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ORIGINAL ARTICLE

Verification of the Japanese staging system for rectal cancer, focusing on differences with the TNM classification

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Abstract

Purpose The 9th Japanese Classification of Colorectal Cancer (9th JSCCR) has two main differences from the TNM classification (8th AJCC): first, main or lateral lymph node metastasis is classified as jN3; second, tumor nodules (ND) are treated as lymph node metastasis. In this study, we verified the 9th JSCCR for rectal cancer, focusing on the differences with the 8th AJCC.

Methods This retrospective analysis involved 212 patients with stage I-III rectal cancer. ND was evaluated using whole-mount sections. We evaluated the relapse-free survival of each staging system, and compared the prognostic significance of the different staging systems using the Akaike information criterion (AIC) and Harrell's concordance index (c-index).

Results Main or lateral lymph node metastasis was detected in nine of 212 (4%) patients. ND was detected in 79 of 212 (37%) patients. The best risk stratification power was observed in the 9th JSCCR (AIC, 759; c-index, 0.708) compared with the 7th JSCCR (AIC, 771; c-index, 0.681), 8th JSCCR (AIC, 768; c-index, 0.696), and the 8th AJCC (AIC, 766; c-index, 0.691).

Conclusions The 9th JSCCR, which includes the concepts of jN3 and ND, is useful for the risk stratification of rectal cancer, and the contributes to precise decision-making for follow-up management and adjuvant therapy.

Keywords Rectal cancer · The Japanese staging system · Whole-mount section · TNM classification · Akaike information criterion

Introduction

The ninth edition of the Japanese Classification of Colorectal Cancer defined by the Japanese Society for Cancer of the Colon and Rectum (9th JSCCR) [1] was modified in agreement with the eighth edition of the TNM classification defined by the American Joint Committee on Cancer (8th AJCC) [2]. In the 8th AJCC, regional lymph nodes are classified as N1 (one to three nodes) or N2 (four or more nodes) according to the number of nodes affected by metastasis. N1 is subdivided into N1a (one node) and N1b (two or three nodes), and N2 is subdivided into N2a (four to six nodes) and N2b (seven or more), because each subgroup represents roughly half the population of N1 and N2 categories, and the subgroups with fewer positive nodes have better survival than those with more positive nodes within the N1 and N2 categories [2–4]. Regarding the classification of lymph node metastasis, the 9th JSCCR was changed following the 8th AJCC.

However, the 9th JSCCR and the 8th AJCC differ mainly in two aspects. First, the JSCCR has a concept of jN3 in the classification of lymph node metastasis ("j" is used to distinguish the JSCCR classification from the TNM classification [5, 6]). To date, the expertise built up over several years has emphasized the importance of the main and lateral lymph nodes in Japan [7–14]. The metastatic disease in the main (i.e., around the root of the feeding artery) or lateral lymph nodes (i.e., internal iliac, common iliac, external iliac, and obturator nodes) is categorized as jN3 in the JSCCR classification. In the

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latest 9th JSCCR, patients with positive nodes are assigned to jN1a, jN1b, jN2a, jN2b, and jN3 categories according to the number and location of metastatic lymph nodes [1].

Second, the concept of "extramural discontinuous cancer spread without any lymph node structure (EX)" in the JSCCR classification differs from that of "tumor deposit" in the TNM classification. EX was first defined in the Japanese staging system in the 8th JSCCR, and it was retained in the 9th JSCCR. In both editions, EX was subclassified into tumor deposits other than vascular/perineural invasion (ND) or tumor deposits predominantly confined to the vascular or perineural spaces (VAS/NI) [1]. Importantly, ND is categorized as an assessment factor for lymph node metastasis, and treated as lymph node metastasis (i.e., if a patient has three lymph nodes affected by metastases and one ND in the mesorectum in the perirectal area, then the assigned category of lymph node metastasis is jN2) [1, 15]. VAS/NI is categorized as an assessment factor for the depth of invasion (i.e., if a patient has continuous spread to submucosa and discontinuous spread of lymphatic invasion in the mesorectum in the perirectal area, the category of the depth of invasion assigned is T3 (Ly)) [1, 15]. In contrast, the categorization of "tumor deposit" in the 8th AJCC is different from that in the 9th JSCCR. "Tumor deposit" is defined as discrete tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neural structure [2]. In cases with "tumor deposit" but no lymph node metastasis, the N1c category is used and is applicable to all T categories. The presence of "tumor deposit" does not change the primary tumor T category, but it does change the node status (N) to N1c if all regional lymph nodes are pathologically negative. Importantly, while the number of "tumor deposits" is not added to the number of positive lymph nodes if one or more lymph nodes contain cancer in the 8th AJCC, the number of ND is added to the number of positive lymph nodes in the 8th and 9th JSCCR.

