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The development and validation of a predictive model for recurrence in rectal cancer based on radiological and clinicopathological data

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Abstract

Objective To develop a prediction model for recurrence by incorporating radiological and clinicopathological prognostic factors in rectal cancer patients.

Methods All radiologic and clinicopathologic data of 489 patients with rectal cancer, retrospectively collected from a single institution between 2009 and 2013, were used to develop a predictive model for recurrence using the Cox regression. The model performance was validated on an independent cohort between 2015 and 2017 ($N = 168$).

Results Out of 489 derivative patients, 103 showed recurrence after surgery. The prediction model was constructed with the following four significant predictors: distance from anal verge, MR-based extramural venous invasion, pathologic nodal stage, and perineural invasion (HR: 1.69, 2.09, 2.59, 2.29, respectively). Each factor was assigned a risk score corresponding to HR. The derivation and validation cohort were classified by sum of risk scores into 3 groups: low, intermediate, and high risk. Each of these groups showed significantly different recurrence rates (derivation cohort: 13.4%, 35.3%, 61.5 %; validation cohort: 6.2%, 23.7%, 64.7%). Our new model showed better performance in risk stratification, compared to recurrence rates of tumor node metastasis (TNM) staging in the validation cohort (stage I: 3.6%, II: 12%, III: 30.2%). The area under the receiver operating characteristic curve of the new prediction model was higher than TNM staging at 3-year recurrence in the validation cohort (0.853 vs. 0.731; $p = .009$).

Conclusions The new risk prediction model was strongly correlated with a recurrence rate after rectal cancer surgery and excellent for selection of high-risk group, who needs more active surveillance.

Key Points

- *Multivariate analysis revealed four significant risk factors to be MR-based extramural venous invasion, perineural invasion, nodal metastasis, and the short distance from anal verge among the radiologic and clinicopathologic data.*
- *Our new recurrence prediction model including radiologic data as well as clinicopathologic data showed high predictive performance of disease recurrence.*
- *This model can be used as a comprehensive approach to evaluate individual prognosis and helpful for the selection of highly recurrent group who needs more active surveillance.*

Keywords Rectal neoplasms · Prognosis · Recurrence · Nomograms · Magnetic resonance imaging

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Abbreviations

CRM	Circumferential resection margin
CRT	Chemoradiotherapy
mrEMVI	MR-based extramural venous invasion
RFS	Recurrence-free survival

Introduction

The prediction of cancer prognosis has increased in importance in recent years following advances in precision medicine and individualized care [1]. Emerging treatment options such as preoperative or postoperative chemotherapy, concurrent chemoradiotherapy (CRT), targeted therapy, and immunotherapy facilitate the management of such spatial and temporal variations in cancer. Based on this background, the need for systematic risk assessment and knowledge of prognostic factors is critical to determine the appropriate treatment method and the follow-up strategy.

Although the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system is widely used for risk assessment of cancer, TNM alone cannot ensure a precise classification of patient's risk and may not include various prognostic factors such as radiological and clinical characteristics, pathology subtypes, or gene mutations. In colorectal cancers, many studies identified prognostic risk factors and developed models to predict recurrence or survival [2–7]. However, most of the previous studies evaluate only clinical and pathological factors. The studies did not explore variables such as imaging factors or genetic profiles that are essential for the evaluation of rectal cancer clinically.

To the best of our knowledge, this study represents the first trial to develop a prognostic model including magnetic resonance imaging (MRI)–based radiological and molecular factors as well as clinicopathological factors. The study explored various radiological and clinicopathological factors related to disease recurrence in patients with rectal cancer after curative resection, to develop a prediction model for disease recurrence. The new predictive model for recurrence could help clinicians with selecting a high-risk group who would need more detailed surveillance.

Materials and methods

Patient population

The institutional review board approved this retrospective study, and patients' informed consent was waived. Between January 2009 and December 2013, 516 consecutive patients with rectal cancer underwent curative resection after rectal magnetic resonance imaging (MRI). Twenty-seven patients were excluded: endoscopic submucosal resection (n = 15), non-curative resection (n = 1), other pathologies (squamous cell carcinoma, n = 4; adenoma, n = 1; Tis, n = 4), image distortion due to metal artifacts (n = 2). Thus, 489 patients (median age, 61 years: age range, 27–89 years; 303 men and 186 women) were finally included in the study. The included patients underwent colonoscopic biopsy, carcinoembryonic antigen level (CEA), computed tomography (CT), and MRI preoperatively for staging work-up and followed up with digital rectal exam, regular blood tests, including CEA level, chest radiography every 3 months for the first year, every 6 months for the next 2 years, and then annually. CT scans were performed every 6 months for the first 2 years after surgery and then yearly. Among 489 patients of the derivation cohort, 193 patients were treated with neoadjuvant CRT, followed by surgery. Neoadjuvant radiation therapy was delivered to the pelvis with a total dose of 50.4 Gy in 25–28 fractions for 5.5–6 weeks in 135 patients. Fifty-three patients underwent short-course radiation therapy with a total dose of 33 Gy (n = 28) for 2 weeks or with 25 Gy (n = 25) for 5 days. Preoperative chemotherapy was concurrently performed with 5-fluorouracil (400–500mg/m^2/day) and leucovorin (20 mg/m^2/day) regimens. Accurate chemotherapy regimen and radiation dose were not obtained for 5 patients who had received neoadjuvant chemoradiation therapy at an outside hospital. Based on the final pathologic results, patients with stage II (68/133) or III (179/200) underwent adjuvant chemotherapy except for patients who were elderly or had refused chemotherapy. For adjuvant chemotherapy, the 5-fluorouracil, leucovorin (LF), or the 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen were used.

