomogram are calculated using the coefficients from logistic regression. A point system of a nomogram is used to assign each predictor, with point ranges from 0 to 100 in a graphic interface. On the basis of the estimated regression coefficients, we rank the estimated effects, disregarding statistical significance as well as direction (absolute beta values). We determined which predictor has the biggest impact in the model, then sequentially assigned other predictors on the basis of their proportions to the point assigned to the biggest impact predictor. Each predictor is influenced by the presence of other predictors. Finally, we used estimated beta coefficients from a main effect logistic model. A more detailed method for nomogram generation has been described earlier.[12] All statistical analyses for nomogram generation were performed by R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) with the rms and eha libraries.

Table 1 Baseline Demographics of Stage I Colorectal Cancer Cohort

Characteristic	Variable	Value
Age (y)	Median (range)	62 (25-88)
Sex	Male	911 (59.2%)
	Female	627 (40.8%)
Location	Cecum	34 (2.2%)
	Ascending	184 (12.0%)
	Transverse	74 (4.8%)
	Descending	50 (3.3%)
	Sigmoid	405 (26.4%)
	RS junction	100 (6.5%)
	Rectum	685 (44.5%)
Histology	Adenocarcinoma, WD	459 (29.8%)
	Adenocarcinoma, MD	970 (63.1%)
	Adenocarcinoma, PD	28 (1.8%)
	Mucinous	14 (0.9%)
	Other	18 (1.2%)
T stage	pT1	781 (50.8%)
	pT2	757 (49.2%)
LVI	Negative	1459 (94.9%)
	Positive	79 (5.1%)
PNI	Negative	1526 (9.2%)
	Positive	12 (0.8%)
Carcinoembryonic antigen (ng/mL)		2.74 ± 4.43
Tumor size (cm)		2.50 ± 1.76
Recurrence	Recurred	58 (3.8%)
	Not recurred	1480 (96.2%)

Abbreviations: LVI = lymphovascular invasion; MD = moderately differentiated; PD = poorly differentiated; PNI = perineural invasion; WD = well differentiated.

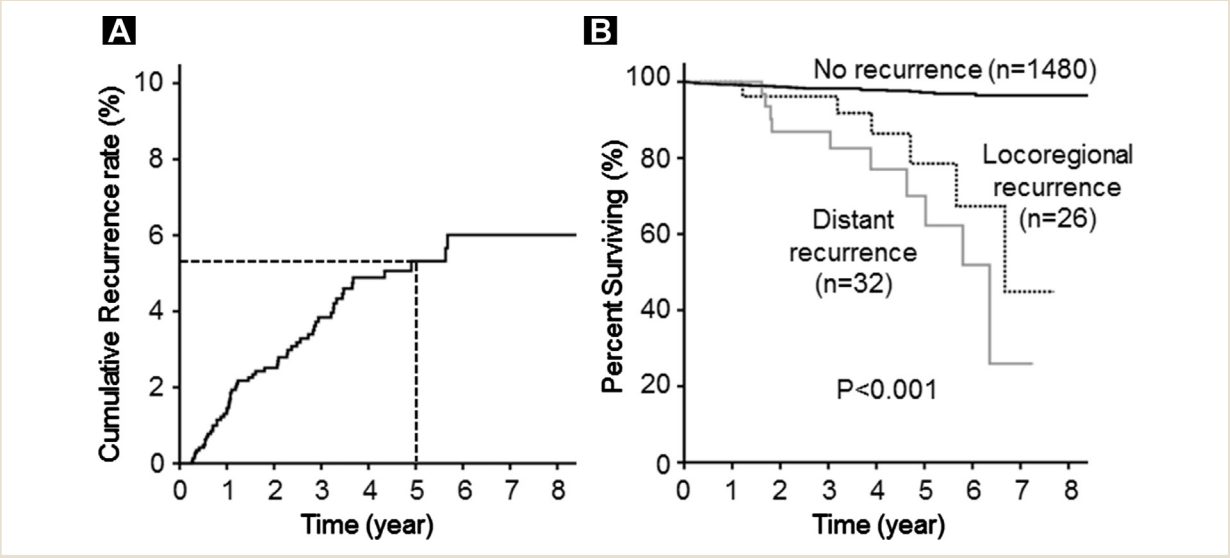
Results

Baseline Patient Characteristics

Between 2005 and 2014, a total of 1538 patients with stage I CRC were enrolled. Baseline demographics are summarized in Table 1. The median age at diagnosis was 62.0 years (range, 25-88 years), and the male-to-female ratio was 1.45:1. Though the cancer of the colon and rectum were almost evenly distributed, the number of colon cancer cases was slightly higher. Most patients had well-differentiated or moderately differentiated adenocarcinoma, and approximately half of cases were pT2 disease. LVI was observed in 5.1% of surgical specimens, and PNI was observed in 0.8% of specimens.

