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Original Article

Optimizing nodal and staging classification in low rectal cancers with lateral node metastasis: multicentre retrospective cohort study

Eiji Shinto[1,*], Hideyuki Ike[2], Masaaki Ito[3], Keiichi Takahashi[4], Masayuki Ohue[5], Yukihide Kanemitsu[6], Takeshi Suto[7], Tetsushi Kinugasa[8], Jun Watanabe[9], Jin-ichi Hida[10], Michio Itabashi[11], Heita Ozawa[12], Hiroaki Nozawa[13], Hirotoshi Kobayashi[14], Yojiro Hashiguchi[15], Kazuo Hase[1] and Kenichi Sugihara[16]

[1]Department of Surgery, National Defense Medical College, Tokorozawa, Japan
[2]Department of Surgery, JCHO Yokohama Hodogaya Central Hospital, Yokohama, Japan
[3]Department of Colorectal Surgery, National Cancer Center Hospital East, Kashiwa, Japan
[4]Department of Surgery, Tokyo Metropolitan Health and Hospitals Corporation Ohkubo Hospital, Tokyo, Japan
[5]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan
[6]Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan
[7]Department of Gastroenterological Surgery, Yamagata Prefectual Central Hospital, Yamagata, Japan
[8]Department of Surgery, Fukuoka Sanno Hospital, Fukuoka, Japan
[9]Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan
[10]Department of Surgery, Kindai University Nara Hospital, Ikoma, Japan
[11]Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan
[12]Department of Colorectal Surgery, Tochigi Cancer Center, Utsunomiya, Japan
[13]Department of Surgical Oncology, The University of Tokyo, Tokyo, Japan
[14]Department of Surgery, Teikyo University Hospital, Mizonokuchi, Kawasaki, Japan
[15]Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan
[16]Tokyo Medical and Dental University, Tokyo, Japan

Correspondence to: Eiji Shinto, Department of Surgery National Defense Medical College 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan (e-mail: eiji-c@zf6.so-net.ne.jp)

Abstract

Background: Patients with lateral node metastasis in low rectal cancers have a poor prognosis. However, variability in patient survival in terms of lateral metastatic status has not been thoroughly investigated. This study was conducted to assess the prognostic value of lateral node involvement and to review nodal classification.

Methods: Patients with stage III low rectal cancers who underwent lateral node dissection were retrospectively reviewed. Two cohorts were set: the first one (1995–2006) was selected using a Japanese multi-institutional database and was used for development of a new nodal system, and the second (2007–2013) was collected from referral institutions for validation of findings. Variables correlated with poor prognosis were investigated. Next, a modified classification of lateral-positive nodal cancers was created. Finally, this new classification was compared with TNM and Japanese classification-based systems according to the Akaike information criterion (AIC) and concordance index (c-index).

Results: Overall, 742 and 508 patients were selected for cohorts 1 and 2, respectively. Based on the analyses on cohort 1, patients with two or more lateral metastatic nodes partially spreading into regions outside of internal iliac area exhibited poor prognosis; accordingly, a modified N classification was created, where TNM-N1 and N2a cancers with this feature were upgraded, respectively, to N2a and N2b. The modified N classification yielded the most favourable indices (AIC = 2661.08; c-index = 0.6477) compared with the TNM (AIC = 2662.36; c-index = 0.6457) and Japanese classification-based systems (AIC = 2684.06; c-index = 0.6302). All findings were confirmed by analysing cohort 2.

Conclusion: A modified nodal system is proposed to account for the significance of lateral node metastasis.

Introduction

Although uncommon, low rectal cancers can exhibit nodal metastases in the lateral area. Currently, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) defines the presence of lateral lymph node metastasis as a N3 nodal stage[1]. A recent retrospective study reported that stage III patients with lateral lymph node metastasis demonstrated worse prognosis than patients with negative lateral nodes but better prognosis than stage IV rectal cancers[2]. Other retrospective analyses from Japan showed that lateral-positive patients treated with curative surgery (R0) without preoperative chemoradiotherapy reported a 5-year survival raging between 40 and 50 per cent[3,4].

A D3 dissection (dissection of mesorectal and lateral lymph nodes) is Japanese standard practice for stage II/III low rectal cancers.[5] However, the TNM classification of rectal cancer does not