For external validation, we collected validation cohort using patient data from 2015 to 2017 (n = 168; 113 men and 55 women). Twenty-one patients were treated with neoadjuvant CRT.

MR imaging techniques

All MRI studies were performed using a 3-T MR scanner (Magnetom Verio; Siemens Healthineers) or 1.5-T MR (Achieva; Philips Healthcare) with a six-channel phased-array surface coil (body matrix) combined with up to six elements of the integrated spine coil. Before starting the MR scan, approximately 50–100 mL of sonography transmission gel was administered for appropriate distension of the rectum, to delineate the tumor, particularly small tumors. The complete MRI protocol with the parameters used for each study is shown in Table 1.

Table 1 MR imaging parameters

	3-T MR scanner				1.5-T MR scanner			
	T2 FSE (sagittal and axial)	T1WI (axial)	CET1WI (axial)	DWI (axial)	T2 FSE (sagittal and axial)	T1WI (axial)	CET1WI (axial)	DWI (axial)
TR (ms)	4000	600	700	5100	3300	500	560	4200
TE (ms)	118	13	13	90	100	100	10	73
Thickness (mm)	3–5	3–5	3–5	3–5	5	5	5	5
FOV (mm^2)	220 × 220	200 × 200	200 × 200	200 × 200	220 × 220	220 × 220	220 × 220	220 × 220
Matrix size	320 × 224	320 × 224	320 × 224	146×102	260 × 176	260 × 200	260 × 200	100 × 90
NEX	2	2	1	3	2	4	3	12
B factor (s/mm^2)				0,500,1000				0,1000

Contrast-enhanced images: an intravenous bolus injection of 0.1 mmol/kg gadobutrol (Gadovist, Schering) at a rate of 3 mL/s, followed by a 25 mL saline flush

FSE, fast spin-echo sequence; *DWI*, diffusion-weighted imaging; *T1WI*, T1-weighted image; *CET1WI*, contrast-enhanced T1-weighted image; *TR*, repetition time; *TE*, echo time; *FOV*, field of view; *NEX*, number of excitations

Clinical, radiologic, and histopathological analysis

To explore recurrence predictor candidates, the following 6 clinical factors were chosen and analyzed: age, sex, clinical TNM staging, preoperative CEA level, anastomotic leakage, and neoadjuvant CRT. MR imaging analysis was performed by a single expert radiologist with 16 years of experience in oncologic MR imaging for rectal cancer, who was blinded to clinical and final pathological data. We included the following radiological factors of pre-treatment MRI as recurrence predictor candidates: tumor length, distance from anal verge and the relationship with peritoneal reflection, depth of invasion (cT stage), LN metastasis (cN stage), pelvic lateral LN metastasis, circumferential resection margin (radiologic CRM [rCRM]), mesorectal tumor extension (MTE), MR extramural venous invasion (mrEMVI) status, mean apparent diffusion coefficient (ADC) from entire tumor, and total tumor volume on diffusion-weighted image (DWI). Metastatic LN was considered if the short diameter of mesorectal LN was ≥ 5 mm and the short diameter for extra-mesorectal (pelvic lateral) LN was ≥ 8 mm, and heterogenous signal intensity (SI) or spiculated margin of LNs was observed. CRM is the surface of the nonperitonealized part of the rectum that is resected during surgery. CRM status can be measured by the shortest distance between the outermost part of the rectal tumor (MTE) and the mesorectal fascia (MRF) and was considered threatened if this measurement was less than 1 mm. EMVI is an extension of the tumor to the vessels in the mesorectum, which is an important prognostic factor and predictor of metastasis [8, 9]. EMVI on MRI, as suggested by Smith et al [10], was considered positive if tumor SI (intermediate SI on T2-weighted imaging) within extramural vessels with or without vessel contour change and caliber expansion, but was negative if no tumor signal within extramural vessels or distant from the tumor extension. In ADC measurement, 13 were excluded due to the absence ($n = 6$) or metallic artifacts ($n = 7$) of DWI. After identification of a lesion on T2WI and DWI, the ADC was measured with the use of manually drawn region of interests along the tumor margin on ADC maps, calculated by DWI with b values of 0, 500, 1000 s/mm^2.

