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Nomograms Predicting Survival, Recurrence and Beneficiary Identification of Adjuvant Chemotherapy in Treatment-naïve Patients with Rectal Cancer who Underwent Upfront Curative Resection

A multi-institutional study

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Objective: To create and validate nomograms predicting overall survival and recurrence in treatment-naïve rectal cancer (RC) patients who underwent upfront surgery.

Background: Although multidisciplinary treatment is standard for locally advanced RC, understanding surgical efficacy is important for determining indications for perioperative adjuvant therapy.

Methods: RC patients who underwent upfront surgery at the Japanese Society for Cancer of the Colon and Rectum institutions were analyzed. A training cohort (n = 1925) of treatment-naïve patients who underwent surgery between 2007 and 2008 was analyzed to construct prognostic models predicting postoperative survival and recurrence. Discrimination and calibration were performed using an external validation cohort (n = 2957; Japanese colorectal cancer registry, procedures in 2005–2006). Effects of adjuvant chemotherapy on survival were evaluated based on nomogram prediction and Surveillance, Epidemiology, and End Results (SEER) data (n = 10,482; upfront surgery for RC in 2010–2015).

Results: In the training cohort, age predicted survival, venous invasion predicted recurrence, and sex, tumor location, histological type, preoperative carcinoembryonic antigen, invasion depth, lymphatic invasion, positive radial margin, and numbers of metastatic nodes and examined nodes predicted both. Internal and external validated Harrell's C-index values were respectively 0.77 and 0.75 for survival and 0.75 and 0.74 for recurrence. RC patients who underwent upfront surgery in the SEER database were stratified into 3 risk levels by nomogram score. Adjuvant chemotherapy did not improve 5-year survival in low-risk patients, but did so for middle-risk (62.4% *vs* 76.8%) and high-risk (39.4% *vs* 63.5%) patients.

Conclusion: These nomograms could predict survival and recurrence after upfront curative resection of RC and identify cases expected to benefit more from adjuvant chemotherapy.

INTRODUCTION

Colorectal cancer (CRC) is among the most prevalent malignancies and a major cause of cancer-related mortality worldwide.[1,2] Despite advances in prevention and detection, CRC is often diagnosed as a locally advanced disease. Neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection with total mesorectal excision (TME) is a standard treatment for locally advanced rectal cancer (LARC).[3,4] Radiotherapy reduces local recurrence but is associated with increased treatment-related adverse events.[5] Many patients do not receive neoadjuvant therapy because of adverse events and high costs, with 64.3% of patients with stage II/III rectal cancer (RC) not receiving nCRT.[6] Upfront surgery is an import treatment in the era of evolving treatment paradigms for LARC.[7]

In Japan, TME with lateral pelvic lymph node dissection (LPLND) without radiotherapy is standard for LARC with a lower margin below the peritoneal reflection.[8] The incidence of lateral pelvic lymph node (LN) metastasis from low RC is

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approximately 15%. The development of the extended LN dissection concept led to the addition of LPLND to TME to reduce local recurrence. To verify the efficacy of LPLND, the noninferiority trial JCOG0212[9] compared TME *versus* TME plus LPLND and failed to find noninferiority of TME alone. Furthermore, TME alone is associated with more frequent local recurrence, especially in the lateral pelvis, suggesting that local recurrence is more likely where LNs are not dissected. It was therefore concluded that TME plus LPLND is effective and should remain standard in Japan, where preoperative CRT is not routinely used.[9]

Surgical resection remains the primary treatment for resectable RC. In such cases, TME combined with adjuvant chemotherapy (ACT) may be an ideal treatment for patients with a higher risk of recurrence. Accurate risk stratification is important for identifying treatment candidates. The TNM anatomic tumor staging system is the current gold standard for risk assessment.[10] However, in patients without distant metastasis, the predictive accuracy of the T and N stages is limited because of their heterogeneous outcomes due to variability in clinicopathological features and tumor biology.[11] Nomograms have been developed to quantify risk by combining prognostic factors in many diseases and may individualize predictions of survival and recurrence.[12] More accurate individualized prognostic prediction would enable more personalized treatments. However, there are no nomograms to predict postoperative survival or recurrence in LARC patients who undergo upfront surgery.

We investigated factors that affected the postoperative survival of LARC patients who underwent upfront surgery based on a large dataset from multiple centers in Japan and created nomograms and a novel risk stratification system to help clinicians make individualized prognostic predictions and guide clinical decisions. The Surveillance, Epidemiology, and End Results (SEER) database was then analyzed to examine whether these nomograms could identify populations that might benefit from postoperative ACT.

METHODS

Dataset

This study was based on medical records collected from January 1, 2007 to December 31, 2008 at 19 major medical centers throughout Japan. Among the patients who underwent curative surgery for stage I-III RC, we collected data from 1925 patients who satisfied the following inclusion criteria: primary rectal cancer, no combined malignancy, no distant metastasis, curative-intent resection, and no missing data.

This dataset included patient demographics, pathologic characteristics, extent of lymphadenectomy, LPLND, preoperative carcinoembryonic antigen (CEA) level, preoperative carbohydrate antigen (CA) 19-9 level, preoperative treatment, ACT, and follow-up data (follow-up duration, recurrence, and survival). Tumor size was measured as the longest diameter. The following were classified according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus"[13] (Supplemental Text, http://links.lww.com/AOSO/A423): tumor location (level of tumor distal edge: P, Rb, Ra, RS), macroscopic type (type 0, superficial type; type I, polypoid; type II, ulcerated with clear margins; ulcerated with infiltration; type IV, diffusely infiltrating; type V, unclassified), histological subtype (papillary adenocarcinoma; differentiated: well-differentiated and moderately differentiated adenocarcinoma; undifferentiated: poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma), invasion depth (T1, T2, T3, T4a, and T4b), and degree of lymphovascular invasion (grades 0–3), and extent of lymphadenectomy (D2, D3) ACT was categorized as received or not received. Follow-up duration was measured from the date of surgery to the end of follow-up, and information on survival status at the final follow-up examination was collected. The protocol was approved by the Ethics Committee of the JSCCR and each hospital.