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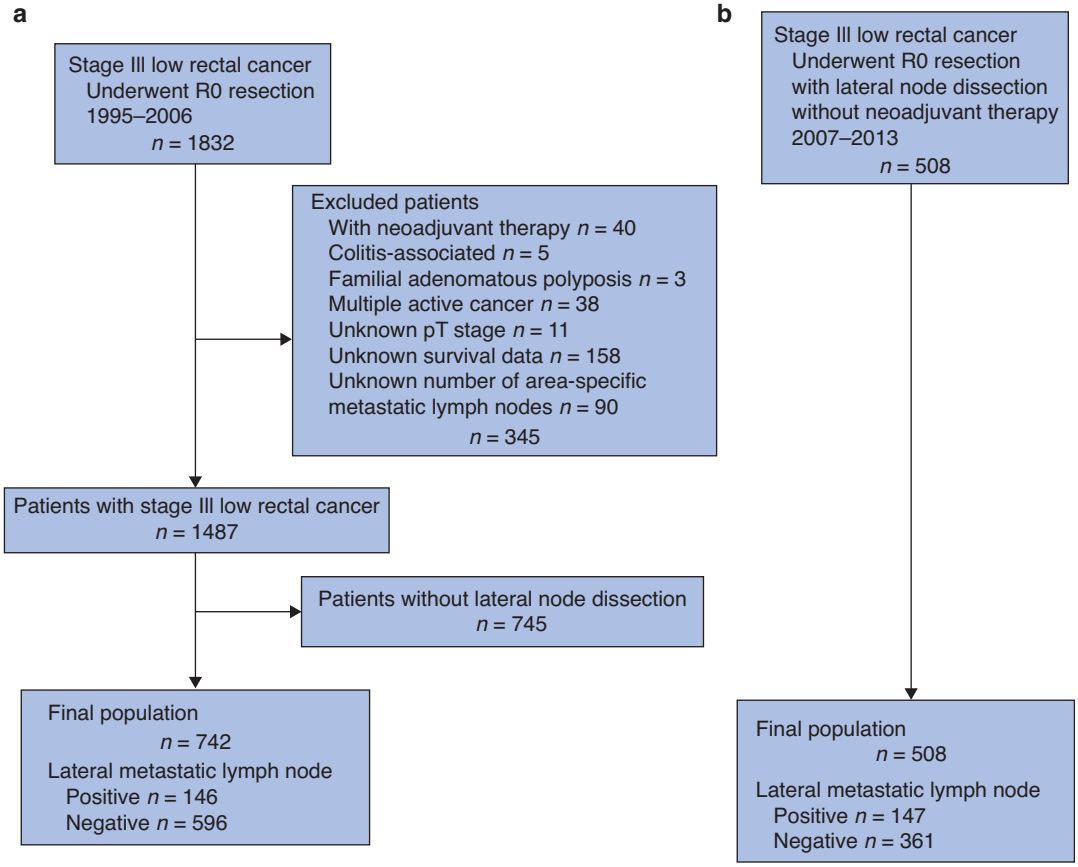

Fig. 1 Consort diagrams
a Cohort 1. **b** Cohort 2.

consider in depth the positivity of lateral pelvic lymph nodes[6], and the variability in patient survival in terms of lateral metastatic status has not been thoroughly investigated. Therefore, it is necessary to investigate whether information on lateral status adds value to the TNM classification system.

This study was conducted to assess the prognostic value of lateral node involvement in low rectal cancers and to propose a new lateral (L) stage and nodal (N) classification based on these findings. Secondary aims were to validate the new classification in a subsequent cohort and to compare the newly proposed categories with the TNM and the Japanese classification systems.

Methods

Definitions

For the purposes of this study, low rectal cancer was defined as a rectal cancer whose distal margin was located below the peritoneal reflection. According to the JSCCR classification, N3 is assigned to both lateral lymph node metastasis and root node metastasis of inferior mesenteric artery in low rectal cancer, whereas N2b is assigned to the presence of metastasis in seven or more lymph nodes[1]. However, as the analyses in the present study were focused on lateral nodal metastasis (and not on the root of the inferior mesenteric artery), N3(L) was newly defined as lateral node metastasis to assess its specific impact in the 'JSCCR-based N classification'. Hence, the JSCCR-based N classification used in this study was partially different from the actual JSCCR-N classification system. Practically, N3(L) was ranked equally with N2b, and these two were combined into one category of N2b/N3(L).

Patients

Two different groups of patients with low rectal cancers were reviewed and analysed. Firstly, all clinical and pathological data of consecutive stage III patients with histologically confirmed lymph node metastasis who underwent upfront R0 resection for primary low rectal cancer between 1 January 1995 and 31 December 2006 were retrieved from a JSCCR multi-institutional database that includes 127 institutions (cohort 1). This cohort was analysed with the aim of investigating the prognostic value of lateral nodal metastasis and to develop the new classification system. Patients with colitis-associated cancer, familial adenomatous polyposis, distant metastases, or multiple active cancers, and those who received neoadjuvant chemotherapy and/or radiotherapy were excluded. Patients were also excluded if registered with unknown or missing data on tumour depth, extent of lymph node dissection, number and area of metastatic lymph nodes, and/or survival. Lastly, patients without lateral node dissection were excluded.

The second cohort was collected from 12 Japanese referral institutions associated with the lymph node committee of the JSCCR to validate of the new N classification system. Consecutive patients with stage III low rectal cancer who underwent R0 resection with lateral node dissection without neoadjuvant chemotherapy and/or radiotherapy between 1 January 2007 and 30 June 2013 were retrospectively identified (cohort 2). Cases were selected at each institution according to the inclusion/exclusion criteria described for cohort 1.

The study protocol was approved by the ethical review board of the JSCCR (protocol number: 90-3) and by the institutional review board of each participating institution. Written informed consent