Thus, great efforts have been made in Japan and Western countries to establish better staging systems. Detailed cancer staging that predicts the patients' prognosis is important for a precise and tailored management of cancer and useful decision-making concerning follow-up management and the adoption of adjuvant therapy. In this study, we verified the 9th JSCCR for rectal cancer, while focusing on the differences with the 8th AJCC.

Materials and methods

Patients

This retrospective analysis was performed in accordance with the Helsinki Declaration, and the Ethics Committee of Niigata Cancer Center Hospital approved the study protocol (2018–34). The analysis involved 212 patients with stage I-III rectal cancer according to the 9th JSCCR and the 8th AJCC [1, 2], who underwent curative-intent surgery at Niigata Cancer Center Hospital between January 2000 and December 2005. The anatomical definition of the rectum was based on the 9th JSCCR [1]. Selected patients fulfilled the following inclusion criteria: adenocarcinoma was confirmed on histological examination, and no preoperative chemotherapy or radiotherapy was prescribed. Lateral lymph node dissection is indicated when the lower border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria [7, 8, 11]. After the operation, the patients were observed for more than 5 years according to the JSCCR follow-up schedule [7, 8]. Disease recurrence was mainly determined by chest-abdominal-pelvic CT scans. Colonoscopy was performed to detect local recurrence at the anastomotic site. Adjuvant chemotherapy including fluorouracil or its derivatives was administered in stage III patients for 6 months. Oxaliplatin was not applied during this period.

Whole-mount sections of surgical specimens

We have previously described the handling of resected specimens [16–18]. Specimens of excised tissue were opened along the antimesenteric border and macroscopically evaluated. The mesenteric lymph nodes were dissected immediately after the operation by removing the mesenteric fatty tissue prior to histological examination. The mesorectum near the primary tumor was not dissected to observe the EX. Bowel specimens, including the mesorectum, were pinned under tension onto a plastic board so that it conformed to the same dimensions as in vivo. After fixation, the specimen was sectioned longitudinally (5–8 mm thick). All slices were embedded in paraffin, thin-sectioned and stained with hematoxylin and eosin.

Staging systems in the 7th, 8th and 9th JSCCR, and the 8th AJCC

The 212 patients were stratified according to each staging system (7th, 8th, and 9th JSCCR, and the 8th AJCC). The differences between the staging systems, which focused on jN3 and EX, are shown in Table 1.

Main or lateral lymph node metastasis, EX, and other clinicopathological characteristics

Main and lateral lymph nodes were defined according to the 9th JSCCR [1]. One of the authors (Y.S.) evaluated ND and VAS/NI using whole-mount sections with the definition of the 9th JSCCR (Fig. 1) [1]. Nine classical clinicopathological

Table 1 Differences between the staging systems focused on jN3 and extramural discontinuous cancer spread without any lymph node structure

Staging system	LNM		EX	
	Categorization of lymph node	Definition	ND (defined by JSCCR) TD (defined by AJCC)	VAS/NI (defined by JSCCR)
JSCCR, 7th edition	jN1	One to three LNMs	Not defined	Not defined
	jN2	Four or more LNMs		
	jN3	Main or lateral LNMs		
JSCCR, 8th edition	jN1	One to three LNMs	Categorized as assessment factor for LNM, and the number of NDs is added to the number of positive LNM	Categorized as assessment factor for depth of invasion
	jN2	Four or more LNMs		
	jN3	Main or lateral LNMs		
JSCCR, 9th edition	jN1a	One LNM	Categorized as assessment factor for LNM, and the number of NDs is added to the number of positive LNM	Categorized as assessment factor for depth of invasion
	jN1b	Two to three LNMs		
	jN2a	Four to six LNMs		
	jN2b	Seven or more LNs		
	jN3	Main or lateral LNMs		
AJCC, 8th edition	N1a	One LNM	Categorized as N1c if all regional LNs are pathologically negative	
	N1b	Two to three LNMs		
	N1c	Tumor deposits but no LNM		
	N2a	Four to six LNMs		
	N2b	Seven or more LNMs		