Nomogram Construction

Multivariable analysis using Cox proportional hazards (PHs) regression was conducted to construct the nomograms. The PH assumption was verified by tests of correlations with time and examination of residual plots. To permit nonlinear relationships, continuous variables were modeled with restricted cubic splines,[14] and transformed to an adequate form for fitting the PH and linearity assumptions. For categorical variables, a log-log survival plot was used to identify the PH assumption, and all variables were fitted to the PH assumption. All decisions regarding the grouping of categorical variables were made before modeling. In the Cox PH regression model, variables were selected by forward stepwise selection. Based on the predictive model with the identified prognostic factors, nomograms were constructed to predict 3- and 5-year overall survival (OS) and recurrence-free survival (RFS).

Validation of the Nomograms

Validation of the nomograms consisted of discrimination and calibration using the validation set. Discrimination was evaluated using the concordance index (C-index), which provides the probability that for 2 randomly selected patients, the patient in whom the nomogram predicted a worse outcome would experience the first event. Harrell's C-index, which is appropriate for censored data, was used for evaluating discrimination[12,14] (>0.75 represents relatively good discrimination). Calibration was performed by comparing the mean predicted survival with the mean actual survival, with Kaplan–Meier[15] estimates after grouping of nomogram-predicted survival by decile.

Validation was performed using an independent dataset from the JSCCR CRC registration system. The validation set (n = 2957) of stage I-III patients who underwent curative rectal cancer surgery between January 1, 2005 and December 31, 2006, and satisfied the aforementioned inclusion criteria were obtained from this registration system, and the clinicopathological variables included in the nomogram were examined.

Effect of ACT on Different Risk Groups

The database was obtained from SEER Stat (version 8.4.2). Patients diagnosed after 2016 were excluded to ensure sufficient follow-up. Only patients with stage I-III RC diagnosed in 2010–2015 were included. The inclusion criteria were (1) rectal cancer as the only primary tumor; (2) histologically confirmed rectal adenocarcinoma; (3) stage I-III RC treated with upfront surgery without neoadjuvant treatment; and (4) complete survival information, demographic data, and clinicopathologic features. We identified 12,033 RC patients who met these criteria.

Statistical Analyses

Statistical analyses were performed using S-plus (version 8.0, Palo Alto, CA). X-tile (Version 3.6.1) divided the variables into different basins based on changes in markers and visualized the optimal cutpoints.[16] OS was calculated from primary surgery to death from any cause. RFS was calculated from the date of surgery to recurrence or death from any cause. By the Kaplan–Meier method,[15] patients who did not experience the defined outcome were censored. Data from the SEER database were

analyzed to assess the effect of ACT on OS in groups with different prognostic risk levels based on the nomogram prediction. All *P* values were two-sided, with $\alpha = 0.05$.

RESULTS

Patient Characteristics

The clinicopathological characteristics of the training set (n = 1925) and JSCCR validation set (n = 2957) are outlined in Table 1. No significant differences were seen between the sets. The training set included 1198 male (62.2%) and 727 female (37.8%) patients. Median age was 63.6 (IQR, 57.0–72.0) years. Tumor location was classified as RS, 565 (29.4%); Ra, 554 (28.8%); Rb, 766 (28.8%); and P, 40 (2.0%). Median tumor size was 3.5 (IQR, 1.5–5.0) cm. D2 and D3 LN dissection was performed in 26.3% and 71.6% of the patients, respectively. The mean number (±standard deviation) of examined LNs was 23.2 ± 16.6, while the mean number of metastatic LNs was 1.3 ± 3.1. In the training set, neoadjuvant treatments were chemoradiotherapy (3.1%), chemotherapy (0.9%), and radiotherapy (0.3%). The remaining 95.7% underwent upfront surgery. ACT was administered to 34.6% of the patients.

Nomogram Variable Screening

After examination and transformation of variables to fit the Cox PH regression model, variables were subjected to forward stepwise selection ($P < 0.05$). Tables 2 and 3 list the selected variables with hazard ratios (HRs).

Multivariable analysis for OS revealed significantly higher HRs for increased age (HR, 1.04), male sex (HR vs. female; 1.30), lower tumor location (HR vs. RS: Ra, 1.89; Rb, 1.92; P, 7.03), undifferentiated tumor (HR vs. papillary: well, 1.39; moderate, 2.76; mucinous/poor/signet, 3.66; other, 2.30), greater invasion depth (HR vs. T1: T2, 1.12; T3, 2.11; T4a, 2.47; T4b, 4.28), greater lymphatic invasion (HR vs. ly0: ly1, 1.11; ly2, 1.54; ly3, 2.10), positive radial margin (HR, 3.08), fewer examined LNs (HR, 1.02), more metastatic LNs (HR, 1.02), and higher preoperative CEA (HR, vs. 0–5.0 ng/ml: 5.1–10.0, 1.82; 10.1–20.0, 1.99; 20.1–40.0, 2.15; ≥40.1, 3.59). Size, macroscopic type, distal margin, extent of lymphadenectomy, and perioperative treatment were not statistically significant (Table 2).

Multivariable analysis for RFS revealed that HRs were significantly higher for male sex (HR vs. female: 1.30), lower tumor location (HR vs RS: Ra, 1.46; Rb, 2.01; P, 5.54), undifferentiated tumor (HR vs. well: moderate, 1.26, mucinous/poor/signet, 1.86; papillary, 0.99; other, 21.40), greater invasion depth (HR vs. T1: T2, 1.54; T3, 2.85; T4a, 3.76; T4b, 4.92), greater lymphatic (HR vs. ly0: ly1, 1.15; ly2, 1.25; ly3, 1.62) or venous invasion (HR vs. v0: v1, 1.47; v2, 1.78; v3, 2.06), positive radial margin (HR, 2.63), fewer examined LNs (HR, 1.02), more metastatic LNs (HR, 1.08), and higher preoperative CEA (HR vs. 0–5.0 ng/ml: 5.1–10.0, 1.45; 10.1–20.0, 1.48; 20.1–40.0, 1.75; and ≥40.1, 2.01) (Table 3).

