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Prognostic Prediction Models for Colorectal Cancer Patients After Curative Resection

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To develop a prediction tool for recurrence and survival in colorectal cancer (CRC) patients following surgically curative resections. We developed a reliable prediction model for CRC patients after surgically curative resections. Using clinicopathologic factors, novel prediction models were constructed with the area under the curve (AUC) of 0.841 and 0.876 for DFS and CSS, respectively. Between January 2004 and December 2007, 376 CRC patients were investigated at the Osaka Medical Center for Cancer and Cardiovascular Diseases. Patients with at least 1 of the following criteria were excluded: preoperative treatment, synchronous distant metastasis, noncurative resection, and incomplete follow-up after operation. All patients were retrospectively analyzed. A Cox proportional hazards model was used to develop a prediction model for disease-free survival (DFS) and cancer-specific survival (CSS). In univariate and multivariate analyses of clinicopathologic factors, the following factors had significant correlation with DFS and CSS: tumor location, preoperative serum carcinoembryonic antigen (CEA), pathologically defined tumor invasion, and lymph node metastasis. Using these variables, novel prediction models were constructed by the logistic regression model with AUC of 0.840 and 0.876 for DFS and CSS, respectively. The prediction models were validated by external datasets in an independent patient group. This study showed novel and reliable personalized prognostic models, integrating not only TNM factors but also tumor location and preoperative serum CEA to predict patient prognosis. These individualized prediction models could help clinicians in the treatment of postoperative CRC patients.

Key words: Prediction tool – Colorectal cancer – Metastasis – Survival

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In developed countries with an ever-increasing aging population, cancer is one of the most prominent illnesses in terms of both public welfare and health measures. Colorectal cancer (CRC) is a frequent malignancy and one of the leading causes of cancer-related deaths.[1] The metastatic dissemination of the primary tumors directly relates to patient survival, and distant metastases are a major cause of death in CRC. Systemic chemotherapy is the standard approach to treat metastatic CRC, and the last decade showed remarkable progress in therapies for CRC. Many new drugs are currently in use for metastatic CRC, and the average median survival duration has increased in recent years largely due to the availability of new active agents, such as irinotecan, oxaliplatin, cetuximab, and bevacizumab.[2–4] Although many patients with metastatic CRC are hard to be cured, a subset of patients with liver- or lung-isolated disease have been reported to be potentially curable with surgery.[5,6]

Development of a prognostic prediction model is important for the determination of the necessity for intensive follow-up and adjuvant therapy. By predicting recurrence and metastases, such a model could lead to adequate treatment of CRC after curative surgical resection.[7,8] The TNM stage system from the Union for International Cancer Control (UICC) is a reliable prognostic system for CRC patients at all stages.[9] However, even TNM staging does not consolidate demographic features, tumor characteristics, and other histopathologic features to predict recurrences and survival. Therefore, development of a model for the prediction of individual outcomes would be a useful tool in this age of personalized medicine.

To develop such a model for the prediction of cancer metastasis and overall survival, we constructed a prediction tool for the recurrence and survival of CRC patients after surgically curative resections. Development of this tool is based on a statistically calculated formula constructed from potential prognostic factors, providing a prediction probability for individual outcomes that will benefit patients to select treatment choices.

Patients and Methods

Between January 2004 and December 2007, 376 patients were identified with a diagnosis of CRC after surgical resection at Osaka Medical Center for Cancer and Cardiovascular Diseases. All of these patients had histologically confirmed CRC and received curative resection for primary lesions. Patients with at least 1 of the following criteria were excluded: preoperative treatment, synchronous distant metastasis, noncurative resection, and incomplete follow-up after operation. This study was approved by the institutional review board of Osaka Medical Centre for Cancer and Cardiovascular Diseases. The patient records were anonymized prior to the analysis.