Table 1 Patient distribution in cohorts 1 and 2

	Cohort 1				Cohort 2			
		Lateral lymph node metastasis		P		Lateral lymph node metastasis		P
	Total $n=742$	Positive $n=146$	Negative $n=596$		Total $n=508$	Positive $n=147$	Negative $n=361$	
Age (years)								
≤59	328	71 (21.7)	257 (78.3)	0.23	216	61 (28.2)	155 (71.8)	0.71
60–69	269	44 (16.4)	225 (83.6)		183	51 (27.9)	132 (72.1)	
≥70	145	31 (21.4)	114 (78.6)		109	35 (32.1)	74 (67.9)	
Sex*								
Male	294	64 (21.8)	230 (78.2)	0.23	335	98 (29.3)	237 (70.7)	0.83
Female	446	81 (18.2)	365 (81.8)		173	49 (28.3)	124 (71.7)	
T status								
T1	17	2 (11.8)	15 (88.2)	0.001	4	1 (25.0)	3 (75.0)	0.093
T2	118	20 (17.0)	98 (83.0)		63	17 (27.0)	46 (73.0)	
T3	557	103 (18.5)	454 (81.5)		397	109 (27.5)	288 (72.5)	
T4b	50	21 (42.0)	29 (58.0)		44	20 (45.5)	24 (54.5)	
TNM-N status								
N1	477	65 (13.6)	412 (86.4)	<0.001	307	60 (19.5)	247 (80.5)	<0.001
N2a	144	29 (20.1)	115 (79.9)		90	32 (35.6)	58 (64.4)	
N2b	121	52 (43.0)	69 (57.0)		111	55 (49.6)	56 (50.4)	
TNM stage								
IIIA	114	16 (14.0)	98 (86.0)	<0.001	55	16 (29.1)	39 (70.9)	<0.001
IIIB	480	72 (15.0)	408 (85.0)		315	67 (21.3)	248 (78.7)	
IIIC	148	58 (39.2)	90 (60.8)		138	64 (46.4)	74 (53.6)	
JSCCR-based N status								
N1	412	0 (0)	412 (100)	<0.001	247	0 (0)	247 (100)	<0.001
N2a	115	0 (0)	115 (100)		58	0 (0)	58 (100)	
N2b/N3(L)	215	146 (67.9)	69 (32.1)		203	147 (72.4)	56 (27.6)	
Number of lymph nodes examined†								
≤11	92	9 (9.8)	83 (90.2)	0.005	9	1 (11.1)	8 (88.9)	0.46
≥12	611	137 (22.4)	474 (77.6)		499	146 (29.3)	353 (70.7)	
Adjuvant chemotherapy‡								
Chemotherapy	187	53 (28.3)	134 (71.7)	0.077	421	120 (28.5)	301 (71.5)	0.64
Surgery alone	87	16 (18.4)	71 (81.6)		87	27 (31.0)	60 (69.0)	

Data are *n* (%). *Information of sex is not available for two patients in cohort 1. †Information of number of lymph nodes examined is not available for 39 patients in cohort 1. ‡Information of adjuvant chemotherapy is not available for 468 patients in cohort 1. JSCCR, Japanese Society for Cancer of the Colon and Rectum.

was obtained from all patients, in accordance with the respective institutional regulations.

Construction of L-stage and modified N classification

L-stage was designed as a prognostic subcategorization system of lateral-positive patients based on lateral factors (the number and area of metastatic lateral lymph nodes). Firstly, using patients with a single metastatic lymph node in the lateral area, the impact of the metastatic area on prognosis was investigated, and then the respective lateral areas were graded according to their impact on prognosis. Next, patients with metastasis in the lateral area were divided into subgroups according to the number and area of metastatic lateral lymph nodes. After ranking the survival rates of these subgroups, they were integrated to create the bisection categorization (L-stage) that yielded the best risk stratification power. To investigate the added value of the L-stage to the TNM-N, the survival rates of the subgroups according to the two systems (TNM-N and L-stage) were carefully evaluated. Then, a TNM-N plus L-stage system (a modified N classification system) was developed where the TNM-N status of cancers in the high-risk category was upgraded according to the L-stage.

Validation of the modified N classification system

The modified classification system was compared with the TNM and JSCCR-based systems based on the Akaike information criterion (AIC)[7] and Harrell's concordance index (c-index) in cohorts 1 and 2, respectively[8]. AIC was analysed in a Cox proportional hazards regression model to identify the grading system with the best ability to stratify patients according to the survival outcome. The model with the lowest AIC value was considered as the optimum (i.e. the simplest effective model with the least information loss when predicting the outcome). Harrell's c-index was also calculated as a measure of predictive accuracy of the survival outcome; a c-index of 0.5 indicates accuracy similar to random guessing, and that of 1.0 indicates 100 per cent predictive accuracy.

Of note, a group of patients treated with surgery alone consisted of those with severe past medical history who could not be treated with standard therapies, even when recurrence was encountered. As these situations could cause bias in the survival analyses, the L-stage and the modified N classification were re-examined among patients receiving adjuvant chemotherapy collected from both cohorts.

Statistical analysis

Group comparisons were conducted using the χ^2 test or Fisher's exact test. Cancer-specific survival (CSS) was defined as the time from surgery to death due to rectal cancer recurrence. Patient survival curves were generated using the Kaplan–Meier method and were compared using the log-rank test. All statistical analyses were conducted using the JMP12 software (SAS Institute, Cary, North Carolina, USA) and STATA/IC 16 (StataCorp, College

Table 2 Prognostic significance of clinicopathological factors in cohorts 1 and 2

	Cohort 1		Cohort 2	
	5-year cancer-specific survival (Kaplan–Meier method; %)	P	5-year cancer-specific survival (Kaplan–Meier method; %)	P
Age (years)				
≤ 59	73.2	0.12	79.3	0.030
60–69	72.4		81.7	
≥ 70	62.6		72.4	
Sex				
Male	72.3	0.19	76.9	0.40
Female	70.1		82.3	
T status				
T1	87.1	<0.001	100	0.055
T2	85.5		88.4	
T3	68.6		77.7	
T4b	55.7		71.4	
TNM-N status				
N1	80.4	<0.001	88.5	<0.001
N2a	63.8		74.0	
N2b	41.0		53.3	
Lateral lymph node metastasis				
Negative	74.1	<0.001	84.0	<0.001
Positive	57.9		65.0	
JSCCR-based N status				
N1	81.2	<0.001	90.1	<0.001
N2a	63.6		80.3	
N2b/N3(L)	55.0		63.3	
Number of lymph nodes examined				
≤ 11	68.0	0.83	87.5	0.21
≥ 12	71.3		78.5	
Adjuvant chemotherapy				
Chemotherapy	77.8	0.23	80.7	0.014
Surgery alone	69.5		68.4	

JSCCR, Japanese Society for Cancer of the Colon and Rectum.