During the median follow-up of 60.0 months, 58 stage I CRC patients experienced recurrence. The 5-year cumulative recurrence rate was 5.3%, and median time to recurrence was 27.5 months (Figure 1A). Most incidences of recurrence occurred within 5 years after surgical resection. Among the 58 recurrent cases, 26 (44.8%) showed locoregional recurrence, while the remaining 32 (55.2%) showed distant recurrence. Most (65.4%) locoregional recurrences occurred in the pelvic cavity, while others (34.6%) recurred at sites of anastomosis. The most frequent site of distant metastasis was the lung (46.9%), followed by liver (31.3%) and peritoneum (9.4%).

Figure 1 Recurrence and Survival of Patients With Stage I Colorectal Cancer. (A) Cumulative Recurrence Rate after Surgical Resection. (B) Kaplan-Meier Survival Analysis of Overall Survival according to Recurrence Pattern



During follow-up, 45 mortalities were recorded; the most common cause of death was disease progression. The 5-year overall survival rate was 97.2% in patients without recurrence, 78.5% in patients with local recurrence, and 62.2% in patients with distant recurrence ($P < .001$) (Figure 1B).

Predictive Factors for Recurrence After Curative Surgery in Stage I CRC

To discover predictive factors for recurrence, the correlation between clinicopathologic variables and recurrence was analyzed (Table 2). In univariate analysis, tumors located at the rectum

Table 2 Predictive Factors for Recurrence in Stage I Colorectal Cancer

Characteristic	Variable	No Recurrence (N = 1480)	Recurrence (N = 58)	*P*
Age (y)		61.0 ± 10.8	60.2 ± 11.4	.564
Sex	Male	870 (95.5%)	41 (4.5%)	.07
	Female	610 (97.3%)	17 (2.7%)	
Location	Cecum	34 (100%)	0	<.001
	Ascending	181 (98.3%)	3 (1.7%)	
	Transverse	72 (97.2%)	2 (2.8%)	
	Descending	49 (98.0%)	1 (2.0%)	
	Sigmoid	397 (98.0%)	8 (2.0%)	
	RS junction	98 (98.0%)	2 (2.0%)	
	Rectum	643 (93.9%)	42 (6.1%)	
Histology	Adenocarcinoma, WD, MD	1393 (96.1%)	56 (3.9%)	.676
	Adenocarcinoma, PD	27 (96.4%)	1 (3.6%)	
	Others	32 (100.0%)	0	
T stage	pT1	763 (97.7%)	18 (2.3%)	.002
	pT2	717 (94.7%)	40 (5.3%)	
LVI	Negative	1143 (96.7%)	39 (3.3%)	.037
	Positive	72 (91.1%)	7 (8.9%)	
PNI	Negative	1468 (99.2%)	58 (100.0%)	.491
	Positive	12 (0.8%)	0	
Carcinoembryonic antigen (ng/mL)		2.76 ± 4.50	2.42 ± 2.18	.571
Tumor size	<5 cm	1363 (96.7%)	47 (3.3%)	.003
	≥5 cm	117 (91.4%)	11 (8.6%)	

Abbreviations: LVI = lymphovascular invasion; MD = moderately differentiated; PD = poorly differentiated; PNI = perineural invasion; WD = well differentiated.

Table 3 Multivariate Cox Regression Analysis for Recurrence-Free Survival in Stage I Colorectal Cancer

Variable	HR (95% CI)	*P*
Sex (male vs. female)	1.52 (0.86-2.67)	.152
Location (rectal vs. nonrectal)	2.87 (1.61-5.14)	<.001
T stage (pT2 vs. pT1)	1.79 (1.00-3.20)	.049
LVI (yes vs. no)	2.32 (1.08-4.97)	.031
Tumor size (≥5 cm vs. <5 cm)	1.69 (0.86-3.33)	.131

Abbreviations: CI = confidence interval; HR = hazard ratio; LVI = lymphovascular invasion.

relapsed 3.2-fold more frequently than those at other locations in the colon (6.1% vs. 1.9%, $P < .001$). Moreover, tumors of pT2 stage, presence of LVI, and maximal tumor size > 5 cm were associated with increased incidence of recurrence. However, there was no significant difference in recurrence with age, sex, histology, presence of PNI, and baseline carcinoembryonic antigen value.

