ORIGINAL CONTRIBUTION

Nomogram Predicting Survival After Recurrence in Patients With Stage I to III Colon Cancer: A Nationwide Multicenter Study

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BACKGROUND: Although a number of studies have been conducted to investigate factors affecting colon cancer recurrence and patient overall survival after surgical treatment, no prognostic risk models have been proposed for predicting survival specifically after postsurgical recurrence.

OBJECTIVE: We aimed to identify factors affecting the survival of the patients with recurrent colon cancer and to construct a nomogram for predicting their survival.

DESIGN: This was a retrospective study.

SETTINGS: This study used the Japanese Study Group for Postoperative Follow-Up of Colorectal Cancer database, which contains retrospectively collected data of all consecutive patients with stage I to III colorectal cancer who underwent surgical curative resection between 1997 and 2008 at 23 referral institutions.

PATIENTS: A total of 2563 patients with stage I to III colon cancer who experienced recurrence after surgery were included in the present study.

MAIN OUTCOME MEASURES: A nomogram predicting survival was constructed using a training cohort composed of patients from 15 hospitals (n = 1721) using a Cox regression hazard model analysis. The clinical applicability of this nomogram was validated in patients from the 8 remaining hospitals (the validation cohort; n = 842).

RESULTS: Eight factors (age, location of the primary tumor, histopathological type, positive lymph node status, presence of peritoneal metastasis, number of organs involved in the first recurrence, treatment for recurrence, and the interval between initial surgery and recurrence) were identified as nomogram variables. Our nomogram showed good calibration, with concordance indexes of 0.744 in the training cohort and 0.730 in the validation cohort. The survival curves stratified by the risk score calculated by the nomogram were almost identical for the training and validation cohorts.

LIMITATIONS: The study was conducted using the data until 2008, and more advanced chemotherapeutic agents and multidisciplinary therapies that might have improved the outcomes predicted by our nomogram were not available. In addition, treatment strategies for recurrence might differ between countries.

CONCLUSIONS: Our nomogram, which is based on a nationwide multicenter study, is the first statistical model predicting survival after recurrence in patients with stage I to III colon cancer. It promises to be of use in postoperative colon cancer surveillance. See **Video Abstract** at http://links.lww.com/DCR/A687.

KEY WORDS: Colon cancer; Nomogram; Prognosis; Recurrence.

Colorectal cancer is one of the most common cancers in the world,[1] and numerous studies have investigated the factors affecting its recurrence after surgery, as well as the ensuing overall survival rate.[2] Postsurgical prognostic models for colorectal cancer have also

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been developed.[3–5] However, relatively little research has been performed on the risk factors affecting survival after the postoperative recurrence of colon cancer, although it is a major issue. Several risk factors have been reported for particular types of recurrence, particularly for patients with resectable metastases. In surgically resectable liver metastases, the primary histology, number of metastatic lymph nodes, and number of hepatic tumors have been reported to be prognostic factors,[6] and the interval between primary surgery and the development of metastasis, number of metastases, and positive hilar and/or mediastinal lymph nodes have been shown to correlate with survival after the resection of lung metastases.[7,8] Recently, Akiyoshi et al[9] reported several risk factors for locoregional recurrence postsalvage surgery, including the margin status, number of locoregional recurrent tumors, and pathological grade.[10] However, these data from previous studies are only applicable to patients who were eligible for surgical resection, and no risk model predicting the general survival of patients who experience any recurrences, regardless of their resectability, has been proposed to date.

In recent years, nomograms have gained increased attention as strong prognostic statistical models with user-friendly interfaces. Since the first report of the clinical application of a nomogram by Henderson,[11] nomograms have been developed for a variety of malignancies, including those of the prostate,[12] bile duct,[13] and stomach,[14] and have been reported to improve prognostic accuracy by combining all of the independent prognostic factors and quantifying their risks.[12–14]

In the present multicenter study, we collected data of patients with stage I to III colon cancer from 23 referral hospitals in Japan and focused on the patients whose recurrences were detected during the surveillance period. With this nationwide study, we first aimed to identify factors that could affect the survival of patients with recurrent colon cancer. Next, we aimed to construct a prognostic nomogram for predicting the survival of these patients using data from 15 hospitals and to validate the clinical applicability of the nomogram using data from the remaining 8 hospitals.