Histopathological analysis was based on pathology reports. The following features were pathological candidates for predicting recurrence: pT/pN stage; pathologic CRM (pCRM); lymphatic, venous, and perineural invasion; pathology subtype (well/moderate/poorly differentiated, mucinous, and signet ring cell); presence of mucinous cancer; and immunohistochemical markers (EGFR, MLH1, MSH2, ERCC1, Thy-Syn0, and KRAS mutations).

Statistical analysis and development of individual risk prediction model

To develop the prediction model, we assessed the radiological and clinicopathological data. To determine recurrence-free survival (RFS), follow-up images of chest-abdomen-pelvis CT, MR or PET-CT, and colonoscopy were reviewed. Local tumor recurrence and distant metastasis were determined by colonoscopic biopsy and imaging modalities. RFS was defined as the time from operation until tumor recurrence or the date of last imaging follow-up without recurrence.

All demographic data are listed in Table 2. For univariate analysis, variables were compared using appropriate statistics (Wilcoxon rank-sum test, chi-square, or Fisher's exact test). Candidate predictors (p value < .2 in the univariate analysis) were used for multivariable Cox regression analysis. For predictor selection, the stepwise elimination method was used.

Table 2 Demographics of study subjects

Characteristics	Derivation cohort (n = 489)	Validation cohort (n = 168)	p value
Sex (male)	303 (62.0)	113 (67.3)	0.219
Age (mean ± sd)	61.4 ± 11.6	60.7 ± 12.4	0.307
Clinical TNM stage (≥ III/IV; n, %)	201 (41.1)	63 (37.5)	0.411
CEA (median (IQR))	2.4 (1.4-4.2)	2.0 (1.2-4.4)	0.098
Anastomotic leak (n, %)	27 (6.5)		
Preoperative CRT	193 (39.5)	21 (12.5)	< 0.001
MRI			
Distance from anal verge (5 < cm; n, %)	104 (21.5)	39 (23.2)	0.650
Tumor length (mean ± sd, cm)	4.2 ± 1.5		
Peritoneal reflection relationship (straddle/below; n, %)	384 (79.5)		
Mucinous tumor on MRI (> 50%; n, %)	11 (2.3)		
T stage (≥ T3/4a/4b; n, %)	376 (77.9)		
N stage (N1/N2; n, %)	278 (57.6)		
Lateral LN metastasis (n, %)	32 (6.6)		
CRM (< 1 mm; n, %)	100 (20.7)		
MTE (≥ 5 mm; n, %)	274 (56.7)		
mrEMVI (positive; n, %)	104 (21.5)	56 (33.3)	0.002
ADC (mean, $\mu m^2/s$)	1229.72 ± 194.3		
Largest single section area (mean, $mm^{2)}$	570.1 ± 507.8		
Total volume (mean, mm^3)	33748.2 ± 50898		
Pathology			
CRM (< 1 mm; n, %)	18 (5.5)		
Lymphatic invasion (n, %)	172 (36.4)		
Venous invasion (n, %)	61 (12.9)		
Perineural invasion (n, %)	83 (17.6)	36 (21.4)	0.271
LN metastasis (≥ 1; n, %)	186 (38.4)		
Tumor subtype (poly or unusual; n, %)	33 (7.2)		
Mucinous (n, %)	31 (6.8)		
EGFR (+; n, %)	265 (60.9)		
MLH1 (+; n, %)	424 (95.9)		
MSH2 (+; n, %)	431 (97.5)		
ERCC1 (+; n, %)	137 (31.1)		
Tyn-Syn0 (+; n, %)	109 (24.7)		
K-ras mutation exon2,3 (+; n, %)	146 (32.9)		
pT (≥ T3/4a/4b; n, %)	276 (56.4)	98 (58.3)	0.669
pN (N1/N2; n, %)	191 (39.1)	58 (34.5)	0.296

p value for difference was determined by using Pearson's chi-square test, Fisher's exact test, or the Kruskal–Wallis test

CEA, carcinoembryonic antigen; *CRT*, chemoradiotherapy; *CRM*, circumferential rectal margin; *MTE*, mesorectal tumor extension; *MRI*, magnetic resonance imaging; *EMVI*, extramural venous invasion; *ADC*, apparent diffusion coefficient

After selecting the predictors for new prediction model, the risk score of each predictor was calculated using hazard ratio (HR) rounded to the nearest integer. The total risk score of each patient was calculated by summing the scores of predictors included in the final model.

The model performance was assessed using discrimination and calibration measures and evaluated by the area under the Harrell C statistics [11], which is considered poor if less than 0.7; good if it is 0.7–0.8; and strongly discriminating if more than 0.8. Calibration is related to the goodness-of-fit, which reflects the agreement between observed outcomes and predictions. It was measured using the Nam-D'Agostino test [12]. A well-calibrated model yields a corresponding p value > .05.