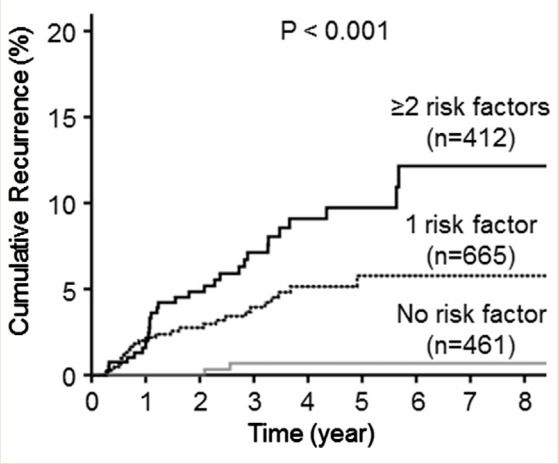
To identify independent predictive factors for recurrence, we performed multivariate analyses for the above-mentioned variables (Table 3). Multivariate Cox regression analysis for RFS revealed 3 independent predictors for recurrence: tumors located at rectum, pT2 stage, and presence of LVI. Next, we examined if the number of risk factors co-occurring at the time of initial diagnosis affected the recurrence after surgery (Figure 2). The cumulative recurrence rate was significantly different according to the number of baseline risk factors. The 5-year recurrence rate in stage I CRC patients with no risk factors (30% of total population) was 0.7%, while with a single risk factor (43% of total) it was 5.8%, and with 2 or more risk factors (27% of total), it was 9.7%. Collectively, we found that the recurrence rate after surgery may differ by a factor of 10, depending on the number of baseline risk factors.

Nomogram for Prediction of Recurrence

We next attempted to generate a nomogram for predicting 2-, 5-, and 10-year recurrence based on risk factors in stage I CRC patients (Figure 3A). Total scores for each patient were calculated by adding individual scores of all 5 risk factors based on the nomogram. Once the total score was calculated, the probability of 2-, 5-, or 10-year RFS was obtained by drawing a vertical line from the "total score" axis to the "recurrence-free probability" axis. In this nomogram, the probability of recurrence increases as the total score decreases. For example, for a total score of 100, the probabilities of 2-, 5-, and 10-year RFS would be 92%, 82%, and 70%, respectively, and those for a total score of 220 would be 97%, 95%, and 91%, respectively. The nomogram was able to accurately predict individual RFS, with a concordance index of 0.71.

Figure 3B illustrates the calibration plot for the nomogram. The *x*-axis represents the prediction calculated with use of the nomogram, and the *y*-axis represents the actual probability of recurrence. An ideal nomogram (dotted line) would be represented in the form of the line $y = x$, in which the predicted outcome perfectly corresponds with actual outcome. The performance of our nomogram, plotted as a solid line, was found to be satisfactory.

Figure 2 Cumulative Recurrence Rate of Stage I Colorectal Cancer According to Number of Risk Factors



Discussion

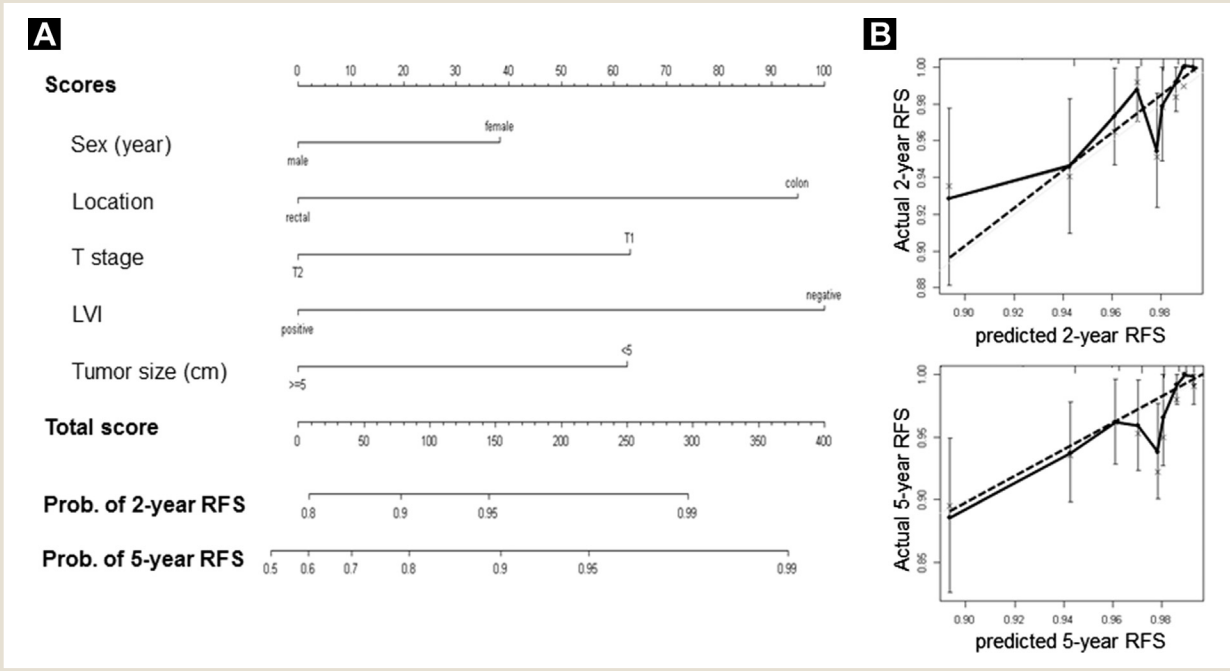
Stage I CRC has not been studied extensively until now because it has an excellent prognosis and low recurrence rates compared with locally advanced disease. However, as the incidence of CRC increases worldwide, the absolute number of stage I patients is increasing significantly, so it is clinically useful to precisely predict the probability of postoperative recurrence in stage I patients.[6,7]