Nomogram Construction and Internal Validation

In the training and validation sets, 5-year OS rates were 89.6% and 83.3%, respectively, and the 5-year RFS rates were 77.9% and 78.1%. To evaluate the OS and RFS in stage I-III RC, nomograms were constructed based on independent variables with HRs for OS (Fig. 1) and RFS (Fig. 2) in the multivariable Cox regression model. The nomogram assigns the survival probability based on the sum of scores on the point scale for each variable. The total score projected onto the bottom scale indicates the probability of 3- and 5-year survival. Harrell's C-index for the OS and RFS nomograms was 0.77 [95% confidence interval (CI) = 0.69–0.79)] and 0.75 (95% CI = 0.73–0.82),

TABLE 1.

Demographic and Clinicopathological Variables of the Training and Validation Sets

	Training Set (n = 1925)	Validation Set (n = 2957)
Sex		
Male	1198 (62.2)	1846 (62.4)
Female	727 (37.8)	1111 (37.6)
Age, years*	63.6 (11.4)	64.4(11.4)
Level of tumor distal edge†		
RS	565 (29.4)	926 (31.3)
Ra	554 (28.8)	920 (31.1)
Rb	766 (39.8)	1074 (36.3)
P	40 (2)	37 (1.3)
Tumor size, cm*	3.5 (2.4)	
Macroscopic type		
Type 0	262 (13.6)	
Type I	132 (6.9)	
Type II	1441 (74.9)	
Type III	58 (3.0)	
Type IV	4 (0.2)	
Type V	28 (1.4)	
Tumor differentiation		
Pap	6 (0.3)	3 (0.1)
Well	765 (39.7)	1302 (44.0)
Moderate	1059 (55.0)	1485 (50.2)
Mucinous/poor/signet	92 (4.8)	161 (5.4)
Other	3 (0.2)	6 (0.2)
pT-stage		
T1	526 (19.2)	397 (13.4)
T2	394 (14.3)	607 (20.5)
T3	1324 (48.2)	1303 (44.1)
T4a	381 (13.9)	543 (18.4)
T4b	121 (4.4)	107 (3.6)
Lymphatic invasion		
0	818 (42.5)	1168 (39.5)
1	793 (41.2)	1236 (41.8)
2	273 (14.2)	465 (15.7)
3	41 (2.1)	88 (3.0)
Venous invasion		
0	584 (30.3)	1849 (41.6)
1	777 (40.4)	1808 (40.7)
2	437 (22.7)	644 (14.4)
3	127 (6.6)	145 (3.3)
Distal margin		
Negative	1922 (99.8)	
Positive	3 (0.2)	
Radial margin		
Negative	1894 (98.4)	2923 (98.8)
Positive	31 (1.6)	34 (1.2)
Lateral pelvic lymph node dissection		
No	1526 (79.2)	
Yes	399 (20.8)	
Examined LNs, No.*	23.2 (16.6)	20.6 (15.4)
Metastatic LNs, No.*	1.3 (3.0)	1.3 (2.9)
Preoperative CEA level, ng/ml		
0–5	1316 (68.4)	1889 (63.9)
5.1–10	302 (15.7)	511 (17.3)
10.1–20	158 (8.2)	292 (9.9)
20.1–40	76 (3.9)	142 (4.8)
>40.1	73 (3.8)	123 (4.2)
JSCCR-stage		
Stage I	527 (27.4)	
Stage II	662 (34.3)	
Stage IIIa	473 (24.6)	
Stage IIIb	263 (13.7)	
Extent of lymphadenectomy		
D0–1	40 (2.1)	
D2	506 (26.3)	
D3	1379 (71.6)	

(*Continued*)

TABLE 1.
Continued

	Training Set (n = 1925)	Validation Set (n = 2957)
Neoadjuvant treatment		
Chemoradiotherapy	59 (3.1)	
Chemotherapy	18 (0.9)	
Radiotherapy	5 (0.3)	
No	1259 (95.7)	
Adjuvant chemotherapy		
No	1259 (65.4)	
Yes	666 (34.6)	

Values in parentheses are percentages unless indicated otherwise. Some percentages do not add up to 100 because of rounding.
*Values are the mean (standard deviation).
†RS, rectosigmoid; Ra, upper rectum above the pritoneal reflection; Rb, lower rectum below the peritoneal reflection; P, anal canal.

respectively. The calibration curves of the nomograms are shown in Figures 3A, B. Actual survival corresponded closely to predicted survival and was always within a 10% margin of error. These curves reveal the acceptability and conformance in the original cohort between the nomogram forecast and actual 5-year OS and RFS rates.

External Validation

The clinicopathological characteristics of the JSCCR validation set (n = 2957) are listed in Table 1. Harrell's C-index values of the OS and RFS nomogram were 0.75 (95% CI = 0.69–0.78) and 0.74 (95% CI = 0.71–0.79), respectively. The nomogram also predicted OS and RFS better than chance in the external dataset. Calibration plots suggest that the nomogram was well-calibrated for all predictions (Figs. 3 C, D).

Patient Characteristics for the SEER Database

Not all OS nomogram components necessarily fit the SEER database. Based on the modified nomogram prediction model using 7 factors for which the amount of missing data did not exceed 20% (age, sex, tumor location, histological type, invasion depth, number of metastatic LNs, and number of examined LNs), the risk scores of all patients from the SEER database were calculated, and X-tile was used to calculate 2 cutoff values. The SEER database only classified tumor location as rectosigmoid or rectum. Therefore, rectosigmoid was extrapolated to RS and rectum was extrapolated to Ra in the nomogram. Finally, from 12,033 patients who underwent upfront surgery with curative intent for stage I-III RC, 10,482 patients were included in the analysis and divided into a surgery-alone group (n = 6524, 62.2%) and surgery followed by ACT group (3958, 37.8%) (see Supplemental Table, http://links.lww.com/AOSO/A424).