AJCC American Joint Committee on Cancer, *EX* extramural discontinuous cancer spread without lymph node structure, *JSCCR* Japanese Society for Cancer of the Colon and Rectum ("j" is used to distinguish the JSCCR classification from the TNM classification), *LNM* lymph node metastasis, *ND* tumor deposits other than vascular/perineural invasion defined by JSCCR, *TD* tumor deposits other than vascular/perineural invasion defined by AJCC, *VAS/NI* tumor deposits predominantly confined to the vascular or perineural spaces

variables were examined to analyze the relationship between EX (both ND and VAS/NI) and other clinicopathological characteristics.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 22 (IBM Japan, Inc., Tokyo, Japan) and software R. Fisher's exact test was used to evaluate the associations between EX and the other clinicopathological characteristics. The five-year relapse-free survival (RFS) rates were estimated using the Kaplan–Meier method in the different staging systems. The log-rank test was used to assess significant differences between subgroups by a univariate analysis. *P*-values of less than 0.05 were considered to be statistically significant. The prognostic stratification of each staging system was evaluated by the Akaike information criterion (AIC) [19] and Harrell's concordance index (c-index) [20]. The optimal model gives the lowest AIC value. A Harrell's c-index of 0.5 indicates an accuracy equivalent to random guessing, and that of 1.0 indicates 100% predictive accuracy.

Results

Main or lateral lymph node metastasis, EX and other clinicopathological characteristics

Main or lateral lymph node metastasis was detected in nine of 212 (4%) patients; one patient with a rectal tumor between the peritoneal reflection and superior border of the puborectal muscle (Rb) had main lymph node metastasis. Eight patients with an Rb tumor had lateral lymph node metastasis.

ND was detected in 79 of 212 (37%) patients and was significantly associated with tumor size (≥ 40 mm), T category (T3, 4), histopathological grade 3, lymphatic invasion, venous invasion, and N category (N1, 2, 3; Table 2). VAS/NI was detected in 43 of 212 (20%) patients, and was significantly associated with tumor size (≥ 40 mm), T category (T3, 4), histopathological grade 3, lymphatic invasion, venous invasion, and N category (N1, 2, 3; Table 3).