PATIENTS AND METHODS

Patients

This study used the Japanese Study Group for Postoperative Follow-Up of Colorectal Cancer database, which contains retrospectively collected data from all consecutive patients with stage I to III colorectal cancer who underwent surgical curative resection between January 1997 and December 2008 at 23 affiliated referral institutions (see Acknowledgments). Of the 24,864 patients registered in the database, 2563 patients with colon adenocarcinoma who experienced recurrence during the postoperative surveillance period were included in the present study (Fig. 1). We defined *colon* as the large bowel from the cecum to the rectosigmoid colon. The bowel proximal to the splenic flexure was defined as the *right side*, and that distal to the splenic flexure was defined as the *left side*. The histopathological type of adenocarcinoma was divided into 2 groups, that is, well- or moderately differentiated and other types, such as mucinous adenocarcinoma, papillary adenocarcinoma, poorly differentiated adenocarcinoma, or signet ring cell adenocarcinoma. Data of the dominant (clinically more advanced) cancer were collected if the patient presented with multiple colon cancers simultaneously.

The 23 hospitals that participated in the study were randomly assigned to 2 groups with a 2:1 ratio. The train-

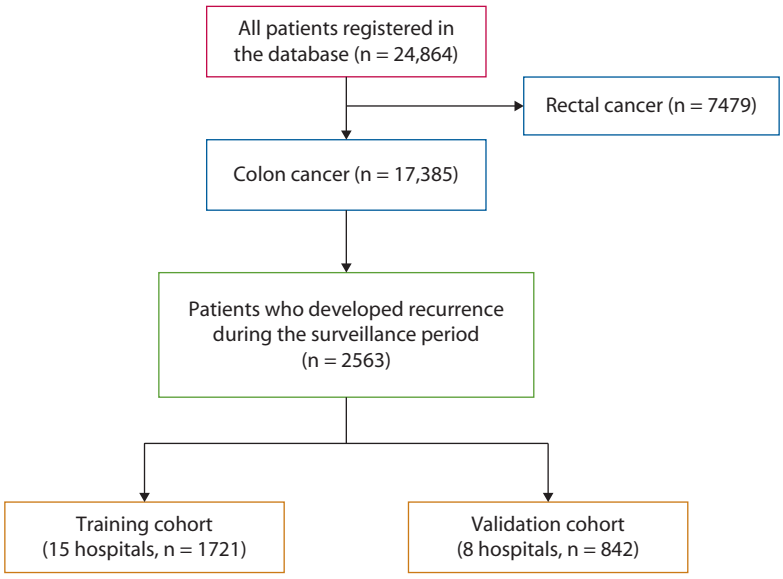


FIGURE 1. Flow diagram of the present study.

ing cohort included patients from 15 hospitals (n = 1721), whereas the validation cohort was composed of patients from 8 hospitals (n = 842). A nomogram was constructed using all of the variables included in the training cohort data, except for the presence of synchronous primary malignancy in other organs because of the excessive number of missing data in this variable and the consequent unsuitability for statistical analysis. The constructed nomogram was then validated in the smaller cohort. Patients were encouraged to undergo intensive postoperative surveillance for ≥5 years, which consisted of CEA and CA19-9 measurement every 3 months, chest and abdominal CT every 6 months, and colonoscopy every year. Patients who developed recurrence during the surveillance were retrospectively enrolled. The number of organs involved at the first recurrence was defined as the number of metastatic organs. The study protocol was approved by the local research ethics committees.

Statistical Analysis and Nomogram Construction

Differences between the training and validation groups were evaluated using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables. The Kaplan–Meier method was used to estimate survival after recurrence, and the log-rank test was used to analyze differences in survival between the groups. Variables with p values <0.05 on univariate analyses were subjected to multivariate Cox proportional hazards analyses; variables with p values <0.05 on multivariate analysis were incorporated into nomograms that were constructed using the methods of Wang et al[15] to predict the 2- and 3-year survival rates after recurrence.

Our nomograms were subjected to 200 bootstrap resamples to calculate the estimated Harrell concordance index (C-index) values, which are indicators of model performance.[16] The C-index estimates the probability of concordance between predicted and observed outcomes in rank order and is equivalent to the area under the receiver–operator characteristic curve (assuming there are no censored cases).[16] In this study, the C-index represents the ability of the model to discriminate between patients who survived versus those who did not. Higher values indicate better discrimination; a value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates a perfect separation of patients with different outcomes.

We also constructed calibration curves, or graphic representations of the relationships between the observed outcome frequencies and the predicted probabilities, for both the training and validation groups. Moreover, both of these groups were stratified into 3 subgroups according to the predictive score (<100, 100–180, and >180), and the actual survival curves were compared in each stratified group. All of the statistical analyses were performed using the statistical software program JMP 11.0 (SAS Institute, Inc, Cary, NC), and R 3.0.1 with the rms and Hmisc packages (R Project for Statistical Computing, Vienna, Austria, www.r-project.org).

RESULTS

The general characteristics of patients included in the study are presented in Table 1. Although the characteristics of the patients in the training and validation cohorts were not identical, the 3-year survival rate after recurrence was 51.4% in the training cohort and 53.1% in the validation cohort, showing similar prognoses. The most frequent site of recurrence was the liver, followed by the lung and peritoneum.