Development of Risk Stratification System and Effect of Adjuvant Chemotherapy on OS in Different Risk Groups in the SEER Database

All patients were stratified into 3 risk levels (see Supplemental Figure, http://links.lww.com/AOSO/A425): low-risk (score ≤51; n = 5874), middle-risk (51–69; n = 2320), and high-risk (>69; n = 2,288). The 3- and 5-year survival rates were 91.3% (95% CI = 90.5–92.0%) and 85.1% (84.2–86.0%), respectively, in the low-risk group, 80.4% (78.7–82.0%) and 69.3% (67.3–71.1%) in the middle-risk group, and 62.8% (60.8–64.8%) and 50.2.% (48.1–52.3%) in the high-risk group ($P < 0.001$) (see Supplemental Figure, http://links.lww.com/AOSO/A426). ACT improved OS in the middle-risk group [62.4% (59.6–65.1%) vs.76.8% (74.2–79.2%), $P < 0.001$] and high-risk group [39.4% (36.7–42.1%) vs.63.5% (60.4–66.4%), $P < 0.001$]. In low-risk patients, the effect of ACT on OS was not significant [85.3% (84.2–86.4%) vs. 84.8% (83.1–86.4%), $P = 0.533$) (Fig. 4).

DISCUSSION

We aimed to create and validate nomograms predicting OS and recurrence in treatment-naïve patients with stage I-III RC who underwent upfront surgery. Eighteen candidate risk factors were selected to form a nomogram by narrowing the regression coefficients. The best predictors were identified using the Cox PH regression model. Finally, 10 variables were identified as predictors of survival or recurrence after surgery with curative intent. Two nomograms were developed and validated for individualized prediction of survival and recurrence in RC patients. The nomogram predicting OS after surgery successfully stratified, based on the risk of poor survival, treatment-naïve patients who received upfront surgery who extracted from the SEER database. ACT significantly prolonged the survival of high-risk and middle-risk patients but not low-risk patients.

Most guidelines from Western countries recommend nCRT for all patients with clinical stage II or III RC to reduce the risk of locoregional recurrence. Furthermore, total neoadjuvant therapy has recently been established to control micrometastases and reduce the risk of distant metastasis. Alternative treatment strategies for RC have emerged. However, considering the adverse effects of neoadjuvant radiotherapy or nCRT, which exacerbate the negative consequences of surgery, neoadjuvant therapy should be reserved for patients at high risk for recurrence and should be avoided if cure is likely by TME alone or TME plus ACT. In fact, the SEER database reports that <50% of patients with advanced RC receive preoperative treatment.[6] In our search of the SEER database, the percentage of patients with stage II and III RC who were treated preoperatively was 52.1%, and the rest of the patients were treated upfront with surgery. Recent prospective trials have reported that preoperative treatment is not necessary for all patients with RC.[17,18] The low incidence of recurrence in the PROSPECT trial[17] could have plausibly been achieved with upfront surgery and the selective use of ACT or pelvic nCRT based on surgical pathological assessment. The findings of the OCUM study[18] support the de-escalation of nCRT in RC OCUM patients according to their recurrence risk. The increasing number of treatment options for LARC has enabled customized treatment based on patient- or tumor-specific features. Therefore, it is important to develop prognostic tools for patients undergoing upfront surgery.

Precision medicine tools for prognostic prediction (e.g., nomograms) enable personalized computation of outcomes based on the clinical and pathological characteristics of both patients and tumors.[19] No nomogram that predicts the prognosis for all stages of CRC has been developed because the prognosis of stages I-III differs substantially from that of stage IV, and due to marked differences in prognostic variables. In addition, a web-based dynamic nomogram can elicit patient outcomes through precise numbers and visual graphics,[20] thereby guiding clinicians in optimizing clinical treatment plans.[21,22] Several prognostic nomograms for RC have been reported.[23–26] Most notably, the nomograms by Valentini *et al*.[24] were developed using data from 5 major European clinical trials. Since OS, local recurrence, and distant metastasis were included in the predicted outcome, and because both validation and calibration were presented, these nomograms should have high clinical applicability. That study analyzed a large number of patients, used only variables available in municipal hospitals, and the developed nomograms were well calibrated. However, their use is limited to patients who undergo radiotherapy or CRT. In 2023, Zhao *et al*.[26] developed a nomogram to predict cancer-specific survival after surgery

TABLE 2.

Variables Selected According to the Cox Proportional Hazards Regression Model (OS)