Surgical specimens were fixed in formalin, processed through graded ethanol, and embedded in paraffin. The sections were stained with hematoxylin and eosin and Elastica van Gieson stain, and the degree of histologic grade, lymphatic invasion, and venous invasion were examined. Data on age; sex; primary tumor site (rectum or colon group); pathologic finding (histologic grade, tumor invasiveness, lymph node metastases, lymphatic invasion, and venous invasion); and perioperative chemotherapy were retrieved from patient medical records for evaluation. Preoperative determination of the extent of tumor spread was done using X-ray, CT, MRI, and/or positron emission tomography. Intraoperative findings contributed to the determination of metastatic tumor involvement. After surgery, all patients had follow-up blood examinations assessing the tumor markers that are serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), and further imaging with abdominal ultrasonography, CT, chest X-ray, and/or PET every 3 to 6 months. Postoperatively, patients received chemotherapy following informed consent; these adjuvant therapies were performed following the Japanese guidelines.[10] Clinicopathologic factors were assessed according to the tumor node metastasis (TNM) classification of the UICC.[9] The primary and secondary endpoints of the study were the disease-free survival (DFS) and cancer-specific survival (CSS) time.

Kaplan–Meier survival curves were plotted and compared with the generalized log-rank test. Univariate and multivariate analyses were performed using a Cox regression model for DFS and CSS that were counted after primary curative resection, to identify independent factors. Two-sided P values $<$ 0.05 were considered statistically significant.

The logistic regression model was utilized to develop the prediction model for DFS and CSS. An independent patient group of consecutive 93 patients who underwent curative operation for stages I through III CRC between January and December 2008 were selected for the validation of the prediction model. Each prediction model was validated by following 2 procedures: an internal

validation using the study patients from which the model was developed and external validation using these independent validation patients. In addition, the area under the curve (AUC) was calculated for each. All statistical analyses were performed using R software, version 3.1.1.[11]

Results

Patient characteristics are listed in Table 1. Patient age ranged from 29 to 87 years (mean age = 62.9 years) and 221 patients (58.8%) were male. Primary tumors were located in the rectum (179 patients, 47.6%) or the colon (197 patients, 52.4%). Distant metastases were observed in 39 patients (10.4%) within 5 years of the operation, and the common sites of the first metastatic lesion after the operation were the lung (19 patients, 48.7%) and the liver (15 patients, 38.5%). Local recurrence was observed in 5 patients (1.3%). DFS and CSS curves were plotted in Figs. 1 and 2.

Table 2 provides the univariate and multivariate analyses of clinicopathologic factors related to patient DFS. In univariate analysis, the following factors were significantly correlated with DFS: tumor location [lower rectum and anal canal versus other locations; hazard ratio (HR) = 2.77; 95% confidence interval (CI) = 1.55 to 4.80, $P < 0.001$]; preoperative serum CEA (HR = 3.97, 95% CI = 2.29–7.09, $P < 0.001$); pathologically defined tumor invasion according to the TNM classification (HR = 6.25, 95% CI = 2.74–18.02, $P < 0.001$); lymph node metastasis (HR = 3.70, 95% CI = 2.12–6.70, $P < 0.001$); lymphatic invasion (HR = 2.50, 95% CI = 1.40–4.69, $P = 0.001$); and venous invasion (HR = 2.43, 95% CI = 1.36–4.65, $P = 0.003$). In multivariate analysis, the independent predictors of DFS were tumor location (HR = 3.30, 95% CI = 1.79–5.95, $P < 0.001$); CEA (HR = 3.33, 95% CI = 1.88–6.08, $P < 0.001$); tumor invasion (HR = 3.64, 95% CI = 1.46–11.05, $P = 0.004$); and lymph node metastasis (HR = 2.23, 95% CI = 1.19–4.35, $P = 0.012$).

Table 3 provides the univariate and multivariate analyses of the factors related to the CSS. The following factors were significantly correlated with CSS: tumor location (lower rectum and anal canal, HR = 4.22, 95% CI = 1.90–9.31, $P < 0.001$); CEA (HR = 4.60, 95% CI = 2.04–11.26, $P < 0.001$); pathologically defined tumor invasion (T3–T4, HR = 7.17, 95% CI = 2.12–44.69, $P < 0.001$); lymph node metastasis (HR = 4.65, 95% CI = 2.02–11.95, $P < 0.001$); and venous invasion (HR = 4.59, 95% CI = 1.75–15.74, $P = 0.001$). In multivariate analysis, independent predictors of CSS were: tumor location (HR = 5.14, 95% CI = 2.27–11.61, $P < 0.001$); CEA (HR = 4.43, 95% CI = 1.91–11.19, $P < 0.001$); tumor invasion (HR = 4.22, 95% CI = 1.08–28.03, $P = 0.037$); and lymph node metastasis (HR = 3.40, 95% CI = 1.29–9.88, $P = 0.012$).