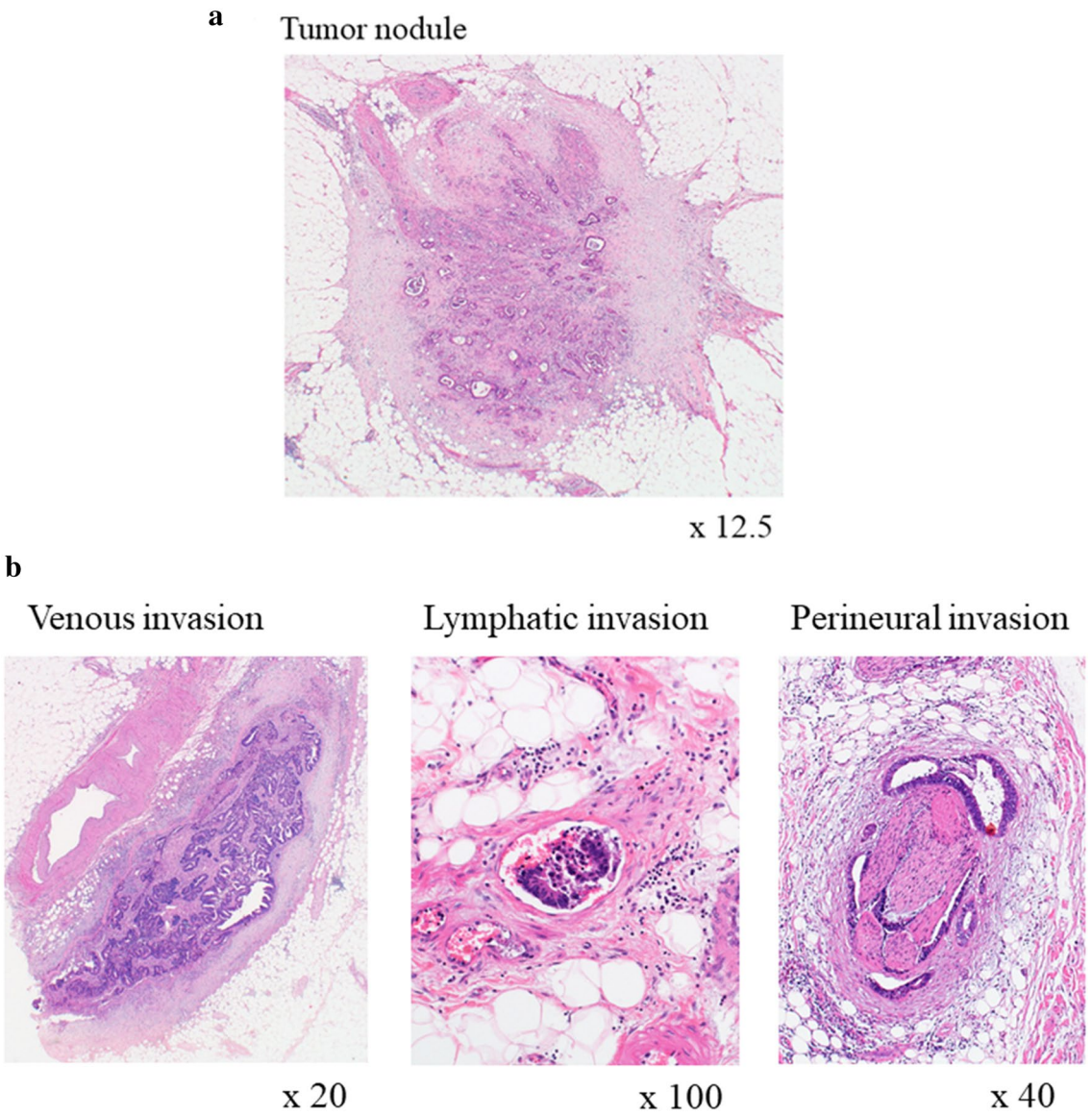

Fig. 1 Extramural discontinuous cancer spread without any lymph node structure. Tumor deposits other than vascular/perineural invasion (ND) (**a**). Tumor deposits predominantly confined to the vascular or perineural spaces (VAS/NI) (**b**)

Comparison of staging systems in the 7th, 8th, and 9th JSCCR, and the 8th AJCC

In Table 4, we show a comparison of the different staging systems according to the proportion of case numbers allocated to each N category. In Fig. 2, we show the Kaplan–Meier survival curves for RFS of each staging system. The best risk stratification power was observed in the 9th JSCCR (AIC, 759; c-index, 0.708) compared with the 7th JSCCR (AIC, 771; c-index, 0.681), 8th JSCCR (AIC, 768; c-index, 0.696), and 8th AJCC (AIC, 766; c-index, 0.691; Table 5). Figure 3 demonstrates the increased prognostic stratification value from the 7th JSCCR to the 9th JSCCR using AIC and c-index.

Discussion

In this study, we demonstrate the appropriateness of the latest JSCCR staging system, which includes the subclassification of jN1 (jN1a and jN1b) and jN2 (jN2a and jN2b), the concept of jN3, and integration of ND, which is treated as lymph node metastasis. Our study revealed two important findings regarding each staging system of rectal cancer. First, we demonstrated the increased prognostic stratification value from the 7th JSCCR to the 9th JSCCR. Second, the 9th JSCCR showed superior prognostic stratification value compared with the 8th AJCC. We believe these results demonstrate the validity of the handling of jN3 (main and lateral lymph nodes) and ND as claimed by Japanese experts.

Table 2 Tumor deposits other than vascular/perineural invasion (ND) and other clinicopathological characteristics

Variable	ND				*P*-value
	Absence (*N* = 133)		Presence (*N* = 79)		
	Number of patients	%	Number of patients	%	
Age (years)					
< 65	64	30	40	19	0.777
≥ 65	69	33	39	18	
Sex					
Male	90	42	60	29	0.215
Female	43	20	19	9	
Tumor location					
RS/Ra	90	42	58	28	0.440
Rb/P	43	20	21	10	
Tumor size (mm)					
< 40	86	41	25	12	< 0.001
≥ 40	47	22	54	25	
T category					
T1, 2	83	40	4	2	< 0.001
T3, 4	50	24	75	34	
Histopathological grading					
G1	98	46	35	17	< 0.001
G2, 3	35	17	44	20	
Lymphatic invasion					
Absence	80	38	3	1	< 0.001
Presence	53	25	76	36	
Venous invasion					
Absence	17	8	1	0	0.004
Presence	116	55	78	37	
N category					
N0	110	52	0	0	< 0.001
N1, 2, 3	23	11	79	37	