	Univariable			Multivariable		
Variable	**HR**	**95%CI**	***P* value**	**HR**	**95%CI**	***P* value**
Age*	1.05	1.04–1.06	<0.001	1.04	1.02–1.05	<0.001
Sex			0.045			0.055
Male	1.00			1.00		
Female	0.79	0.59–0.95		0.77	0.57–1.03	
Level of tumor distal edge			<0.001			<0.001
RS	1.00			1.00		
Ra	1.40	0.97–2.02		1.89	1.26–2.83	
Rb	1.85	1.27–2.68		1.92	1.32–2.86	
P	8.37	4.88–14.35		7.03	3.71–13.3	
Tumor size, cm*	1.01	1.00–1.02	<0.001	1.96	0.82–4.74	0.134
Macroscopic type			<0.001			0.447
Type 0	1.00			1.00		
Type I	1.78	0.60–5.30		1.83	0.49–6.76	
Type II	4.86	2.28–10.33		2.28	0.72–7.20	
Type III	13.06	5.37–31.75		3.21	0.48–21.61	
Type IV	55.22	14.26–213.87		3.41	0.96–12.2	
Type V	9.61	3.23–28.60		1.78	0.43–7.41	
Tumor differentiation			<0.001			0.003
Well	1.00			1.00		
Moderate	1.87	1.36–2.56		1.39	1.00–1.93	
Mucinous/poor/signet	6.19	3.99–9.59		2.76	1.67–4.58	
Papillary	6.92e–9	0		2.84e–9	0	
Other	11.23	1.55–81.39		2.30	0.28–18.87	
pT-stage			<0.001			<0.001
T1	1.00			1.00		
T2	1.37	0.63–2.96		1.12	0.44–2.11	
T3	4.73	2.49–8.98		2.11	0.87–5.05	
T4a	7.58	3.70–15.50		2.47	1.26–4.83	
T4b	9.64	4.45–20.89		4.28	1.99–9.21	
Lymphatic invasion			<0.001			0.029
0	1.00			1.00		
1	1.28	0.93–1.77		1.11	0.93–1.42	
2	2.78	1.94–3.97		1.54	1.05–2.26	
3	7.79	4.57–13.29		2.10	1.06–4.16	
Venous invasion			<0.001			0.109
0	1.00			1.00		
1	1.27	0.87–1.85		0.86	0.58–1.28	
2	2.50	1.72–3.64		1.23	0.72–2.13	
3	3.15	1.94–5.09		1.30	0.85–1.98	
Distal margin			0.025			0.191
Negative	1.00			1.00		
Positive	8.43	2.09–33.94		3.53	0.82–15.28	
Radial margin			<0.001			<0.001
Negative	1.00			1.00		
Positive	8.49	5.16–13.95		3.08	1.73–5.49	
Lateral lymph node dissection			0.152			
No	1.00					
Yes	1.38	0.89–1.86				
Examined LNs, No.*	0.98	0.97–0.99	0.032	0.98	0.97–0.99	0.044
Metastatic LNs, No.*	1.11	1.09–1.13	<0.001	1.11	1.02–1.09	<0.001
Preoperative CEA level, ng/ml			<0.001			<0.001
0–5	1.00			1.00		
5.1–10	2.24	1.59–3.15		1.82	1.28–2.58	
10.1–20	2.96	1.98–4.43		1.99	1.17–3.42	
20.1–40	3.23	1.93–5.40		2.15	1.41–3.28	
>40.1	5.38	3.42–8.47		3.59	2.24–5.74	
Extent of lymphadenectomy			<0.001			0.149
D0–1	1.00			1.00		
D2	0.57	0.24–1.33		0.82	0.33–2.07	
D3	0.59	0.26–1.35		0.55	0.22–1.38	
Neoadjuvant treatment			0.335			
No						
Chemoradiotherapy	1.35	0.69–2.63				
Chemotherapy	2.60	0.77–6.33				
Radiotherapy	3.68	0.89–30.01				
Adjuvant chemotherapy			0.106			
No	1.00					
Yes	1.25	0.95–1.63				

*Hazard ratios are not presented for continuous variables because the data are transformed by restricted cubic spline function with 3 or 4 knots.

TABLE 3.

Variables Selected According to the Cox Proportional Hazards Regression Model (RFS)

	Univariable			Multivariable		
Variable	**HR**	**95%CI**	***P* value**	**HR**	**95%CI**	***P* value**
Age*	1.00	0.99–1.01	0.888			
Sex			0.022			0.018
Male	1.00			1.00		
Female	0.79	0.64–0.97		0.77	0.62–0.95	
Level of tumor distal edge			<0.001			<0.001
RS	1.00			1.00		
Ra	1.49	1.13–1.99		1.46	1.09–1.95	
Rb	1.81	1.39–2.34		2.01	1.51–2.68	
P	7.13	4.59–11.09		5.54	3.28–9.35	
Tumor size, cm*	1.01	1.00–1.02	<0.001	1.00	0.99–1.01	0.934
Macroscopic type			<0.001			0.416
Type 0	1.00			1.00		
Type I	1.59	0.79–3.17		0.77	0.33–1.77	
Type II	3.63	2.29–5.76		0.88	0.43–1.80	
Type III	9.36	5.23–16.78		1.37	0.60–3.11	
Type IV	20.17	5.97–68.21		1.06	0.22–5.04	
Type V	6.27	2.91–13.48		0.87	0.33–2.28	
Tumor differentiation			<0.001			<0.001
Well	1.00			1.00		
Moderate	1.49	1.20–1.85		1.26	0.18–9.11	
Mucinous/poor/signet	3.89	2.76–5.50		1.86	1.26–2.75	
Papillary	0.89	0.12–6.34		0.99	0.79–1.25	
Other	37.49	11.83–118.84		21.40	6.39–71.68	
pT-stage			<0.001			<0.001
T1	1.00			1.00		
T2	2.03	1.19–3.45		1.54	0.90–2.64	
T3	4.98	3.13–7.95		2.85	1.74–4.67	
T4a	7.52	4.44–12.75		3.76	1.99–7.09	
T4b	11.39	6.48–20.04		4.92	2.77–8.73	
Lymphatic invasion			<0.001			0.011
0	1.00			1.00		
1	1.56	1.23–1.97		1.15	0.63–2.12	
2	3.01	2.31–3.93		1.25	0.98–1.59	
3	5.39	3.39–8.59		1.62	1.21–2.18	
Venous invasion			<0.001			<0.001
0	1.00			1.00		
1	2.24	1.65–3.02		1.47	1.07–2.01	
2	4.08	3.00–5.54		1.78	1.16–2.74	
3	4.49	3.03–6.63		2.06	1.48–2.88	
Distal margin			0.042			0.726
Negative	1.00			1.00		
Positive	4.22	1.05–16.93		1.29	0.30–5.53	
Radial margin			<0.001			0.041
Negative	1.00			1.00		
Positive	5.16	3.25–8.19		2.63	1.24–3.82	
Lateral lymph node dissection			0.231			
No	1.00					
Yes	1.83	0.79–2.25				
Examined LNs, No.*	0.98	0.97–0.99	0.013	0.98	0.97–0.99	0.002
Metastatic LNs, No.*	1.12	1.09–1.13	<0.001	1.08	1.04–1.10	<0.001
Preoperative CEA level, ng/ml			<0.001			<0.001
0–5	1.00			1.00		
5.1–10	1.73	1.34–2.23		1.45	1.05–2.01	
10.1–20	2.01	1.52–2.85		1.48	1.14–1.93	
20.1–40	3.18	2.16–4.69		1.75	1.17–2.60	
>40.1	3.41	2.37–4.89		2.01	1.37–2.94	
Extent of lymphadenectomy			0.002			0.749
D0–1	1.00			1.00		
D2	0.91	0.37–2.26		0.95	0.73–1.25	
D3	0.61	0.25–1.49		0.70	0.27–1.80	
Neoadjuvant treatment			0.003			
No						
Chemoradiotherapy	1.75	1.10–2.77				
Chemotherapy	2.31	1.15–4.67				
Radiotherapy	5.41	1.74–16.86				
Adjuvant chemotherapy			<0.001			
No	1.00					
Yes	1.86	1.53–2.26				

*Hazard ratios are not presented for continuous variables because the data were transformed by restricted cubic spline function with 3 or 4 knots.