The differences in the recurrence rate for increased total risk scores were assessed via the Cochran–Armitage test for trend. The relative hazard for recurrence between 3 different risk groups defined by the range of risk score was estimated by Kaplan-Meier curves and Cox regression analysis.

Model validation

The final prediction model was validated both internally and externally. Harrell C statistics and calibration measures were analyzed for internal and external validation sets. In addition, the C statistic of new model was compared with that of TNM staging in external validation set.

For internal validation, the simulation study was performed, which was formed with 1000 iterations of random data partition into training and validation sets (50:50 train/test split within model creation data). The risk score obtained from the training data was applied to the samples in the validation set and the corresponding risk groups were predicted for each sample. This process was iterated 1000 times to calculate the average prediction rate and its SD for accurate prediction of risk groups.

In the external validation set, RFS among risk groups classified by a new model was estimated by Kaplan-Meier curves. For comparison of the new model and TNM staging, the receiver operating characteristic curve (ROC) and area under the curve (AUC) were used. All the analyses were performed using SAS software, version 9.4 (SAS Institute). For all tests, $p < .05$ was considered indicative of a statistically significant difference.

Results

In the derivation cohort, disease recurrence was observed in 103 out of 489 patients (21.1%) comprising 19 cases of local recurrence, 67 distant metastases, and 17 cases showing a combination of local recurrence and distant metastasis. The median follow-up period of a total of 489 patients was 49.7 months (1–3048 days). The median disease-free period of 103 recurrent patients was 18.2 months. The remaining 386 disease-free patients were followed for a median period of 57.9 months. The distribution of pT stage was as follows: pT0 (n = 27), pT1 (n = 57), pT2 (n = 129), pT3 (n = 255), and pT4 (n = 21). The preoperative clinical stages were as follows: I (n = 155), II (n = 133), III (n = 200), and IV (n = 1; final pathologic stage of this patient was III because the suspicious hepatic metastasis was surgically confirmed as granuloma).

In the external validation cohort (n = 168), the median follow-up period was 33.4 months (2–1761 days), and disease recurrence was observed in 27 (16%). The clinical TNM stages were stages I (n = 55), II (n = 50), and III (n = 63). Detailed patient characteristics including clinical, radiologic, and pathologic variables are shown in Table 2.

Univariate and multivariate regression analysis for risk predictor selection

Univariate analysis showed that clinical stage, CEA, preoperative CRT, tumor length, and tumor location in relationship to peritoneal reflection, cT, cN, rCRM, MTE, mrEMVI pCRM, lymphatic/venous/perineural invasion, pT, and pN were significant predictors of recurrence (Table 3, all $p < .05$). For variable selection, we performed a stepwise elimination method with radiologic and clinicopathologic factors less than 0.2 of p value in univariate analyses. Since preoperative CRT is only performed for patients with advanced rectal cancer, this factor was excluded from multivariate analysis to avoid selection bias. MLH1 also excluded because there were a few MLH 1 negative cases (18/489, 4.1%), which acted as a possible confounding factor. We found following four significant risk factors and included them to build a prediction model for recurrence (Table 3): pN stage (HR = 2.59; p = <.001), perineural invasion (HR = 2.29; p = <.001), mrEMVI (HR = 2.09; p = .001), and distance from anal verge (HR = 1.69; p = .024).

Development of the final prediction model for recurrence

To simplify the estimation, HRs rounded to the nearest integer were used as the model score weights. Three points were assigned to pN and 2 points for distance from anal verge, mrEMVI, and perineural invasion (Table 4). Individual risk score was calculated as the sum of these four predictors.

In addition, we analyzed data by dividing it into only local recurrence group (n = 19) and systemic recurrence group (n = 84). Cox regression showed CRM, EMVI, perineural invasion, and tumor subtype as predictor of local recurrence in the univariate analysis (multivariable analysis was not done due to a very small number or local recurrence). And the predictors of systemic recurrence were EMVI, pN, and perineural invasion in the multivariate analysis. More details are described in Supplement.

Performance assessment and validation of a prognostic risk scoring system as a prediction model for disease recurrence

The performance of the disease prediction model for recurrence yielded a Harrell C statistic of 0.716 (95% CI, 0.666–0.766 suggesting good discrimination ability) and very good calibration (p >.999). In internal validation, the average