To develop prediction models for DFS as well as CSS, all patients listed in Table 1 were included (n = 376). The events in the prediction models for DFS and CSS depended on identification of distant metastases and cancer-related deaths, respectively.

Table 1 Clinicopathologic factors of 376 colorectal cancer patients

Factors	n = 376
Age, y	62.9 (29–87)
Sex	
Male	221 (58.8%)
Female	155 (41.2%)
Primary colorectal tumor	
Rectum group	179 (47.6%)
Rectosigmoid	55
Upper rectum	57
Lower rectum	63
Anal canal	4
Colon group	197 (52.4%)
Cecum	18
Ascending	28
Transverse	31
Descending	21
Sigmoid	99
Histologic grade	
Wel	125 (33.2%)
Mod	230 (61.2%)
Por	9 (2.4%)
Muc	11 (2.9%)
Sig	1 (0.3%)
Tumor invasion	
T1	66 (17.6%)
T2	78 (20.4%)
T3	180 (47.9%)
T4a	43 (11.4%)
T4b	9 (2.4%)
Lymph node metastasis	
N0	242 (64.4%)
N1	93 (24.7%)
N2a	23 (6.1%)
N2b	14 (3.7%)
M1a[a] (Lat. LN)	4 (1.1%)
Lymphatic invasion	
Absent	182 (48.4%)
Present	194 (51.6%)
Venous invasion	
Absent	171 (45.5%)
Present	205 (54.5%)

Wel, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Por, poorly differentiated adenocarcinoma; Muc, mucinous adenocarcinoma; Sig, signet-ring cell carcinoma.

[a]M1a, lateral lymph node metastasis in rectal group.

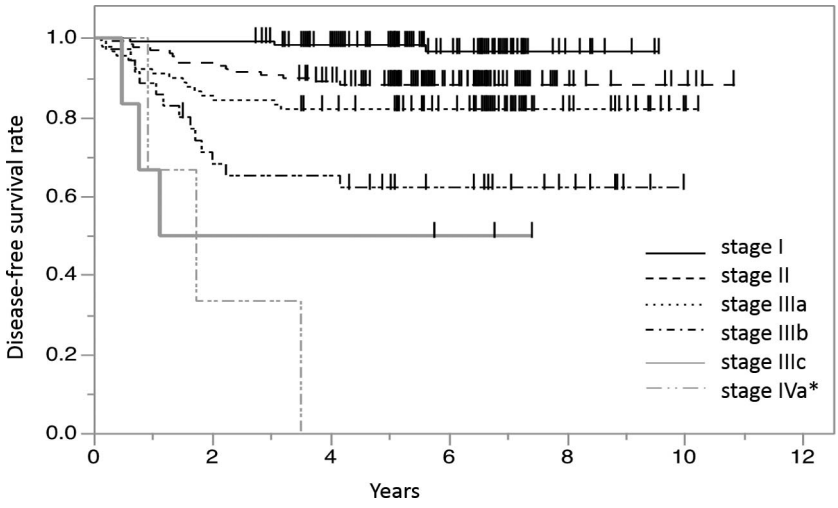

Fig. 1 DFS curves based on UICC staging of CRC patients after curative surgery. Kaplan–Meier plots show postoperative DFS curves for stages I, II, III, and IVa according to the TNM classification of UICC. All stage IVa were categorized by the diagnosis of lateral lymph node metastasis in rectal cancer.

The prediction models were constructed using the logistic regression model as follows: $P = 1/\{1 + \exp[-(b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_pX_p)]\}$.

Factors in prediction of DFS and CSS include preoperative serum CEA, tumor location, pathologically defined tumor invasion, and lymph node metastasis (Figs. 3 and 4, Tables 4 and 5). The predictive performance was evaluated by measuring the calibration comparing the prediction probability with actual survival in relation to DFS and CSS (Supplementary Figs. S1 and S2). Each prediction model was validated using the external dataset as an independent patient group (N = 93). For DFS, the area under the curve (AUC) was 0.840, and AUC in external validation was 0.819. For CSS, the c-index was 0.876, and the AUC was 0.843.