In previous studies, several factors were identified to be associated with recurrence of stage I CRC: tumors located in rectum, T2 stage, LVI-positive status, tumor budding, genomic aberrations, and intratumoral infiltration of immune cells.[4,6,8,13,14] Although these factors are associated with an increased recurrence rate, there is no easy-to-use clinical tool to comprehensively analyze all factors together and calculate the recurrence rate quantitatively. Previously, Weiser et al[15] developed a nomogram that predicted recurrence after surgery in CRC patients of all stages. This study was primarily aimed at patients with advanced stage disease, and because stage I patients constituted less than one third of the total population, the nomogram performance for stage I CRC patients was not satisfactory. Valentini et al[16] also suggested a nomogram to predict recurrence. However, this study was limited to rectal cancer patients, and most of the patients were treated with chemoradiotherapy for locally advanced disease, so this model cannot be applied to stage I CRC patients.

Therefore, the present study focused on stage I CRC to overcome the limitations of the previous studies. Although this study was retrospective, it was based on a prospectively managed database of CRC patients. In addition, this study included more than 1500 patients with stage I CRC, which is the largest number of stage I CRC patients enrolled to date.

We confirmed that the 5-year cumulative recurrence rate of stage I CRC is 5.3% and that multivariate analysis can identify risk factors for recurrence: tumors located at rectum, pT2 stage, and presence of LVI. Furthermore, on this basis, we developed a recurrence prediction nomogram that comprehensively reflects the various risk factors for patients with stage I CRC. This nomogram was internally validated and showed relatively good performance.

Figure 3 Predictive Nomogram for Recurrence in Stage I Colorectal Cancer. (A) Nomogram for Prediction of Recurrence. Methodology for Using Nomogram: Find Value of Each Patient Variable on Graph, Draw a Vertical Line Upward to "Scores" Axis, and Check Corresponding Points for Variable. Then Add Values for Each Variable and Locate This Sum on "Total Score" Axis. Draw a Vertical Line Down to Recurrence-Free Probability Axis to Determine patient's Individual Probability of Developing Recurrence at a Given Time (2 or 5 Years After Surgery). (B) Calibration Plot for Nomogram Prediction: Ideal Nomogram (Dashed Line) and Current Nomogram (Solid Line). Vertical Bars Indicate 95% Confidence Intervals Based on Bootstrap Analysis



Using this nomogram, the postoperative recurrence rate can be calculated quantitatively on the basis of the clinicopathologic factors of the patient at the time of surgery. It is thus possible to identify patients at high risk of recurrence after surgery and conduct a more active surveillance program to detect the recurrence as early as possible. Indeed, in some of the patients involved in this study whose recurrence was found relatively early, removal of metastases and multidisciplinary treatment resulted in long disease-free survival outcomes.

The main limitation of our study is its retrospective patient selection. In addition, although both the institutions involved in the study followed the same treatment and follow-up guidelines, adherence to the protocol may have been different, possibly affecting recurrence and survival analyses. Although we analyzed more than 1500 stage I CRC patients in 2 independent cancer centers in Korea, further studies conducted within and outside Korea are essential to externally validate our findings. Another limitation of the nomogram in this study is its performance. While 5 variables are included to improve the *c* index in the final nomogram, only 3 were independent variables in multivariate analysis, and the performance of nomogram is not the best. In certain clinical situations, the recurrence prediction plot using the number of risk factors shown in Figure 2 may replace the nomogram for ease of use. Therefore, the nomogram needs to be further improved in subsequent studies by adding novel independent predictive biomarkers.

Conclusion

We developed a simple and accurate nomogram that predicts recurrence of stage I CRC. This nomogram will assist physicians to more accurately identify high-risk patients who need more active surveillance and to ensure efficient disease management.

Clinical Practice Points

- Approximately 5% to 10% of stage I CRC patients experience recurrence and have a poor prognosis.
- This study developed and internally validated a predictive nomogram for recurrence in stage I CRC patients after curative resection.
- This nomogram can be used to more accurately identify high-risk patients who need more active surveillance and will help ensure more efficient disease management.

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Disclosure

The authors have stated that they have no conflict of interest.

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