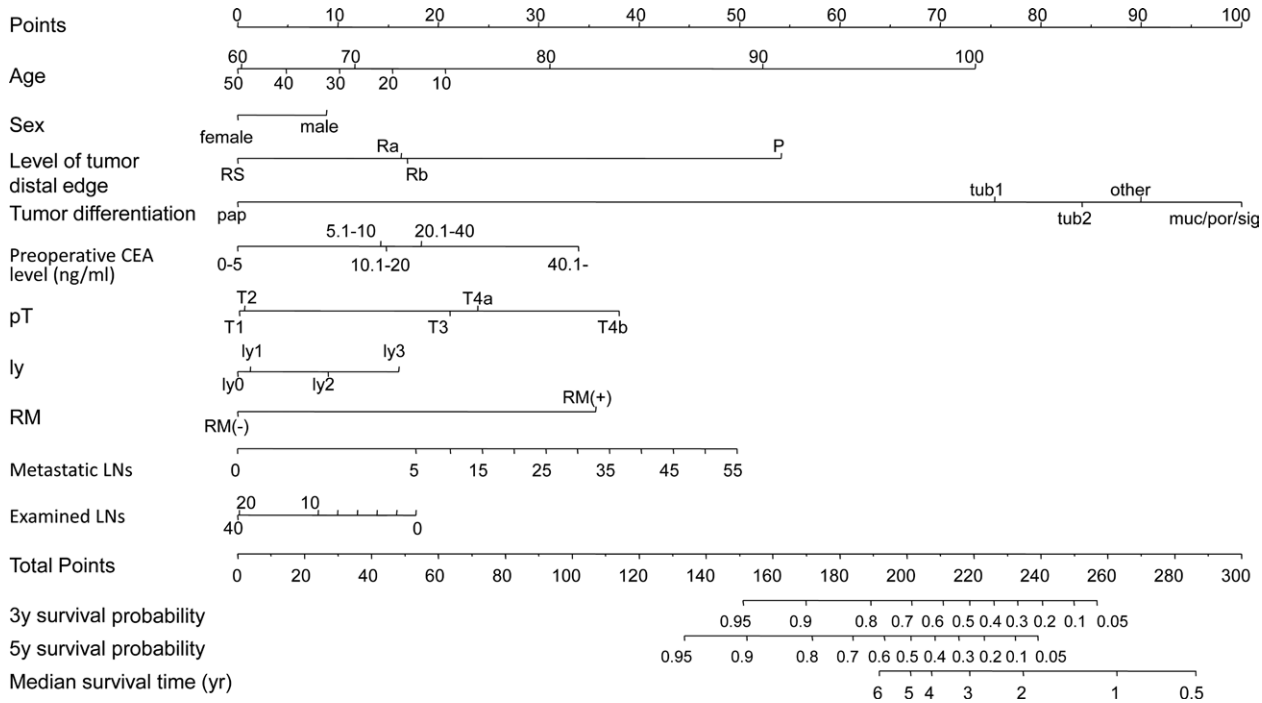

FIGURE 1. Prognostic nomogram for predicting OS of patients with rectal cancer. The nomogram is used by summing the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 3- and 5-year survival.

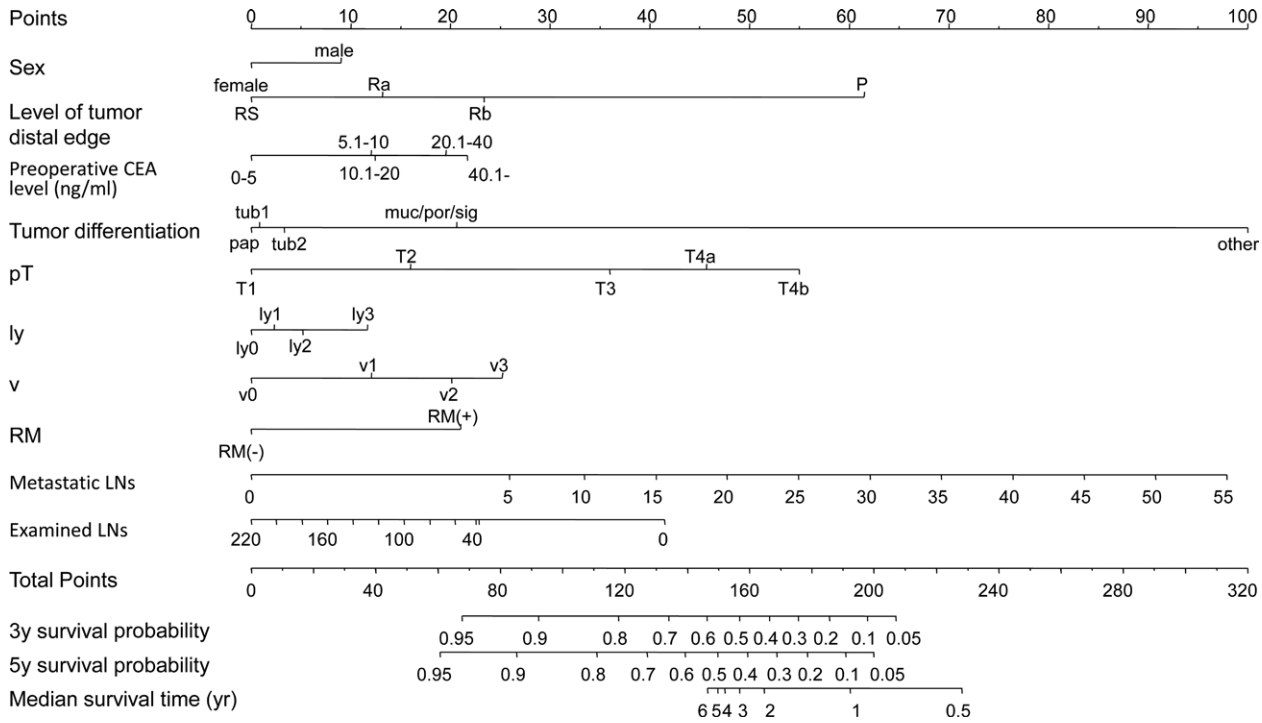

FIGURE 2. Prognostic nomogram for predicting RFS of patients with rectal cancer. The nomogram is used by summing the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 3- and 5-year survival.