Predictive Factors for Survival After Recurrence

The results of the univariate and multivariate analyses of the associations between variables and postrecurrence survival are shown in Table 2. Based on these results, the following 8 variables were chosen as predictors of shorter survival: age ≥60 years, primary cancer location on the right side of the colon, histological type other than well- or moderately differentiated adenocarcinoma, lymph node metastasis (N ≥ 1), presence of peritoneal metastasis, recurrence in ≥2 organs, surgically unresectable recurrence, and an interval between initial surgery and recurrence of >2 years. Although most variables related to the primary tumor, including T stage and lymphatic or venous invasion, were strongly predictive of shorter survival in univariate analysis, only histological type and positive lymph node status were independent factors correlating with survival in multivariate analysis.

Figure 2 shows the correlations between variables and survival rates after recurrence. The survival rates were lower in patients >70 years of age. Moreover, the prognoses of N0-stage patients were significantly better than those of other populations, whereas those of N2b-stage patients were significantly worse; however, patients with N1a/b/c and N2a disease exhibited similar survival rates. Therefore, we stratified the N stage into 3 groups to simplify the nomogram: N0, N1/2a, and N2b. As shown in Figure 2, patients who underwent surgical resection of metastasis with curative intent showed markedly better prognoses. The median survival time of patients who received only palliative therapy or best supportive care was 1.14 years, that of patients who underwent systemic chemotherapy was 2.02 years (10.6 months longer), and that of patients who underwent local treatment of metastasis via a modality other than surgical resection (eg, radiofrequency ablation) was 2.22 years, producing an additional 2.4 months of survival. However, the 5-year survival rates in these 3 populations were 16.1%, 13.4%, and 22.5%; hence, the benefits of these treatments on survival time were smaller than those of surgical resection with curative intent. We analyzed chemotherapy and local treatment together to

TABLE 1. Patient characteristics

Variables	*Training cohort*	*Validation cohort*	*p*
No. of patients	1721	842	
Men, n (%)	1041 (60.5)	497 (59.0)	0.4782
Age, mean ± SD, y	65.8 ± 11.3	65.1 ± 11.1	0.1389
Primary lesion-related variables, n (%)			
Right-sided colon	625 (36.3)	306 (36.3)	0.9898
Well or moderately differentiated adenocarcinoma	1590 (92.4)	779 (92.5)	0.9071
T stage, n (%)			0.0199
1	56 (3.3)	23 (2.8)	
2	82 (4.8)	45 (5.4)	
3	870 (50.6)	438 (52.7)	
4a	572 (33.3)	233 (28.0)	
4b	139 (8.1)	92 (11.1)	
Lymphatic invasion positive, n (%)	1306 (76.4)	687 (83.5)	<0.0001
Venous invasion positive, n (%)	1204 (70.8)	683 (83.3)	<0.0001
N stage, n (%)			0.0986
0	586 (34.3)	274 (33.6)	
1a	345 (20.2)	140 (17.2)	
1b/c	371 (21.7)	171 (21.0)	
2a	222 (13.0)	132 (16.2)	
2b	183 (10.7)	99 (12.1)	
Adjuvant chemotherapy after initial surgery, n (%)	601 (34.9)	357 (42.4)	0.0003
Recurrence-related variables, n (%)			
Liver metastasis	772 (44.9)	383 (45.5)	0.7636
Lung metastasis	505 (29.3)	228 (27.1)	0.2320
Peritoneal metastasis	227 (13.2)	128 (15.2)	0.1689
No. of metastatic organs, n (%)			0.2186
1	1379 (81.7)	652 (78.8)	
2	255 (15.1)	137 (16.6)	
≥3	54 (3.2)	38 (4.6)	
Treatment for recurrence			0.0003
Surgical resection	702 (40.8)	412 (49.0)	
Other therapeutic treatments[a]	640 (37.2)	282 (33.5)	
Palliative therapy or best supportive care	379 (22.0)	147 (17.5)	
Interval between initial surgery and recurrence, mean ± SD, y	1.64 ± 1.37	1.73 ± 1.54	0.1324
Median follow-up time, y[b]	4.30	5.21	
Two-year survival after recurrence, %	63.1%	67.1%	
Three-year survival after recurrence, %	51.4%	53.1%	

[a]This category included systemic chemotherapy and local treatments for metastasis such as chemotherapy with hepatic arterial infusion, radiotherapy, chemoradiotherapy, and radiofrequency ablation.
[b]Data show the median follow-up time after recurrence of those who survived until the end of the surveillance period.

simplify the nomogram, because only a small proportion of patients underwent local treatment (5.3%) and categorized the treatments for recurrence into 3 subgroups: surgical resection, palliative therapy or best supportive care, and other therapeutic treatments.