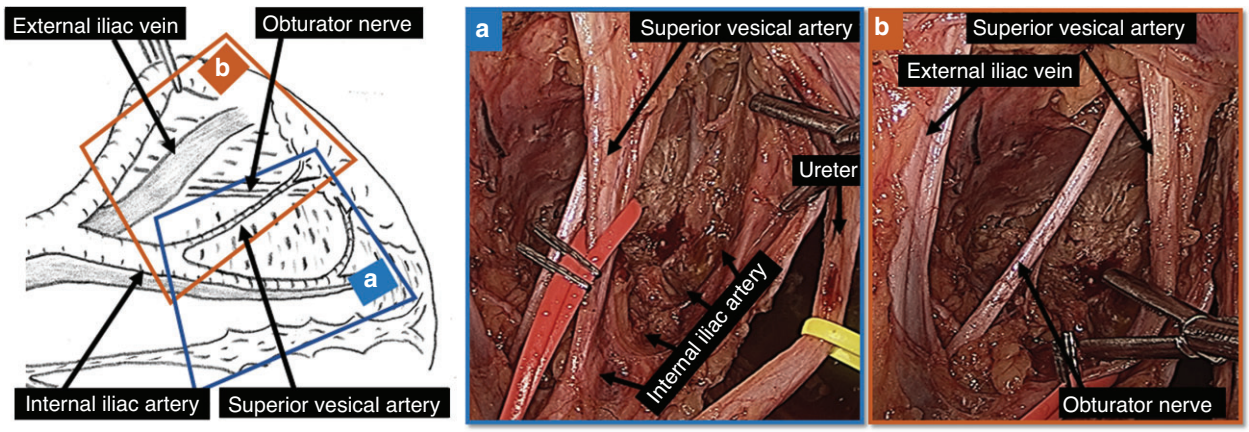

Fig. 2 Schema of the left-sided lateral pelvic area

a Representative view of the internal iliac area (area 1) after node dissection around the internal iliac artery. **b** Representative view of the obturator area (area 2) after node dissection around the obturator nerve.

Station, Texas, USA). *P* values of less than 0.05 were considered to be statistically significant.

Results

Patients

Of 1832 patients with stage III low rectal cancer reviewed in cohort 1, 345 patients were excluded owing to their medical history and clinical factors, and of the remaining 1487 patients 745 were excluded as they were not treated with lateral node dissection. The remaining 742 patients (40.5 per cent) met study criteria and were treated with lateral node dissection. For cohort 2, 508 patients were reviewed and all cases were selected for data analysis based on the abovementioned criteria (*Fig. 1*). *Table 1* shows the results of the comparisons of the clinicopathological characteristics between lateral node-positive and node-negative cancer patients in cohorts 1 and 2. In the first cohort, patients with lateral node-positive nodes displayed worse T status and N status, and a higher prevalence of patients with more than 12 nodes examined. The same trend for the N status was reported in cohort 2.

Survivals

Of the patients enrolled in cohort 1, 219 died as a result of the recurrence of rectal cancer, with a median time from surgery to

Table 3 Cancer-specific survival according to the number and area of metastatic lateral lymph nodes among lateral lymph node-positive patients

	Total	5-year cancer-specific survival (number of patients) [Rank among divisions in cohort 1]			
		Number of metastatic lateral lymph nodes			
		1	2–3	4–6	≥ 7
Cohort 1					
All patients	57.9% (146)	66.8% (92)	55.0% (34)	25.0% (12)	18.8% (8)
According to forefront area of metastatic lateral lymph node					
Internal iliac (area 1)	75.3% (59)	75.5% (46) [1]	75.0% (9) [2]	75.0% (4) [3]	n.a. (0)
Obturator (area 2)	52.5% (45)	61.7% (28) [4]	44.4% (14) [7]	0% (2) [9-11]	0% (1) [9-11]
Other areas (area 3)	40.2% (42)	55.0% (18) [5]	48.0% (11) [6]	0% (6) [9-11]	21.4% (7) [8]
Cohort 2					
All patients	65.0% (147)	76.4% (91)	59.1% (32)	28.0% (17)	33.3% (7)
According to forefront area of metastatic lateral lymph node					
Internal iliac (area 1)	74.9% (68)	78.0% (51)	74.6% (14)	0% (3)	n.a. (0)
Obturator (area 2)	60.5% (58)	70.7% (36)	53.5% (12)	44.4% (6)	25.0% (4)
Other areas (area 3)	45.1% (21)	100% (4)	33.3% (6)	25.0% (8)	50.0% (3)
Patients receiving adjuvant chemotherapy					
All patients	66.1% (173)	80.3% (102)	61.7% (39)	28.6% (21)	30.0% (11)
According to forefront area of metastatic lateral lymph node					
Internal iliac (area 1)	80.2% (76)	85.4% (55)	76.2% (16)	40.0% (5)	n.a. (0)
Obturator (area 2)	62.8% (64)	74.5% (38)	56.5% (16)	33.3% (6)	25.0% (4)
Other areas (area 3)	43.1% (33)	77.8% (9)	42.9% (7)	20.0% (10)	33.3% (7)

n.a., not applicable.