without preoperative treatment using general clinicopathological variables (patient age, pT stage, pN stage, differentiation type, tumor size, circumferential resection margin involvement, perineural invasion, inadequate LN yield, and serum CEA level). The C-index of this nomogram was modest (C-index: 0.72) and OS was not included in the outcome. External validation was performed, but the size of the validation cohort was very small (only 200 cases). In the present study, several prognostic variables, including the tumor location, lymphatic and/or venous invasion, radial margin involvement, LN yield, and metastatic LN number were included in the nomogram model, which showed better predictive value (C-index: 0.75, 0.77). To avoid overfitting, it is essential to verify the generality of the nomogram. Using a large internal cohort (approximately 2000 cases) from a multi-institutional study database and an independent external cohort (approximately 3000 cases) from

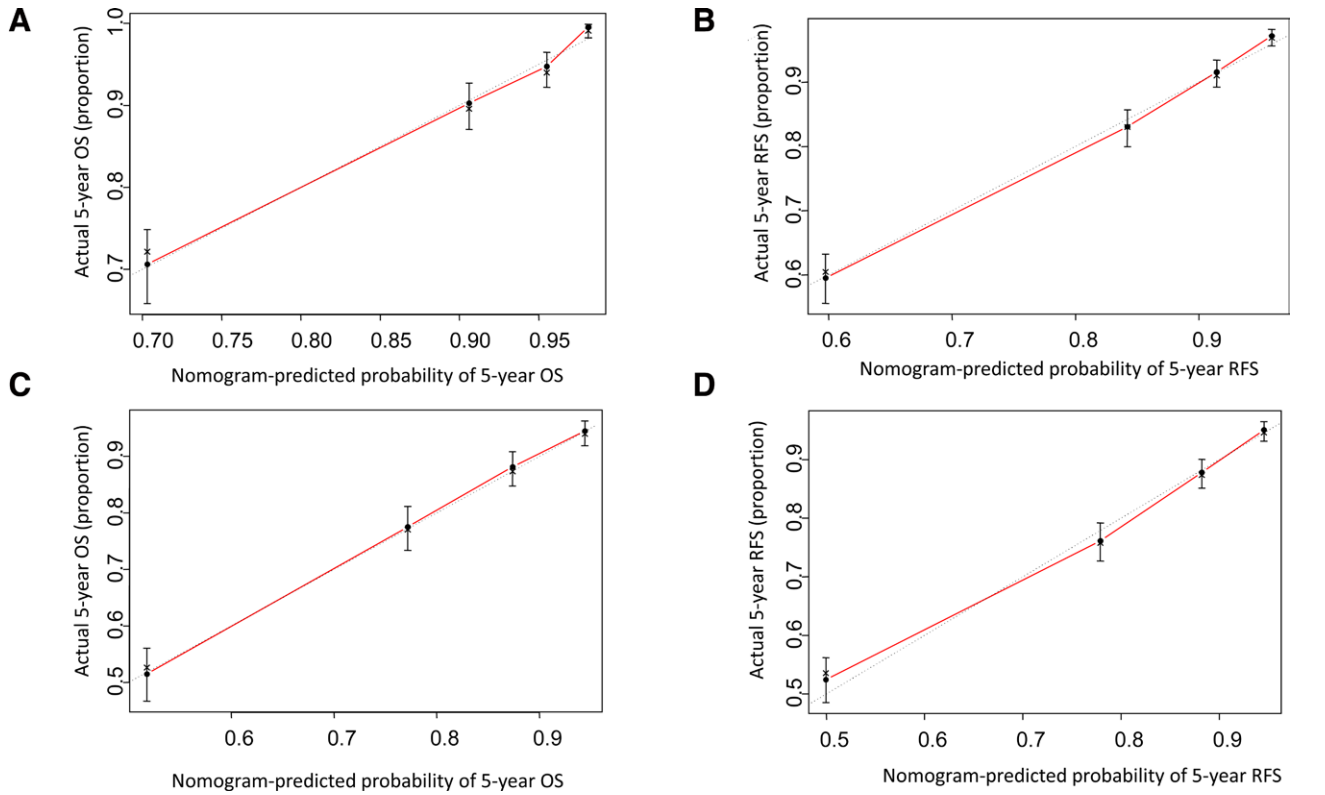

FIGURE 3. Calibration of the nomograms. The x-axis represents the nomogram-predicted survival, and the y-axis represents actual and 95% CIs by Kaplan–Meier analysis. (A) 5-year OS in the training dataset. (B) 5-year RFS in the training data set. (C) 5-year OS in the validation dataset. (D) 5-year RFS in the training set in the validation dataset. The solid line represents the ideal reference line, where the predicted survival corresponds to the actual survival, and the dotted lines represent a 10% margin of error.