Nomogram Construction and Validation

The nomogram was constructed using variable point scales (Fig. 3), and the sum of each variable point was plotted on the total point axis. The estimated median 3-year survival rates were obtained by drawing a vertical line from the plotted total point axis straight down to the outcome axis. The C-index of this model was 0.744, indicating good discrimination. Figure 4A shows the calibration graph for the nomogram wherein the predicted 3-year survival rate is plotted against the corresponding observed survival rates that were calculated using the Kaplan–Meier method. This comparison indicates that the nomogram is well calibrated.

We next conducted a validation test for the nomogram. The C-index of the validation cohort was 0.730, and good calibration was observed (Fig. 4B). These data showed that the constructed nomograms were sufficiently predictive in the validation patient group. Furthermore, we stratified the validation group into 3 subgroups according to the nomogram-predicted score and compared the survival curves of the training and validation groups within each subgroup. Cutoff values were determined to make the 3-year survival after recurrence >70% in the low-risk group and <30% in the high-risk group, considering that the 3-year survival of all patients was ≈50% (Table 1). As shown in Figures 4 and 5, the prognoses were almost identical between the cohorts in each subgroup.

TABLE 2. A multivariate analysis of survival after recurrence in the derivation group

Variables	Univariate analysis, p	Multivariate analysis		
		HR	95% CI	p
Sex (men vs women)	0.4186			
Age (<60 vs ≥60 u)	0.0014	1.17	1.01–1.35	0.0339
Cancer location (left side vs right side)	<0.0001	1.35	1.18–1.55	<0.0001
Histological type of adenocarcinoma (differentiated vs other)	<0.0001	1.08	0.94–1.23	0.2942
Depth of invasion (T1/2/3 vs T4)	<0.0001	1.08	0.94–1.23	0.2942
Lymphatic invasion (absent vs present)	<0.0001	1.13	0.96–1.34	0.1544
Venous invasion (absent vs present)	<0.0001	1.08	0.93–1.26	0.3201
Lymph node metastasis (N0 vs N ≥1)	<0.0001	1.30	1.18–1.51	0.0006
Adjuvant chemotherapy after initial surgery (absent vs present)	0.5802			
Recurrence-related variables				
Liver metastasis (absent vs present)	0.0423	1.04	0.91–1.20	0.5594
Lung metastasis (absent vs present)	0.2776			
Peritoneal metastasis (absent vs present)	<0.0001	1.55	1.31–1.83	0.0025
No. of recurrent organs (1 vs ≥2)	<0.0001	1.55	1.31–1.83	<0.0001
Treatment for the recurrence (surgical resection vs other treatment)	<0.0001	0.27	0.23–0.31	<0.0001
Interval between initial surgery and recurrence (<2 vs ≥2 y)	<0.0001	0.77	0.66–0.90	<0.0001

DISCUSSION

Eight variables were found to be pivotal factors determining the outcome of recurrence. As shown in Figure 2, older patients had shorter survival times than their younger counterparts. The prognostic impact of age remains controversial; some studies found that younger age was a poor prognostic factor,[17] whereas others demonstrated that the prognoses of young patients were similar to those of older patients or even more favorable.[18,19] One reason for the poor survival of elderly patients could be attributed to the increased rates of cancer-unrelated death; however, 90.7% of deaths in the training cohort of our study were related to primary cancer progression, and 85.4% of those in the validation cohort were also cancer related. Therefore, the shorter survival times after recurrence among the elderly population were primarily attributable to the aggressiveness of the recurrent disease or a decrease in radical therapy options (eg, radical surgical resection or intensive chemotherapy) for patients with recurrence.

We found that patient survival times after recurrence in the right side of the colon were shorter than for those after recurrence in the left side. Recent studies showed poorer prognoses in patients with right-side colon tumors even after background adjustment, which is possibly because of the difference in malignant potential.[20,21] Our study showed that the poorer prognoses in patients with cancers located on the right side of the colon were also true for recurrent tumors. These findings might be explained by the reported differences in the molecular and cellular features of right-side tumors, such as microsatellite instability or CpG island methylation.[22,23]

Two other factors related to the primary cancer were found to correlate with survival after recurrence. One was a high tumor grade, which also reflects the malignant potential of the tumor, and the other was the extent of lymph node metastasis, which is indicative of the degree of cancer progression. Both of these variables have been reported to be possible prognostic factors in liver or lung metastasis.[24–26] Interestingly, a history of adjuvant chemotherapy after primary surgery showed no effect on survival once a patient developed recurrence, although the benefit of adjuvant chemotherapy on overall survival has been well established.[27,28] Recurrent disease without adjuvant chemotherapy after initial surgery should be chemotherapy naïve, whereas recurrence that develops after adjuvant chemotherapy could be chemotherapy resistant, resulting in a poorer prognosis after recurrence. On the other hand, adjuvant chemotherapy might prevent not only recurrence but also tumor progression after recurrence, resulting in a better prognosis after recurrence. Therefore, adjuvant chemotherapy could affect the survival after recurrence either favorably or unfavorably. However, as we demonstrated in this study, it did not actually affect survival once the patient experienced recurrence.