Table 4 Exploration of the best L-staging system in lateral lymph node-positive patients in cohort 1

Bisection categorization	5-year cancer-specific survival (number of patients)			P	AIC	Rank
Division (rank, 1) *versus* division (2)(3)(4)(5)(6)(7)(8)(9–11)	75.5% (46)	*versus*	50.2% (100)	0.016	558.163	8
Division (rank, 1)(2) *versus* division (3)(4)(5)(6)(7)(8)(9–11)	75.4% (55)	*versus*	47.8% (91)	0.006	557.081	7
Division (rank, 1)(2)(3) *versus* division (4)(5)(6)(7)(8)(9–11)	75.3% (59)	*versus*	46.3% (87)	0.002	555.144	6
Division (rank, 1)(2)(3)(4) *versus* division (5)(6)(7)(8)(9–11)	70.7% (87)	*versus*	38.8% (59)	< 0.001	550.509	2
Division (rank, 1)(2)(3)(4)(5) *versus* division (6)(7)(8)(9–11)	67.9% (105)	*versus*	30.5% (41)	< 0.001	549.669	1
Division (rank,1)(2)(3)(4)(5)(6) *versus* division (7)(8)(9–11)	66.2% (116)	*versus*	23.4% (30)	< 0.001	551.264	3
Division (rank,1)(2)(3)(4)(5)(6)(7) *versus* division (8)(9–11)	64.3% (130)	*versus*	7.8% (16)	< 0.001	551.329	4
Division (rank,1)(2)(3)(4)(5)(6)(7)(8) *versus* division (9–11)	62.2% (137)	*versus*	0% (9)	< 0.001	554.076	5

AIC, Akaike information criterion.

death of 31.4 (range 2.1 to 103.4) months. The median follow-up period for the remaining 523 patients was 75.7 (range 1.3 to 116.8) months. In cohort 2, 141 died owing to the recurrence of rectal cancer, with a median time from surgery to death of 39.0 (range 4.0–148.8) months. The median follow-up period for the remaining 367 patients was 81.5 (range 1.8–150.7) months.

CSS rates according to the clinicopathological characteristics of patients included in the present study are shown in *Table 2*. T status, N status, and lateral lymph node metastasis were significant prognostic factors in patients in cohort 1. In addition, age and adjuvant chemotherapy were estimated as significant prognostic factors, including N status and lateral lymph node metastasis, in cohort 2.

Modified N classification and L-stage for low rectal cancer

The first analysis was conducted in cohort 1 with the aim of assessing the impact of metastatic area on the survival of patients with a single lateral lymph node metastasis.

Of 92 patients with metastasis to a single lateral lymph node, 46 (50 per cent) and 28 (30 per cent) had metastatic disease in the internal iliac area and the obturator area, respectively (*Fig. 2*). Other areas ($n = 18$; 20 per cent) were less frequently involved as metastatic sites; in detail, metastasis was observed in the common iliac in 13 patients, lateral sacral in two patients, external iliac in two patients, and median sacral areas in one patient.

Kaplan–Meier curves for 5-year CSS analysis defined three groups with different survivals: metastasis in the internal iliac area (5-year CSS, 75.5 per cent (area 1)), followed by the obturator area (61.7 per cent (area 2)) and other areas (55.0 per cent (area 3)) ($P = 0.168$, area 1 *versus* area 2/3; $P = 0.151$, area 1/2 *versus* area 3).

All lateral node-positive patients were then categorized on the basis of the involved area and the number of positive lateral lymph nodes. The 5-year CSSs are documented in *Table 3*. For this analysis, if lateral nodal metastases were found across different areas, the case was classified based on the highest number. The subgroup of patients with one metastatic lateral lymph node in area 1 (rank, 1) demonstrated the most favourable prognosis in terms of 5-year CSS (75.5 per cent); in contrast, the

Table 5 Cancer-specific survival in respective sections according to the number of metastatic lymph nodes (TNM-N status) and L-stage among all stage III patients

Lateral lymph node status and L-stage	Total	5-year cancer-specific survival (number of patients)		
		Number of metastatic lymph nodes (TNM-N status)		
		1–3 (N1)	4–6 (N2a)	7 or more (N2b)
Cohort 1				
Lateral lymph node-negative	74.1% (596)	81.2% (412)	63.6% (115)	48.7% (69)
Lateral lymph node-positive (L-stage low-risk)	67.9% (105)	77.1% (60)	66.3% (20)	45.6% (25)
Lateral lymph node-positive (L-stage high-risk)	30.5% (41)	53.3% (5)	60.0% (9)	15.8% (27)
Cohort 2				
Lateral lymph node-negative	84.0% (361)	90.1% (247)	80.3% (58)	58.8% (56)
Lateral lymph node-positive (L-stage low-risk)	74.7% (108)	81.7% (54)	70.9% (27)	62.2% (27)
Lateral lymph node-positive (L-stage high-risk)	38.8% (39)	80.0% (6)	20.0% (5)	34.4% (28)
Patients receiving adjuvant chemotherapy				
Lateral lymph node-negative	85.1% (435)	91.4% (297)	76.6% (78)	63.0% (60)
Lateral lymph node-positive (L-stage low-risk)	78.1% (123)	90.4% (57)	74.2% (27)	60.8% (39)
Lateral lymph node-positive (L-stage high-risk)	37.8% (50)	83.3% (7)	33.3% (6)	30.6% (37)