Table 3 Univariate and multivariate Cox regression analysis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Clinical variables				
Sex	0.95 (0.64–1.42)	.810		
Age	1.00 (0.98–1.02)	.802		
Clinical TNM stage	2.91 (1.95–4.36)	< .001		
CEA	1.01 (1.00–1.02)	.005		
Anastomotic leak	1.50 (0.74–3.04)	.260		
Preoperative CRT (no/yes)	1.94 (1.32–2.86)	< .001		
MRI variables				
Distance from anal verge (5 < cm)	1.38 (0.89–2.15)	.149	1.69 (1.07–2.66)	0.024
Tumor length	1.18 (1.06–1.32)	.004		
Peritoneal reflection (staddle, below)	1.75 (1.00–3.07)	.049		
T stage (≥ T3/4a/4b)	2.90 (1.52–5.50)	.001		
N stage (N1 or 2)	2.01 (1.31–3.09)	.002		
Lateral LN metastasis	1.78 (0.94–3.38)	.079		
CRM (< 1mm)	1.88 (1.22–2.89)	.004		
MTE (≥ 5mm)	2.05 (1.38–3.04)	< .001		
EMVI (+)	2.91 (1.95–4.34)	< .001	2.09 (1.35–3.24)	0.001
Mean ADC value	0.86 (0.72–1.02)	.086		
Whole tumor volume	1.11 (0.98–1.26)	.097		
Pathologic variables				
CRM (< 1mm)	2.67 (1.24–5.75)	.012		
Lymphatic invasion	2.81 (1.89–4.18)	< .001		
Venous invasion	2.15 (1.33–3.48)	.002		
Perineural invasion	3.51 (2.33–5.26)	< .001	2.29 (1.47–3.56)	< 0.001
Tumor subtype (poly or unusual)	1.84 (0.99–3.40)	.053		
EGFR	0.86 (0.57–1.28)	.449		
MLH1	2.09 (0.99–4.43)	.054		
MSH2	1.38 (0.47–4.04)	.554		
ERCC1	1.24 (0.79–1.96)	.357		
Tyn-Syn0	1.11 (0.69–1.81)	.662		
K-ras mutation exon2,3	1.05 (0.69–1.60)	.835		
T stage (≥ T3/4a/4b)	2.46 (1.59–3.82)	< .001		
N stage (N1 or 2)	3.24 (2.17–4.85)	< .001	2.59 (1.69–3.96)	< 0.001
Mucinous adenocarcinoma	1.81 (0.70–4.69)	.223		

Multivariate Cox regression analysis was done

Preoperative CRT was not included in the multivariate analysis because highly associated with tumor characteristics such as TNM stage or distance from anal verge, CRM, etc.

MLH was also excluded from the multivariate analysis owing to small negative cases (18/489, 4.1%) with the possibility of acting as a confounding factor

prediction rate and its SD in the training and validation sets were 0.941 (SD 0.235) and 0.940 (SD 0.238), respectively. In the external validation set, the Harrell C statistic of new prediction model was 0.794 (0.718–0.871), higher than TNM staging 0.709 (0.630–0.789), but not statistically significant (p = .132).

Patient recurrence risk stratification based on the new prediction model in the derivation and validation cohort

Applying our prediction model to individual patients of derivation ($n1$ = 489) and validation cohort ($n2$ = 168) yielded a

Table 4 Development of a risk prediction model

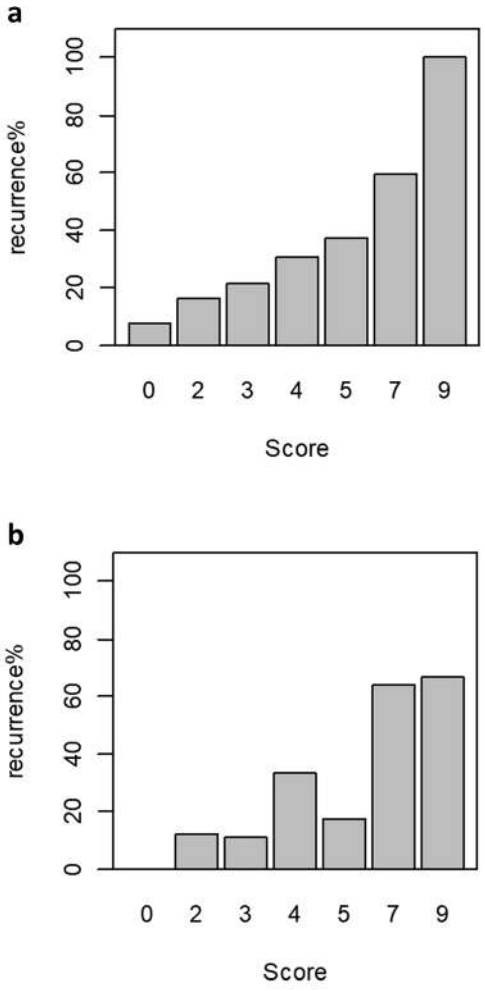
	β	Adjusted HR (95% CI)	p value	Assigned score
Distance from anal verge, cm				
< 5	0.52	1.69 (1.07–2.66)	0.024	2
≥ 5		Reference		0
EMVI				
Negative		Reference		0
Positive	0.74	2.09 (1.35–3.24)	0.001	2
Perineural invasion				
No		Reference		0
+/++/+++	0.83	2.29 (1.47–3.56)	< 0.001	2
Pathologic N stage				
N0		Reference		0
N1/N2	0.95	2.59 (1.69–3.96)	< 0.001	3