Two variables related to the status of recurrence were revealed by multivariate analysis; these were peritoneal metastasis and metastasis in multiple organs. We reported previously that these 2 factors were also indicative of a poor prognosis in patients with stage IV colorectal cancer who underwent R0 resection.[29] Because stage IV cancer can be considered analogous to synchronous recurrence of stage I to III cancer, these factors affected survival in both situations. The remaining variables incorporated into the nomogram were treatment for metastasis and the interval between the resection of the primary tumor and detection of recurrence. Although complete resection of the metastatic lesion is generally recognized as the only potentially curative treatment and is therefore most desirable (especially for liver metastasis),[30] only a few studies have directly compared the outcomes of surgical resec-

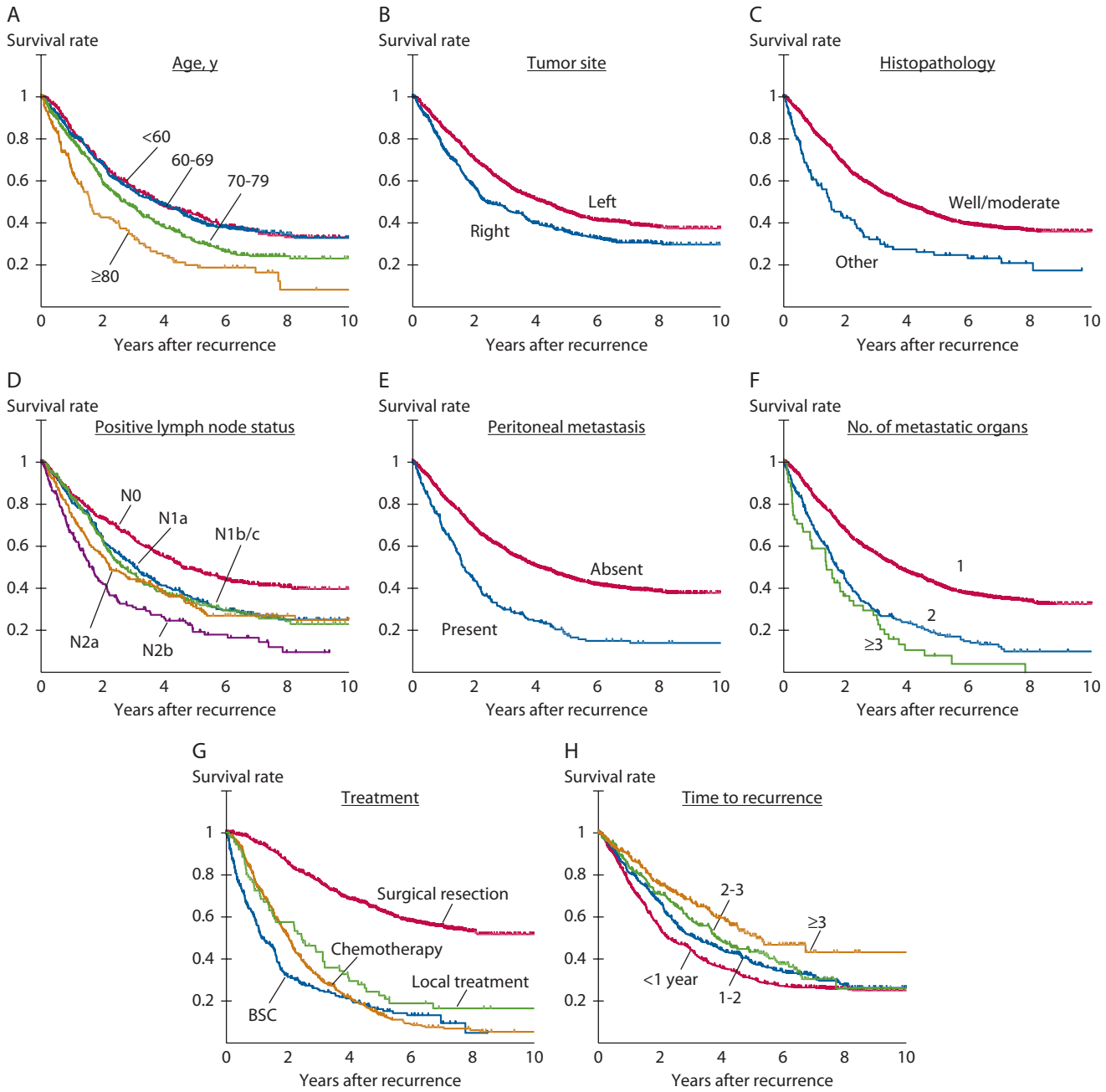


FIGURE 2. Factors affecting survival after recurrence. Survival curves in the training cohort are presented. Each of the factors affected the survival after recurrence on multivariate analysis. A, Age, red line: <60 years; blue line: 60–69 years; green line: 70–79 years; gold line: ≥80 years. B, Location of the initial colon cancer, red line: left-sided colon; blue line: right-sided colon. C, Histopathological type of cancer, red line: well- or poorly differentiated adenocarcinoma; blue line, other histological types of cancer. D, Positive lymph node status, red line: N0; blue line: N1a; green line: N1b/c; gold line: N2a; purple line: N2b. E, Peritoneal metastasis at the time of recurrence, red line: absent; blue line: present. F, Number of metastatic organs, red line: 1; blue line: 2; green line: ≥3. G, Treatment of metastasis, red line: surgical resection with curative intent; blue line: palliative therapy or best supportive care (BSC); gold line: systemic chemotherapy; green line: local treatment with or without systemic chemotherapy, such as chemotherapy via hepatic arterial infusion, radiotherapy, chemoradiotherapy, or radiofrequency ablation. H, Interval between surgery for primary cancer and identification of recurrence, red line: <1 year; blue line: 1–2 years; green line: 2–3 years; gold line: ≥3 years.

tion of metastasis with those of other therapeutic treatments.[31] We found that the 5-year survival of patients who underwent resection of metastasis was 63.0%, which was considerably higher than for those who did not undergo resection. Although chemotherapy prolonged survival, its benefit was not appreciable by 4 years postrecurrence. The interval between surgery and recurrence was also found to be an important prognostic factor, which was consistent with several previous studies of outcomes after hepatectomy or lung resection for metastasis.[32,33]

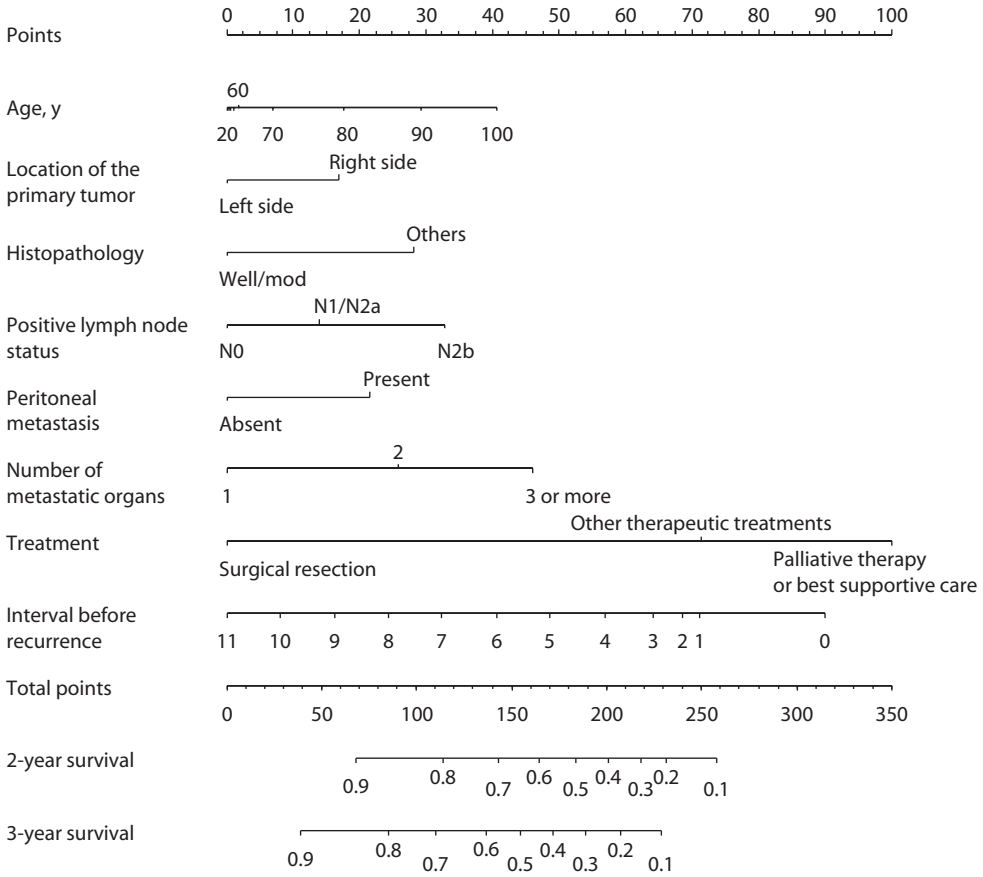


FIGURE 3. Nomograms for predicting survival after recurrence of stage I to III colon cancer. The 2-year and 3-year probabilities of survival after recurrence were estimated by summing the scores of each variable. Well/mod: well- or moderately differentiated adenocarcinoma.