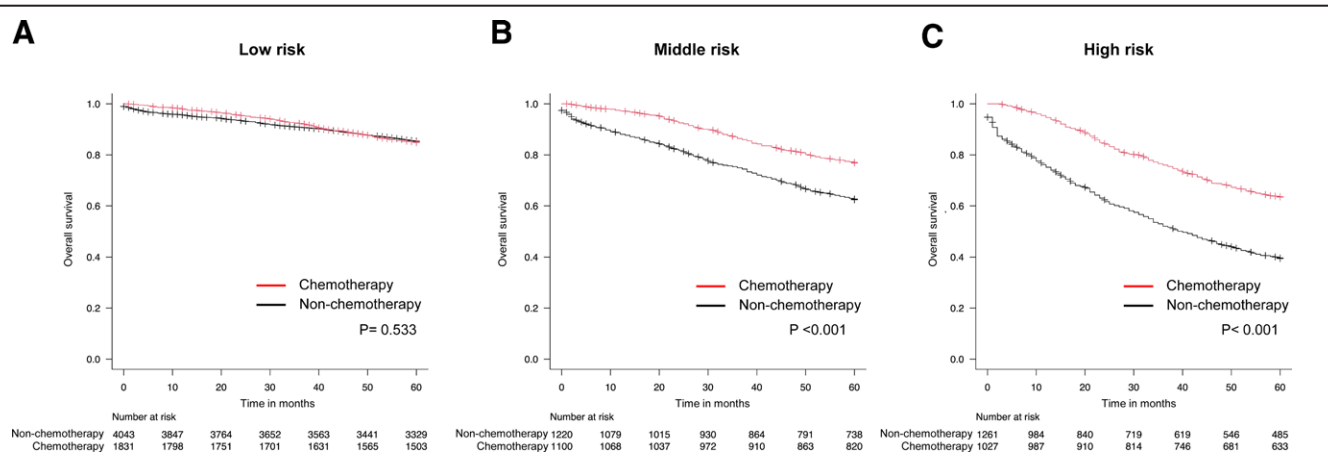

FIGURE 4. Effect of adjuvant chemotherapy on OS of the (A) low-risk, (B) middle-risk, and (C) high-risk groups.

the Japanese Colorectal Cancer Registry, we demonstrated satisfactory discriminative ability and stability of OS and RFS prediction in RC patients.

Current recommendations on ACT for RC are based on evidence largely extrapolated from studies in colon cancer.[27–29] However, the clinical course and biology of colon cancer and RC differ significantly. Furthermore, the colon and rectum have distinct embryological origins and distinct anatomical and physiological characteristics. Clinically, early-stage RC has a poorer prognosis, and compared with colon cancer, it is more difficult to achieve complete resection of RC with circumferential margin involvement due to multi-organ involvement.[30] Accordingly, it is scientifically justifiable to consider colon cancer and RC as distinct diseases, and the benefits of ACT cannot be assumed to be equal in these distinct diseases. Several studies have suggested that not all patients with RC benefit from ACT and that only certain groups may respond to treatment. While many studies have investigated the benefits of chemotherapy in certain subgroups of patients,[31–33] the results have been conflicting. The value of postoperative chemotherapy in patients treated with curative surgery alone has also been investigated in a large number of trials.[34] Most evidence comes from post hoc subgroup analyses of randomized control trials or retrospective/prospective nonrandomized studies; hence, they are subject to the inherent weaknesses of those designs. Concerns about study quality remain, including inadequate staging modalities, outdated chemotherapeutic regimens, non-TME surgical approaches, and small sample sizes. However, many clinicians

worldwide are reluctant to discontinue ACT. Identification of at-risk groups using advanced imaging modalities, nomograms, and biomarkers is the future of personalized treatment for RC.[35] In this study, a risk stratification model based on our OS nomogram was established to screen high- or middle-risk populations with a worse postoperative prognosis. The model integrated 7 parameters extracted from the original nomogram: age, sex, tumor location, histological type, pT, number of metastatic LNs, and number of examined LNs. Relative to the low-risk group, middle- and high-risk patients were more likely to have worse OS (all $P < 0.001$). In addition, we confirmed that ACT could improve OS in middle- or high-risk patients. Our model may have implications for the postoperative management of some patients who undergo surgery alone (e.g., deciding whether to provide ACT or to intensify follow-up monitoring).

This study has several limitations. First, there was selection bias due to the retrospective design and the inclusion of only patients with complete information. Some variables with prognostic value (e.g., perineal invasion and circumferential resection margin) were not included in the analysis due to significant amounts of missing data, especially in the SEER database. Second, comorbidities were not reflected in this nomogram. We expect that comorbidities will affect OS to some extent. However, because of the diversity of comorbidities, it is difficult to create categorized variables and quantify risk. Given that patients with other malignancies were excluded from the study, the impact of comorbidities on survival is expected to be minimal. Third, the dataset spans more than 10 years, which raises the question of whether this nomogram can be applied to patients today. In most institutions in Japan, however, the overall strategies for D2/D3 LN dissection ± LPLND and pathologic examination have not changed during this period. In this study, approximately 72% of the patients underwent D3 lymphadenectomy and 21% underwent LPLND. Radical LN dissection could lead to the eradication of possible residual tumor cells during surgery, thereby enabling the retrieval of more LNs and helping expert pathologists identify positive LNs. Fourth, there were no data on molecular information, such as deficient mismatch repair (MMR) and *RAS*/*RAF* status. *RAS* mutations combined with pMMR in the tumor are considered to be strong independent prognostic factors for tumors with *RAS*/*RAF* mutations. The inclusion of these molecular data may make these nomograms more useful. Despite these limitations, the prognostic nomograms were successfully developed based on a large-scale analysis of a real-world population and were validated using an independent external cohort. Furthermore, our OS nomogram provided clear prognostic stratification to identify individuals who might benefit from ACT among RC patients in the SEER database, which supported the reliability and reproducibility of the prognostic nomogram.

CONCLUSIONS

We developed and externally validated nomograms predicting 5-year OS and RFS after curative resection with radical LN dissection in treatment-naïve RC patients. The nomograms may provide accurate prognostic stratification, which can be used to identify patients who can be expected to benefit more from ACT after RC surgery and to help clinicians make decisions on individualized treatment strategies.

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AUTHOR CONTRIBUTIONS

Conception and design: Y.K. Collection and assembly of data: Y.K., T.U., S.T., H.U., M.I., S.I., and K.K. Data analysis and interpretation: Y.K., T.U., and M.I. Manuscript writing and final manuscript approval: All authors.

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