The risk score was calculated by using HR rounded to the nearest integer Harrell C statistics (95% CI)) = 0.72 (0.67–0.77), Nam-D'Agostino test, p value = 0.957

statistically significant increase in recurrence rate with increasing individual risk scores (Fig. 1). Recurrence rates of low-, intermediate-, and high-risk groups varied significantly in both derivation (13.4%, 35.3%, 61.5%) and validation cohorts (6.2%, 23.7%, 64.7%, respectively, Fig. 2). The Kaplan-Meier curve for RFS showed significant risk stratification among the low-, intermediate-, and high-risk groups in both derivation and validation cohorts (Fig. 3, log-rank test, $p <$ .001). The recurrence rate of stage I (n = 55), II (n = 50), and III (n = 63) subgroups of the validation set according to TNM classification were 3.6%, 12%, and 30.2% respectively. The risk grouping based on our new prediction model for recurrence showed an excellent ability to stratify the patients who underwent rectal cancer surgery according to recurrence rates, comparable with TNM staging classification (Fig. 3). For comparison, the ROC curve of 3-year recurrence was drawn by using TNM staging and the new prediction model. The AUC value of the new model was 0.853, significantly higher than 0.731 of TNM staging (p value = .009) (Fig. 4).

Discussion

Our prediction model for recurrence in rectal cancer was constructed with significant radiological, and clinicopathological variables including pN, perineural invasion, mrEMVI, and short distance from anal verge (< 5 cm). Although a few studies have attempted to develop prediction models for recurrence after rectal cancer surgery, they did not include radiological factors such as rCRM, MTE, mrEMVI, tumor volume, and ADC, which have been identified as potential prognostic factors. Our study added those radiological factors and showed excellent risk stratification in both derivation and validation cohorts.



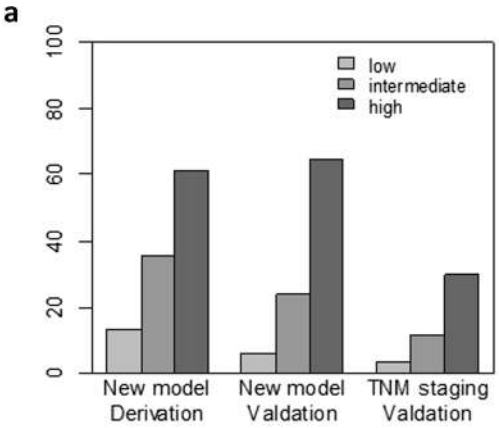
c

score	Derivation recurrence %	External validation recurrence %
0	13(7.6)	0(0.0)
2	16(16.0)	5(12.2)
3	20(21.5)	2(11.1)
4	8(30.8)	5(33.3)
5	22(37.3)	4(17.4)
7	22(59.5)	9(64.3)
9	2(100.0)	2(66.7)
P value	<0.001	<0.001

Fig. 1 The distribution of recurrence incidence according to the new prediction model for recurrence in the derivation (**a**) and validation (**b**) cohort. p value (**c**) for difference was determined using Cochran–Armitage test for trend

Prior studies used only clinical and pathological variables to develop prediction models for recurrence. Valentini et al [4] developed nomograms to predict local recurrence, distant metastasis, and overall survival in rectal cancer patients after preoperative radiotherapy (RT) or CRT and surgery. They reported that ypT,

a



b

	Derivation			validation			TNM staging (validation)			
	recurrence score %	HR(95% CI)	*p* value	recurrence score %	HR(95% CI)	*p* value		recurrence score %	HR(95% CI)	*p* value
low risk (score 0,2,3)	49/365(13.4)	reference		7/113(6.2)	reference		stage I	2(3.6)	reference	
intermediate risk (score4,5)	30/85(35.3)	3.14(1.99-4.95)	<0.001	9/38(23.7)	4.28(1.60-11.45)	0.004	stage II	6(12.0)	3.19(0.71-14.28)	0.130
high risk (score 7,9)	24/39(61.5)	7.42(4.53-12.15)	<0.001	11/17(64.7)	19.16(7.26-50.55)	<0.001	stage III	19(30.2)	8.05(2.08-31.15)	0.003

Fig. 2 **a**, **b** Recurrence risk between three different risk groups based on the new prediction model for recurrence in the derivation and validation cohort and TNM staging in the validation cohort

ypN, adjuvant chemotherapy, and surgical procedure were significant variables. Tumor location was not included in their model, unlike our study. However, the tumor location is a decisive factor in determining surgical procedure such as abdominoperineal resection (APR) or low anterior resection (LAR), so the fact that the surgery type was included in their model suggests the prognostic relevance of the tumor location.