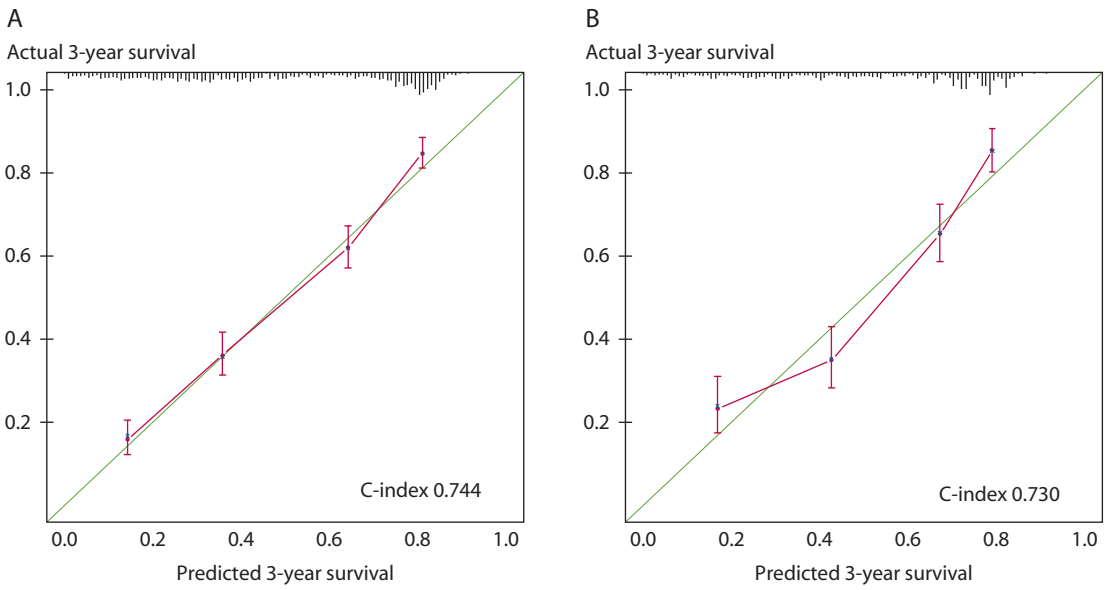
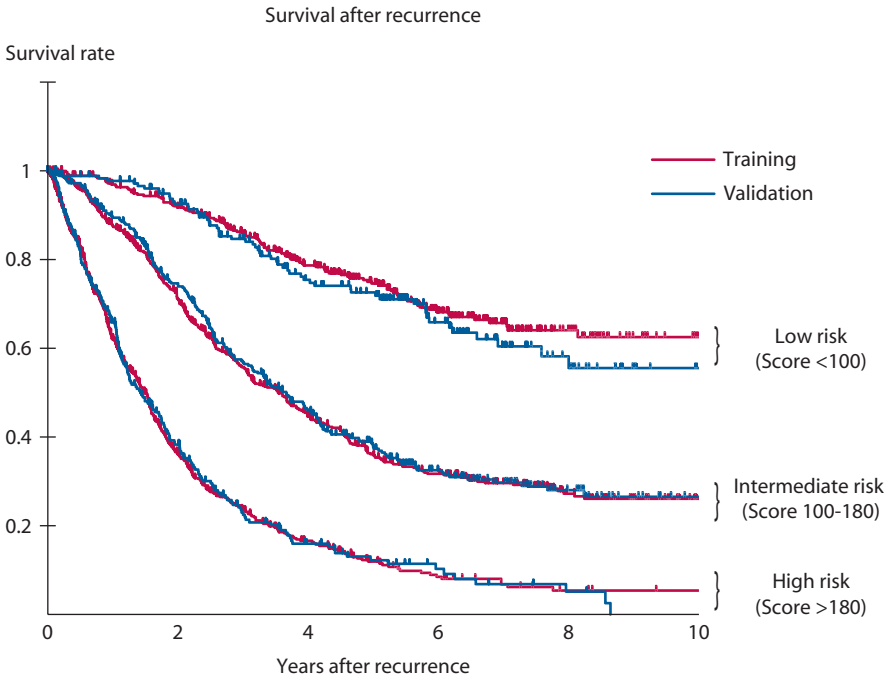


FIGURE 4. Calibration of nomograms in the training (A) and validation (B) cohorts. The horizontal axes display the nomogram-predicted probabilities of survival after recurrence at 3 years, whereas the vertical axes display the actual survival rates estimated at 3 years using the Kaplan–Meier method. The diagonal line from the lower left to the upper right corner of the plot area is a reference line indicating the ideal prediction. Bars indicate 95% CIs.