Discussion

CRC with distant metastases has a poor prognosis although several recent chemotherapeutic advances have helped the overall outcomes of advanced metastatic CRC.[12–15] Patients with localized metastases, such as liver or lung, can achieve long-term survival through curative resection of the metastatic lesions.[8,12] As such, models to predict the prognosis after curative surgical resection would be useful to determine the necessity of intensive follow-up to select adjuvant therapy. Although the choice of adjuvant chemotherapies was excluded from the analyses of the present study due to multicollinearity in relation to the lymph node metastatic statuses, clinicopathologic analysis revealed that the tumor

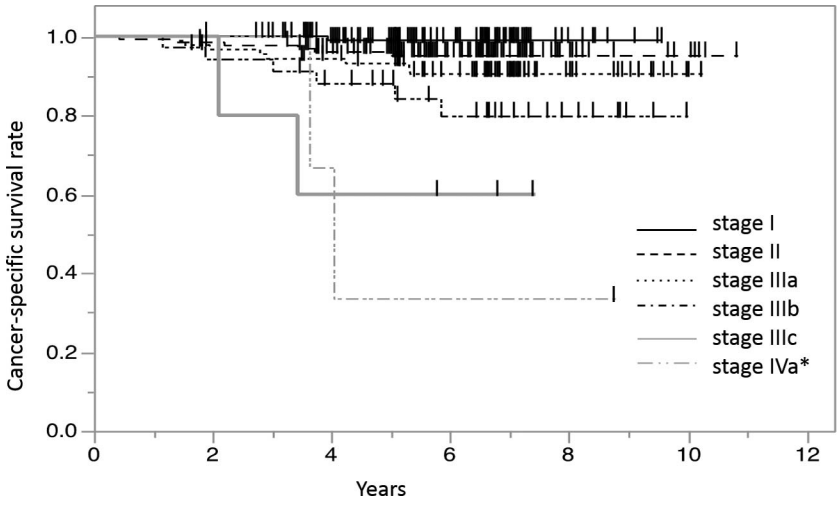

Fig. 2 Overall survival curves based on UICC staging of CRC patients after curative surgery. Kaplan–Meier survival plots show cancer-related survival curves for stages I, II, III, and IVa according to the TNM classification of UICC. Deaths due to causes not related to colorectal cancer were treated as censored observations. All stage IVa were categorized by the diagnosis of lateral lymph node metastasis in rectal cancer.

Table 2 Univariate and multivariate analyses for DFS (Cox proportional hazards regression model)

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥65/≤64)	1.00	0.58–1.72	0.986			
Sex (male/female)	1.05	0.61–1.85	0.856			
Tumor location (lower rectum and anal canal/others)	2.77	1.55–4.80	**<0.001**	3.30	1.79–5.95	**<0.001**
Histologic grade (others[a]/Wel–Mod)	1.82	0.63–4.16	0.238			
CEA (≥5/<5)	3.97	2.29–7.09	**<0.001**	3.33	1.88–6.08	**<0.001**
CA19-9 (≥37/<37)	2.10	0.99–4.00	0.052			
Tumor invasion (T3–T4/T1–T2)	6.25	2.74–18.02	**<0.001**	3.64	1.46–11.05	**0.004**
Lymph node metastasis (present/absent)	3.70	2.12–6.70	**<0.001**	2.23	1.19–4.35	**0.012**
Lymphatic invasion (present/absent)	2.50	1.40–4.69	**0.001**	1.16	0.61–2.30	0.661
Venous invasion (present/absent)	2.43	1.36–4.65	**0.003**	1.17	0.62–2.33	0.629

Values in boldface type indicate statistical significance.

[a]Poorly differentiated, mucinous adenocarcinoma, or signet-ring cell carcinoma.