In a similar study reported by Peng et al [6] evaluating prognostic factors for stage II–III rectal cancer patients without preoperative treatment, they added CEA level and LN ratio as predictors to their nomogram for distant metastasis and overall survival in addition to the variables reported in Valentini's study. The CEA level showed significant correlation with local recurrence, and marginally with distant metastasis and overall survival in univariate analysis but not in multivariate analysis, similar to our results. Like our results, they found that perineural invasion was associated with both distant metastasis and overall survival. Other studies also reported perineural invasion as a poor prognostic factor [13, 14]. Peng et al did not include perineural invasion to develop nomogram. However, our study included both perineural invasion and N stage among pathologic factors in the prediction model and showed good performance for recurrence prediction in both derivation and validation cohorts.

In our study, pT was not an independently significant variable in multivariate analysis, although it was significant in univariate analysis. Peng's study also showed a statistical significance only in the comparison between pT4 and pT1-2 groups, and not in the comparison between pT3 and pT1-2 groups. Therefore, it is presumed that pT in our study (pT3-4 vs. pT1-2) may exhibit a low statistical power.

In a prediction model involving the Asian population from 2005 to 2010, Hida et al [5] explored factors related to local recurrence after rectal cancer surgery. Unlike other studies, Hida's study developed a prediction model for local recurrence regardless of distant metastasis as the primary endpoint and found that tumor differentiation and anastomotic leakage might be attributed to local recurrence.

The exploration of radiological factors for the prediction of individual prognosis is new and noteworthy. MR imaging has been established as a robust tool for the evaluation of rectal cancer based on reliable staging in pre- and post-radiation therapy [13, 14]. In addition, functional imagings such as DWI or perfusion MRI are also useful tools to evaluate tumor cellularity, necrosis, or hemorrhage, reflecting biologic aggressiveness [15, 16]. In recent studies, MR imaging factors such as rCRM, MTE, mrEMVI, tumor volume, and ADC value were identified as prognostic factors, and thus, our study included these potential MR prognostic factors. Our results suggest that MR-based EMVI status was the only significant prognostic factor in multivariate analysis. EMVI was already established as a poor prognostic factor associated with tumor recurrence and overall survival [17–21]. In particular, MR evaluation of EMVI status was recommended due to huge variation in pathologic EMVI assessment and excellent correlation of mrEMVI with survival [20, 22, 23]. Our new prediction model, which included the image factor of EMVI, showed excellent correlation of recurrence rates and the risk stratification of model. The high-risk group of our new model