Number at risk

Training cohort						
Low	365	312	225	130	51	11
Intermediate	585	367	199	118	47	15
High	641	169	58	19	6	3
Validation cohort						
Low	182	158	109	60	22	3
Intermediate	331	226	127	64	26	5
High	244	78	24	9	3	-

FIGURE 5. Survival curves stratified by the score calculated by the nomogram in the training (A) and the validation (B) cohorts. Each of the cohorts was stratified according to the risk score as follows: <100, low risk; 100–180, intermediate risk; and <180, high risk.

In recent years, many nomograms designed to predict the prognosis of colorectal cancer have been developed at an accelerated pace, possibly owing to its high utility in daily clinical practice. Nomograms predicting the prognosis of stage I–III colon and/or rectal cancer[3–5]and of stage IV colorectal cancer,[29] as well as survival after hepatectomy for liver metastasis[32] and pulmonary resection for lung metastasis,[7] have been published. In addition, nomograms that predict short-term events, such as postoperative complications, have also been proposed.[34,35] Reported C-indexes, which are indicative of the predictive accuracy of nomograms, were comparatively high for stage I to III colorectal cancer nomograms (0.70–0.80), because risk factors predicting the outcomes of these patients have been well established. Conversely, most C-indexes of nomograms constructed for metastatic diseases were <0.70, showing relatively low predictive accuracy; this was likely because of the wide range of disease statuses that the nomograms were expected to predict. The C-indexes of our nomogram were 0.744 in the training cohort and 0.730 in the validation cohort, indicating good predictability compared with pre-existing nomograms considering that it covered a wide variety of metastatic conditions, from single small liver metastasis to disseminated lesions in multiple organs. Although the patient backgrounds between the training and validation cohorts were not identical, both the survival curves of the training and validation cohorts were very similar when stratified by the nomogram risk score, indicating that the nomogram was universally applicable, regardless of the differences in patient backgrounds.

This study had 2 aims. One was the identification of factors affecting survival after recurrence, which has not been fully investigated. From the results of the present study, some of the factors associated with primary cancer, such as N stage or tumor location, correlated with the prognosis after recurrence. In contrast, other factors that are usually considered to be prognostic factors, such as T stage or adjuvant therapy, showed no correlation with

survival once the recurrence developed; this is possibly because of the high collinearity between these variables. Instead, several recurrence-related factors, such as peritoneal metastasis or the number of recurrent organs, were found to be strong factors affecting survival after recurrence. The other aim was to construct a tool predicting survival after recurrence, which is a priority for patients. Although the nomogram might not be directly useful in the determination of therapeutic options, the calculated probability of survival is helpful for both doctors and patients with recurrence, because the care of patients with recurrence is becoming increasingly recognized as a vital component of cancer care.[36]

Our study had limitations; it was conducted using the data of patients who underwent surgery for primary colon cancer between 1997 and 2008 to ensure a sufficient surveillance period for the development of recurrence and the calculation of postrecurrence survival. Therefore, more advanced chemotherapeutic agents and multidisciplinary therapies that might have improved the outcomes predicted by our nomogram were not available. The improvement in these therapeutic options could also have widened the indication for surgical resection with curative intent as the conversion therapy.[37] Furthermore, precision medicine using biomarkers, such as microsatellite instability status, Ras mutations, or consensus molecular subtypes, has been increasingly focused in recent years[38]; however, these markers were not available from our database. Furthermore, the detailed surgical treatment information for recurrence was also unavailable, such as cytoreductive surgery for peritoneal disease or laparoscopic or open surgery. There were a number of censored cases in the database that could have impaired the accuracy of the nomogram. In addition, treatment strategies for recurrence might differ between countries. For example, the presence of peritoneal metastasis was one of the critical prognostic factors in our nomogram. In Japan, hyperthermic intraperitoneal chemotherapy is rarely performed for peritoneal recurrence, whereas it is one of the standard treatments in Western countries.[39] Additional validation of our nomogram in Western countries is therefore desired.

CONCLUSION

Our nomogram is a well-validated, world-first statistical tool to predict survival after recurrence in patients with stage I to III colon cancer and is based on a nationwide multicenter study. This nomogram will greatly assist physicians and patients with treatment planning for postrecurrence therapy.

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