Table 3 Univariate and multivariate analyses for CSS (Cox proportional hazards regression model)

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥65/≤64)	1.33	0.61–3.01	0.473			
Sex (female/male)	1.58	0.72–3.52	0.253			
Tumor location (lower rectum and anal canal/others)	4.22	1.90–9.31	**<0.001**	5.14	2.27–11.61	**<0.001**
Histologic grade (others[a]/Wel–Mod)	1.62	0.26–5.46	0.542			
CEA (≥5/<5)	4.60	2.04–11.26	**<0.001**	4.43	1.91–11.19	**<0.001**
CA19-9 (≥37/<37)	1.18	0.28–3.41	0.791			
Tumor invasion (T3–T4/T1–T2)	7.17	2.12–44.69	**<0.001**	4.22	1.08–28.03	**0.037**
Lymph node metastasis (present/absent)	4.65	2.02–11.95	**<0.001**	3.40	1.29–9.88	**0.012**
Lymphatic invasion (present/absent)	1.60	0.72–3.79	0.250			
Venous invasion (present/absent)	4.59	1.75–15.74	**0.001**	1.92	0.73–4.81	0.181

Values in boldface type indicate statistical significance.

[a]Poorly differentiated, mucinous adenocarcinoma, or signet-ring cell carcinoma.

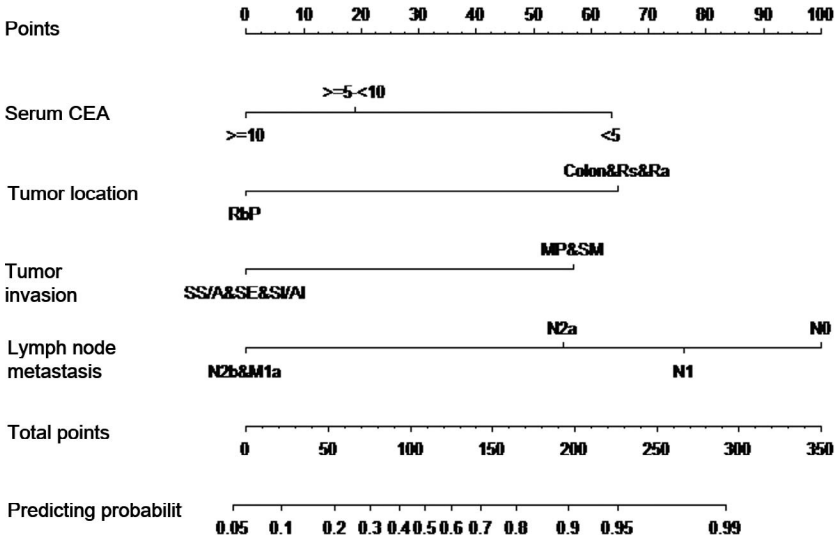

Fig. 3 Prediction model for DFS after curative surgical resection. The prediction model for DFS after curative surgical resection was constructed using the logistic regression model. Clinicopathologic factors utilized were the preoperative serum CEA level, tumor location, tumor invasion, and lymph node metastasis pathologically defined.

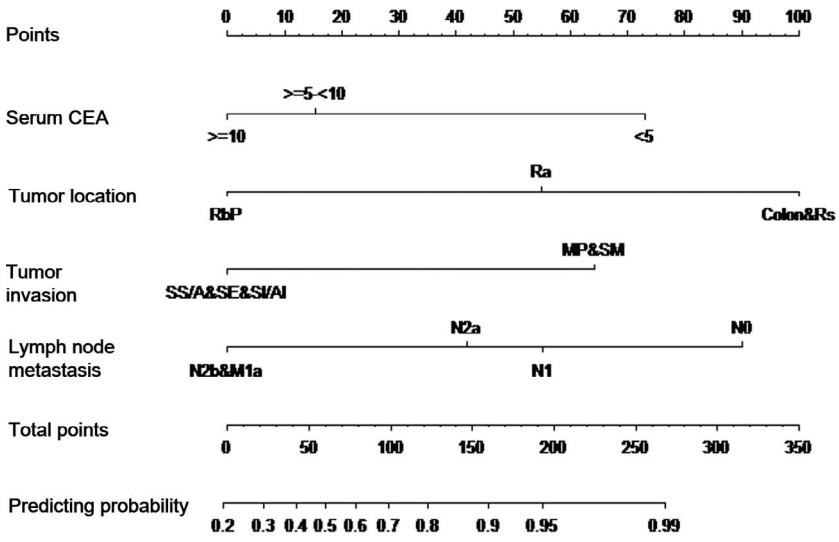

Fig. 4 Prediction model for CSS after curative surgical resection. The prediction model for CSS after curative surgical resection was constructed using the logistic regression model. Clinicopathologic factors utilized were the preoperative serum CEA level, tumor location, tumor invasion, and lymph node metastasis pathologically defined.