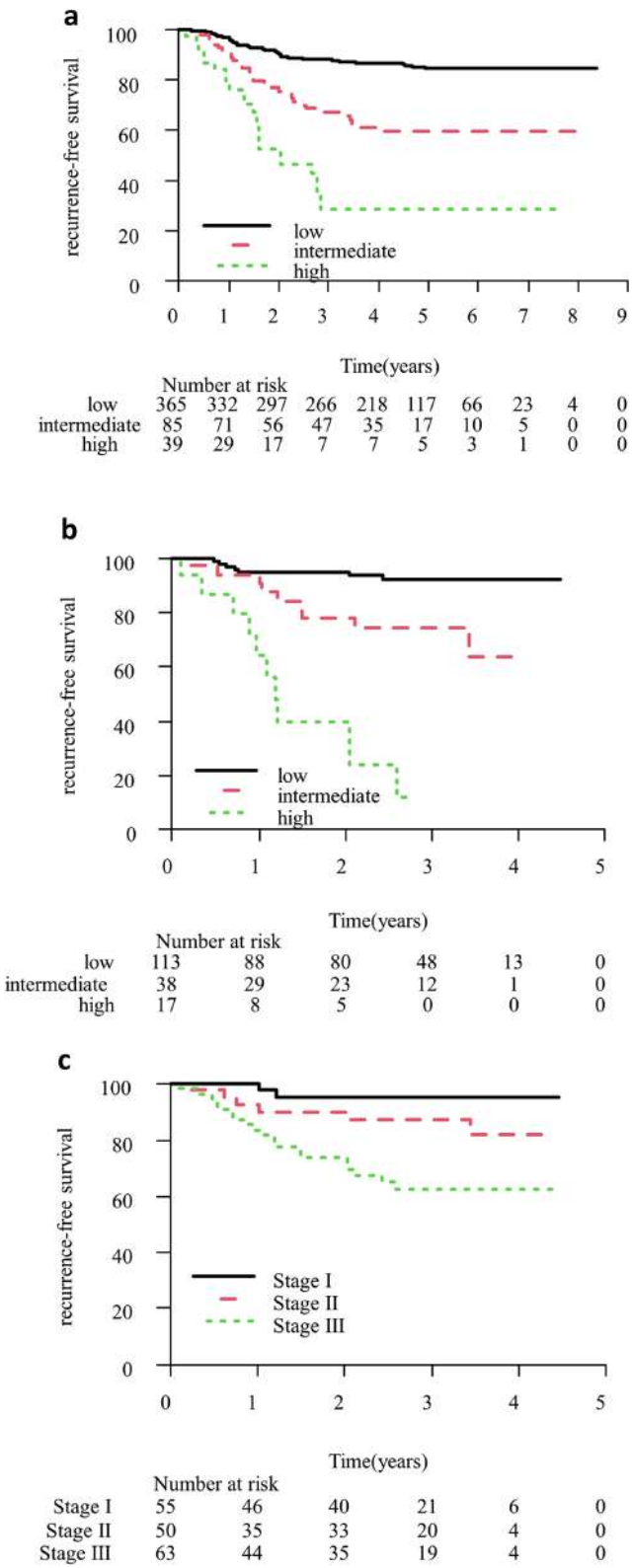


Fig. 3 Kaplan-Meier curve for recurrence-free survival of the three risk groups of new model (**a**, derivation cohort). Comparison of Kaplan-Meier curve for recurrence-free survival in validation cohort between new model risk groups (**b**) and TNM staging groups (**c**)

showed recurrence of 60% or more in both derivation and validation set. Compared with the recurrence rate of 30% in the TNM stage III of the validation set, we can see that our new prediction model better selected the range of the high-risk group. This could suggest that the high-risk group of our new model may need a tailored surveillance such as more frequent follow-up CT or tumor markers.

Our study has several limitations. First, this is a retrospective study and has a selection bias. Second, our variables did not include treatment factors such as surgery types or CRT protocol. Because this was a single institutional study with a relatively concordant treatment strategy determined by the patient's stages, the simultaneous analysis of stages and treatment factors could be a confounding factor. Third is the single observer who evaluated all scans in the study. Though she has 16 years of experience in oncologic MR imaging for rectal cancer, multiple reader's reviews could enhance the reliability of our results since EMVI assessment on MRI is subjective. Fourth, due to the small number of patients with local recurrences in our derivation cohort, the predictive role of local recurrence in our model is still unclear. Finally, our cohort was a heterogeneous group with cancer stages I to III compared with previous studies including patients with locally advanced cancer. This study is our preliminary trial to build an easy and simple risk assessment model for all postoperative patients. Our final goal was to select a highly recurrent group among all patients with stages I to III and to offer them more active surveillance during follow-up.

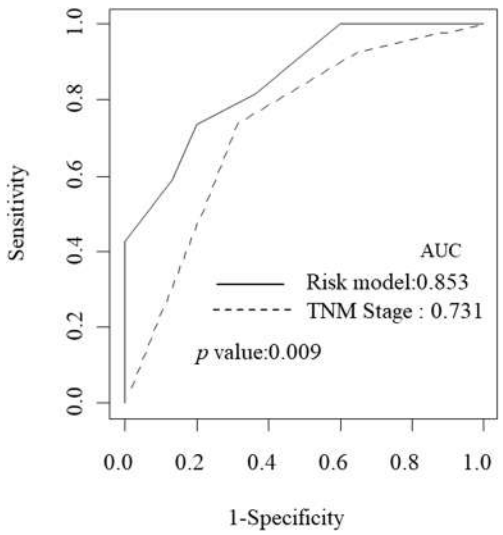


Fig. 4 Receiver operating characteristic curve. Comparison of 3-year recurrence-free survival of validation cohort between classical TNM staging and the new prediction model for recurrence

In conclusion, a multifactorial prediction model based on radiologic and clinicopathologic variables correlated strongly with disease recurrence rate after rectal cancer surgery. It can be used as a comprehensive approach to evaluate individual prognosis and helpful for the selection of highly recurrent group who needs more active surveillance.

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Declarations

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Statistics and biometry Two of the authors have significant statistical expertise (Mi Sun Park, MS, and Hyeon Woo Yim, MD, Ph.D).

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some cohorts of my previous two papers have been previously reported in the *Journal of Magnetic Resonance Imaging*, *JMRI* (2016), and *Diagnostic and Interventional Imaging* (2016), but the subjects were different from this current paper.

The *current study* focused on developing a risk prediction model for recurrence by incorporating radiological and clinicopathological factors in *489 patients* underwent rectal cancer surgery *between 2009 and 2013.*

The *JMRI* paper (2016, Diffusion-weighted imaging: apparent diffusion coefficient histogram analysis for detecting pathologic complete response to chemoradiotherapy in locally advanced rectal cancer) reported that the ability of DWI for treatment response evaluation in 86 rectal cancer patients who underwent post CRT surgery from *2012 July to 2014 November. Sixty-one out of 489* patients of the current study cohort overlap with the cohorts of the*JMRI* paper.

The paper reported in *Diagnostic Interventional Imaging* (2016, Clinical impact of tumor volume reduction in rectal cancer following preoperative chemoradiation) studied the usefulness of tumor volume reduction rate in response evaluation in 74 rectal cancer patients who underwent post CRT surgery between *2007 and 2010. Sixty-seven out of 489* patients of the current study cohort overlap with the cohorts of the *Diagn Interv Imaging* paper.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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