Fisher's exact test was applied to assess associations

P from superior border of puborectal muscle to anal verge, *Ra* rectum between inferior border of 2nd sacral vertebra and peritoneal reflection, *Rb* rectum between peritoneal reflection and superior border of puborectal muscle, *RS* rectum between the promontory and inferior border of the 2nd sacral vertebra

Table 3 Tumor deposits predominantly confined to the vascular or perineural spaces (VAS/NI) and other clinicopathological characteristics

Variable	VAS/NI				*P*-value
	Absence (*N* = 169)		Presence (*N* = 43)		
	Number of patients	%	Number of patients	%	
Age (years)					
< 65	85	40	19	9	0.499
≥ 65	84	40	24	11	
Sex					
Male	114	54	36	17	0.040
Female	55	26	7	3	
Tumor location					
RS/Ra	119	56	29	14	0.713
Rb/P	50	24	14	6	
Tumor size (mm)					
< 40	98	46	13	6	0.002
≥ 40	71	34	30	14	
T category					
T1, 2	85	40	2	1	< 0.001
T3, 4	84	40	41	19	
Histopathological grading					
G1	115	54	18	8	0.002
G2, 3	54	26	25	12	
Lymphatic invasion					
Absence	78	37	5	2	< 0.001
Presence	91	43	38	18	
Venous invasion					
Absence	18	8	0	0	0.027
Presence	151	72	43	20	
N category					
N0	102	48	8	3	< 0.001
N1, 2, 3	67	32	35	17	

Fisher's exact test was applied to assess associations

P from superior border of puborectal muscle to anal verge, *Ra* rectum between inferior border of 2nd sacral vertebra and peritoneal reflection, *Rb* rectum between peritoneal reflection and superior border of puborectal muscle, *RS* rectum between the promontory and inferior border of the 2nd sacral vertebra

In rectal cancer, lymphatic spread corresponds to the anatomical location of the tumor [21, 22]. When the tumor is situated above the peritoneal reflection, then metastasis predominantly spreads along perirectal vessels originating from the inferior mesenteric artery. In contrast, when the primary tumor is located at or below the peritoneal reflection, lymphatic cancer metastasis can demonstrate an upward mesenteric and lateral extramesenteric spread along the internal iliac vessels. Japanese surgeons perform "D3 dissection" to control both main and lateral lymph node metastases in rectal cancer [23], while preoperative chemoradiation and total mesorectal excision is the standard treatment in Western countries [24, 25].

In this study, we evaluated EX using whole-mount sections, which may have affected the high rate of ND (37%). The incidence of EX in colorectal cancer is reported to be 5.2–44.2% [15, 16, 26, 27]. In these reports, investigations not using whole-mount sections showed a 5.2–25.6% incidence of EX, while studies using whole-mount sections reported a 34.0–44.2% incidence of EX [16].

Table 4 Comparison of 7th JSCCR, 8th JSCCR, 9th JSCCR, and 8th AJCC according to the proportion of cases allocated to each N category

	Categorization of lymph node	Number of patients	%
JSCCR, 7th edition	jN0	131	62
	jN1	46	22
	jN2	26	12
	jN3	9	4
JSCCR, 8th edition	jN0	110	52
	jN1	55	26
	jN2	38	18
	jN3	9	4
JSCCR, 9th edition	jN0	110	52
	jN1a	27	13
	jN1b	28	13
	jN2a	11	5
	jN2b	27	13
	jN3	9	4
AJCC, 8th edition	N0	110	52
	N1a	33	15
	N1b	15	7
	N1c	21	10
	N2a	14	7
	N2b	19	9

AJCC American Joint Committee on Cancer, *JSCCR* Japanese Society for Cancer of the Colon and Rectum ("j" is used to distinguish the JSCCR classification from the TNM classification)