subgroups of patients with 4 to 6 metastatic lateral lymph nodes within area 2, seven or more metastatic lateral lymph nodes within area 2, and 4 to 6 metastatic lateral lymph nodes within area 3 (rank, 9–11) demonstrated the worst survival (0 per cent). *Table 4* presents each AIC score according to a single boundary, indicating that the smallest AIC (considered as the most efficient categorization) was achieved when the lateral node metastasis was classified as a low-risk category comprising ranks 1 to 5 ($n = 105$; 5-year CSS, 67.9 per cent) and as a high-risk category comprising ranks 6–11 ($n = 41$; 5-year CSS, 30.5 per cent; $P < 0.001$); these results were the basis of defining the L-stage. Indeed, the L-stage low-risk category consisted of cancers with a single metastatic lateral lymph node and cancers whose metastatic area was confined to the internal iliac lesion (area 1), whereas the L-stage high-risk category consisted of patients with two or more metastatic lateral lymph nodes, some of which spread into area 2 or area 3.

Finally, the 5-year CSSs of patients grouped according to TNM-N status and L-stage are shown in *Table 5*. These results implied that L-stage-low-risk rectal cancers did not deserve an N upgrade, whereas L-stage high-risk needed to be N upgraded. Two N upgrading methods to revise the TNM system were considered likely candidates. With the first method, L-stage high-risk cancers of TNM-N1 and N2a were grouped together into modified N2b; conversely, in another computation (second upgrade method), L-stage high-risk cancers with TNM-N1 and N2a cancers were upgraded to modified N2a and N2b, respectively. The AIC and c-index analyses demonstrated the same result, and better performance was achieved when stage III was reclassified using the second upgrade method (modified N1 (5-year CSS, 80.7 per cent), modified N2a (63.6 per cent), and modified N2b (42.3 per cent); AIC = 2661.08; c-index = 0.6477) compared with that obtained using the first upgrade method (modified N1 (5-year CSS, 80.7 per cent), modified N2a (5-year CSS, 64.0 per cent), and modified N2b (5-year CSS, 42.8 per cent), AIC = 2661.49; c-index = 0.6475). Therefore, the second upgrade method was determined to be a modified N classification system and used in subsequent analyses (*Fig. 3*).

Comparison with current classification systems

Survival curves, AIC, and c-index scores of the TNM-N, JSCCR-based N, and the modified N classifications are presented in *Fig. 4*. The modified N classification system yielded the most favourable indices (AIC = 2661.08; c-index = 0.6477), followed by the TNM (AIC = 2662.36; c-index = 0.6457) and JSCCR-based (AIC = 2684.06; c-index = 0.6302) classification systems.

Validation study using cohort 2

As previously illustrated, this analysis was conducted using cohort 2 data. The 5-year CSSs of 12 divisions according to the involved area and the number of positive lateral lymph nodes are shown in *Table 3*, which were found to be similar to the CSSs of cohort 1 patients. According to the foregoing L-stage, the low-risk category ($n = 108$; 5-year CSS, 74.7 per cent) exhibited significantly better prognosis than the high-risk category ($n = 39$; 5-year CSS, 38.8 per cent; $P < 0.001$), which confirmed the efficacy of the L-stage. The 5-year CSSs of individual sections according to the TNM-N status and L-stage are presented in *Table 5*. The survival curves, AIC, and c-index scores of the TNM-N, JSCCR-based N, and the modified N classifications are illustrated in *Fig. 4*. The modified N classification system again had the most favourable indices (AIC = 1578.04; c-index = 0.6787), followed by the TNM (AIC = 1582.77; c-index = 0.6729) and JSCCR-based (AIC = 1591.55; c-index = 0.6633) classification systems.

Analyses of patients receiving adjuvant chemotherapy

Table 6 shows the results of the comparisons of the clinicopathological characteristics between lateral node-positive and node-negative cancer patients receiving adjuvant chemotherapy ($n = 608$). Patients with lateral node-positive nodes displayed worse T status and N status. CSS rates according to the clinicopathological characteristics of patients included in the present study are shown in *Table 7*. The T status, N status, and