Table 4 Logistic regression model for DFS

Variables	Estimate	Ratio	95% CI	*P* value
(Intercept)	–4.425	83.529	27.795–251.019	**<0.001**
Tumor location				
Lower rectum and anal canal	–1.624	0.197	0.085–0.456	**<0.001**
CEA				
≥5, <10	–1.124	0.325	0.127–0.833	**0.019**
≥10	–1.599	0.202	0.089–0.459	**<0.001**
Tumor invasion				
T3–T4	–1.429	0.240	0.083–0.689	**0.008**
Lymph node metastasis				
N1	–0.599	0.549	0.248–1.216	0.146
N2a	–1.128	0.324	0.101–1.040	0.058
N2b and M1a[a]	–2.512	0.081	0.022–0.299	**<0.001**

Values in boldface type indicate statistical significance.

[a]M1a diagnosed for lateral lymph node metastasis in rectal cancer.

Table 5 Logistic regression model for CSS

Variables	Estimate	Ratio	95% CI	*P* value
(Intercept)	5.904	366.433	62.808–2137.841	**<0.001**
Tumor location				
Upper rectum	–0.997	0.369	0.110–1.234	0.106
Lower rectum and anal canal	–2.212	0.109	0.034–0.350	**<0.001**
CEA				
≥5, <10	–1.272	0.280	0.075–1.046	0.058
≥10	–1.614	0.199	0.064–0.620	**0.005**
Tumor invasion				
T3–T4	–1.419	0.242	0.048–1.225	0.086
Lymph node metastasis				
N1	–0.771	0.463	0.146–1.463	0.189
N2a	–1.065	0.345	0.069–1.722	0.194
N2b and M1a[a] (Lat. LN)	–1.990	0.137	0.031–0.602	**0.009**

Values in boldface type indicate statistical significance.

[a]M1a diagnosed for lateral lymph node metastasis.

location, preoperative serum CEA level, pathologically defined T factor (T3–T4), and metastatic status of the lymph nodes showed poor prognosis for both DFS and CSS. Regarding the location, tumors located in the lower rectum and anal canal showed worse prognosis than those located in other locations. Per Japanese guidelines, lateral lymph node dissection was performed for the primary rectal cancers located in the lower rectum and anal canal.[10] In this study, they were categorized as M1a according to the TNM classification of UICC.[9]

In CRC therapy, it is essential to prevent metachronous metastasis. Fluorouracil (FU) was the only effective chemotherapeutic drug for treatment until the mid-1990s. The therapeutic effect to FU is enhanced by modulation using leucovorin (LV).[16] The Intergroup-0035 (INT-0035) trial first demonstrated a significant benefit of adjuvant treatment in patients with stage III cancers.[17] FU and LV administration has since become standard adjuvant chemotherapy for stage III and high-risk stage II CRC.[18,19] Adjuvant chemotherapy is promising for CRC that is highly suspicious for metastasis after curative surgical resection. Furthermore, new active agents such as irinotecan, oxaliplatin, cetuximab, and bevacizumab, have been reported in use for distant-metastatic CRC.[3,4] The prognostic model reported to integrate demographic and clinicopathological factors to provide for postoperative treatment in rectal cancer.[20] In our study, a novel and reliable personalized prognostic model integrates not only tumor invasion and lymph node metastasis, but also tumor location and preoperative serum CEA for predicting DFS and CSS of postoperative CRC patients.

In this study, CRC patients who underwent curative surgical resection after 2004 were investigated to develop the prediction model; this period was selected to minimize potential limitations, as detailed information could not be obtained from medical records prior to 2004, and treatment has changed over the past two decades. There are several limitations, as this study is a retrospective analysis, and preoperative treatment and synchronous distant metastasis were excluded because of multicollinearity in relation to the tumor location, tumor invasion, and lymph node metastatic statuses. However, we believe the models we have generated will provide a valuable tool to help physicians managing CRC patients after curative surgical resection. In addition to the recent advances in chemotherapy, this prediction model will contribute in selecting CRC patients who will require adjuvant therapies, resulting in a better outcome.

Conclusions

We have developed prognostic prediction models using multiple clinicopathologic factors beyond TNM staging to provide individualized prognostic outcomes. This model should help clinicians counsel patients on personalized treatments and follow-up.

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