EX has been investigated in studies of colorectal cancer for two decades [15, 26, 27]. The categorization of EX by the AJCC has changed several times. The 5th AJCC proposed the first categorization of EX, determined on the basis of size: an EX with a diameter greater than 3 mm was classified in the N category as a lymph node metastasis, whereas an EX with a diameter up to, but not exceeding, 3 mm was classified in the T category as a discontinuous tumor extension [28]. In contrast, the criteria for EX categorization relied on the contour in the 6th AJCC, which recommended that a tumor nodule be classified in the N category if the nodule had a smooth contour and in the T category if the nodule had an irregular contour [29]. Currently, the categorizations of EX according to size and contour have been abandoned. Instead, the 7th AJCC denoted that a peritumoral deposit or satellite nodule in the pericolic or perirectal fat, which may represent discontinuous spread, extravascular spread, or a totally replaced lymph node, is recorded as a "tumor deposit". Regarding the treatment of "tumor deposit" in the TNM classification, the 7th AJCC stated that totally "replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the site-specific factor category" [30].

In the latest AJCC, the N1c category is used in cases with tumor deposits but no lymph node metastasis, and the number of "tumor deposits" is not added to the number of positive lymph nodes if one or more lymph nodes contain cancer [2]. In contrast, in the 9th JSCCR, ND is categorized as an assessment factor for lymph node metastasis, and the number of ND is added to the number of positive lymph nodes. So far, no consensus has been reached as to which classification has better prognostic discrimination. In this study, we, therefore, evaluated the risk stratification power of the 9th JSCCR compared with the 8th AJCC, and found that the risk stratification power of the 9th JSCCR was superior to that of the 8th AJCC. The result implies that the 8th AJCC may have missed the importance of the stratification capacity of "tumor deposit".

This study is associated with some limitations. First, it was a retrospective analysis that included a small number of patients. Second, this analysis did not include patients with preoperative therapy. However, to the best of our knowledge, this is the first report that demonstrates the clinical utility of the 9th JSCCR for rectal cancer, which includes the concept of jN3 (both main and lateral lymph nodes) and ND.

In conclusion, the 9th JSCCR is useful for the risk stratification of rectal cancer, and it positively contributes to precise decision-making concerning the follow-up management and the administration of adjuvant therapy.