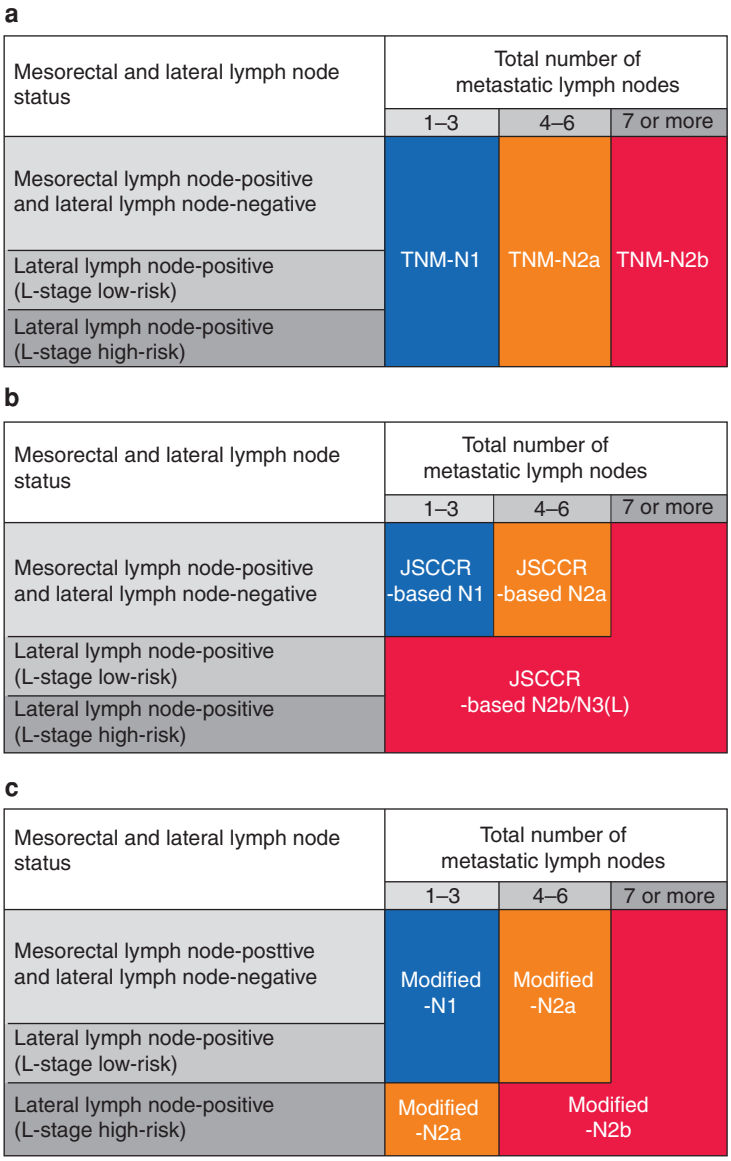

Fig. 3 TNM, JSCCR, and modified classification system for N status

a The TNM classification defines N status according to the number of metastatic lymph nodes, whereas **b** the JSCCR-based classification for lymph node metastasis includes both the number and lateral spread of metastatic lymph nodes. In the JSCCR-based N classification, N3(L) was defined as lateral node metastasis and was combined with N2b into N2b/N3(L) category. **c** The modified N classification system is described, where TNM-N1 and N2a cancers were respectively upgraded to modified N2a and N2b in L-stage high-risk rectal cancers (i.e. having two or more metastatic lateral lymph nodes partially spreading into the obturator area or further outside). JSCCR, Japanese Society for Cancer of the Colon and Rectum.

lateral lymph node metastasis were significant prognostic factors.

The 5-year CSSs of 12 divisions are displayed in the lower part of *Table 3*. According to the L-stage, the low-risk category ($n = 123$; 5-year CSS, 78.1 per cent) demonstrated a significantly better prognosis than the high-risk category ($n = 50$; 5-year CSS, 37.8 per cent; $P < 0.001$), which justified the efficacy of the L-stage. The 5-year CSSs of individual sections according to the TNM-N status and L-stage are depicted in the lower part of *Table 5*. The survival curves, AIC, and c-index scores of the TNM-N, JSCCR-based N, and the modified N classifications are described in *Fig. 4*. The modified N classification system yielded the most favourable indices (AIC = 1766.02; c-index = 0.7114), followed by the TNM (AIC = 1769.49; c-index = 0.7066) and JSCCR-based (AIC = 1797.42; c-index = 0.6732) classification systems.

Discussion

Adverse prognostic effects of lateral node metastasis in low rectal cancer were reported;[2,3] however, an appropriate reflection of lateral metastasis on N classification considering the diversity of lateral conditions has not been determined. In this study, the L-stage system using lateral factors and a modified N classification, where the N status of L-stage-high-risk patients was upgraded, were newly proposed. Finally, comparisons with current N systems revealed that the modified N classification yielded the most favourable scores of AIC and c-index. However, it must be acknowledged that the new model was established based on the data of patients who underwent lateral node dissection without preoperative therapies and accounted for less than half of all stage III patients. Thus, the relevance of patient-selection bias in the results should