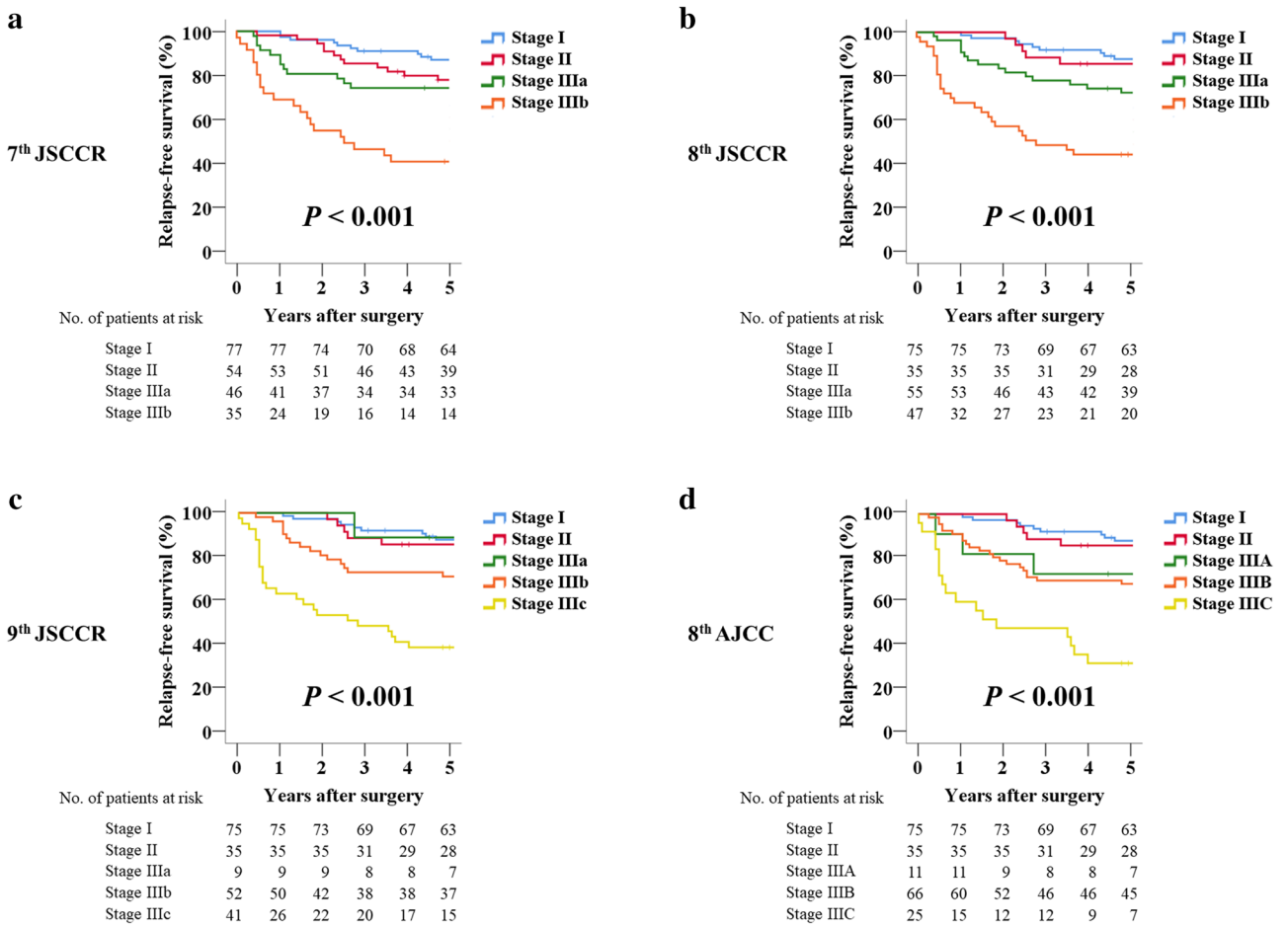

Fig. 2 Relapse-free survival of each staging system. Kaplan–Meier curves of relapse-free survival for stage I–III patients in the 7th JSCCR (**a**), 8th JSCCR (**b**), 9th JSCCR (**c**), and 8th AJCC (**d**)

Table 5 Comparison of 7th JSCCR, 8th JSCCR, 9th JSCCR, and 8th AJCC according to the proportion of cases allocated to each tumor stage and prognostic value

Stage and edition	Number of patients	5-year RFS (%)	AIC	c-index
JSCCR, 7th edition				
I	77	83.1	770.9	0.6815
II	54	72.2		
IIIa	46	71.7		
IIIb	35	40.0		
JSCCR, 8th edition				
I	75	84.0	768.0	0.6968
II	35	80.0		
IIIa	55	70.9		
IIIb	47	42.6		
JSCCR, 9th edition				
I	75	84.0	759.4	0.7087
II	35	80.0		
IIIa	9	77.8		
IIIb	52	71.2		
IIIc	41	35.7		
AJCC, 8th edition				
I	75	84.0	766.0	0.6910
II	35	80.0		
IIIA	11	63.6		
IIIB	66	68.2		
IIIC	25	28.0		

AIC The Akaike Information Criterion, *AJCC* American Joint Committee on Cancer, *c-index* Harrell's concordance index, *JSCCR* Japanese Society for Cancer of the Colon and Rectum, *RFS* relapse-free survival

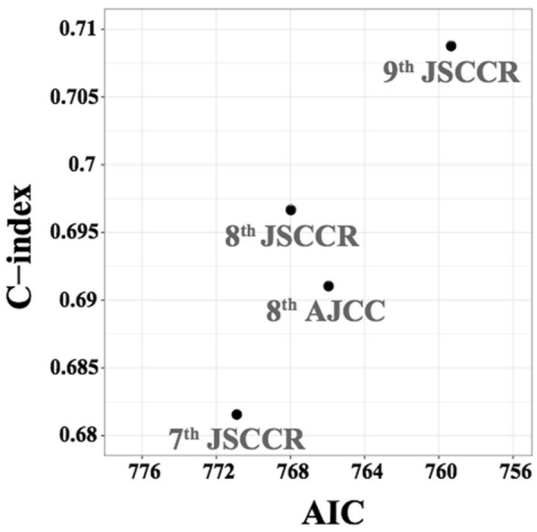

Fig. 3 Prognostic stratification values of each staging system. Plots of each staging system using the Akaike information criterion (AIC) and Harrell's concordance index (c-index)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest in association with this study.

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