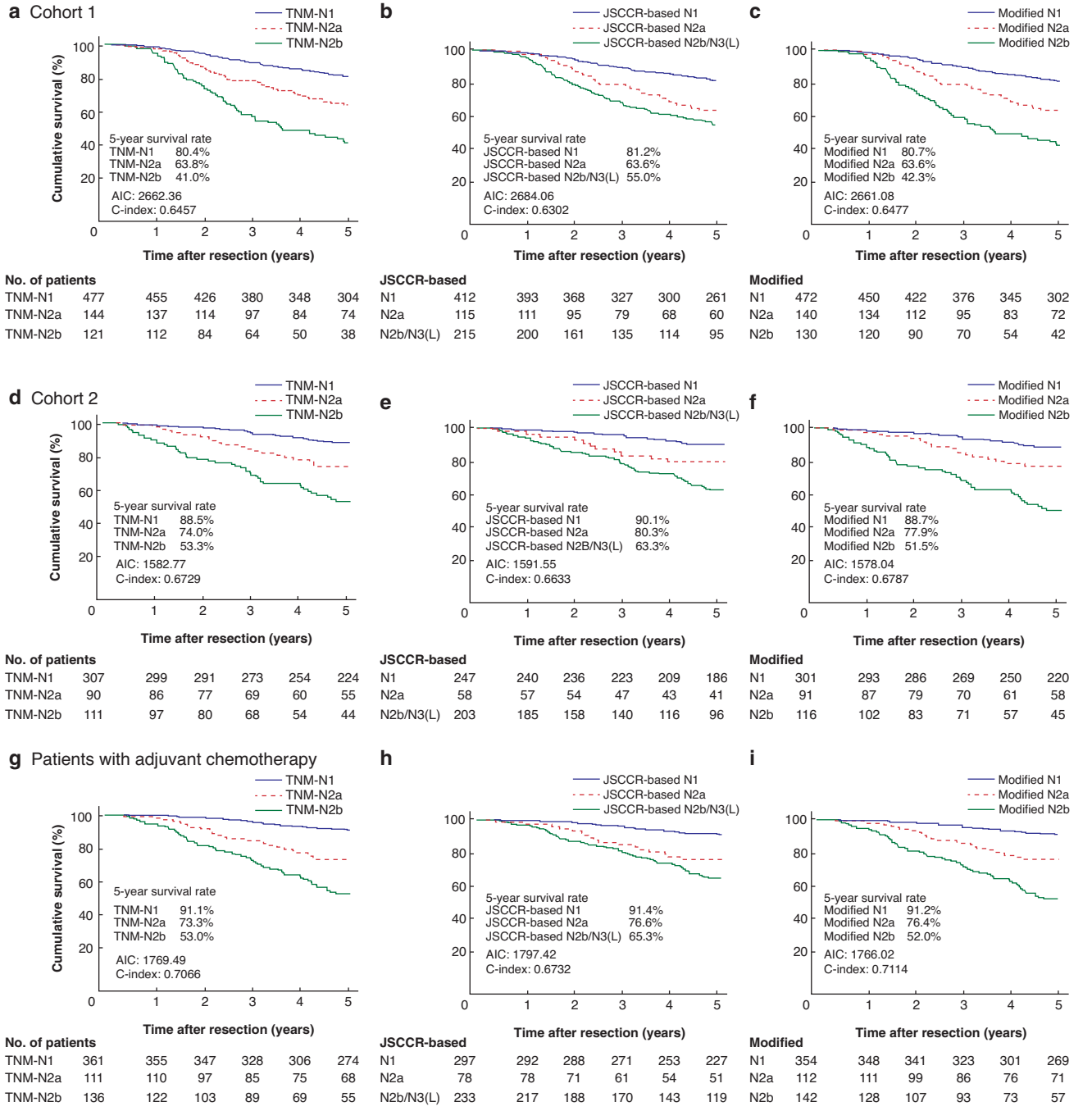

Fig. 4 The cumulative cancer-specific survival curves

The cumulative cancer-specific survival curves for cohort 1 patients stratified by **a** TNM-N classification, **b** Japanese Society for Cancer of the Colon and Rectum (JSCCR)-based N classification, and **c** modified N classification. The modified N classification showed the most favourable Akaike information criterion (AIC; 2661.08) and concordance index (c-index; 0.6477) compared with the TNM-N (2662.36, 0.6457) or the JSCCR-based N (2684.06, 0.6302) systems. **d–f** Similarly, the modified N classification showed the most favourable AIC (1578.04) and c-index (0.6787) in cohort 2 compared with the TNM-N (1582.77, 0.6729) or the JSCCR-based N (1591.55, 0.6633) systems. **g–i** Among patients receiving adjuvant chemotherapy, the modified N classification also demonstrated the most favourable AIC (1766.02) and c-index (0.7114) compared with the TNM-N (1769.49, 0.7066) or the JSCCR-based N (1797.42, 0.6732) systems.

be discussed. In clinical practice, vulnerable patients without lateral lymph node swelling observed in pretreatment images possibly avoided lateral node dissection. Additionally, patients with a locally advanced low rectal cancer, suspicious for intensive metastasis in the lateral area, tended to accept preceding chemotherapy or chemoradiotherapy. Such patients were excluded from the study cohort. The eventual imbalance in the study population could have resulted in a higher rate of lateral-positive patients in the stage III cohort and a higher proportion of L-stage low-risk in lateral-positive patients than those existing in reality, which might overemphasize the value of relatively good prognosis in L-stage low-risk patients. However, patients without lateral node dissection have the potential to have their N status underestimated[9]. Moreover, original N status is not clearly determined through pathological examinations of patients with preoperative therapies. Thus, arrangement of N classification using patients with definitive N status after lateral node dissection without preoperative therapies became the necessary first step. In future

Table 6 Patients receiving adjuvant chemotherapy

		Lateral lymph node metastasis		*P*
	Total $n=608$	Positive $n=173$	Negative $n=435$	
Age (years)				
≤ 59	279	84 (30.1)	195 (69.9)	0.67
60–69	223	59 (26.5)	164 (73.5)	
≥ 70	106	30 (28.3)	76 (71.7)	
Sex				
Male	341	102 (29.9)	239 (70.1)	0.37
Female	267	71 (26.6)	196 (73.4)	
T status				
T1	7	1 (14.3)	6 (85.7)	0.021
T2	80	19 (23.8)	61 (76.2)	
T3	469	129 (27.5)	340 (72.5)	
T4b	52	24 (46.2)	28 (53.8)	
TNM-N status				
N1	361	64 (17.7)	297 (82.3)	<0.001
N2a	111	33 (29.7)	78 (70.3)	
N2b	136	76 (55.9)	60 (44.1)	
TNM stage				
IIIA	70	15 (21.4)	55 (78.6)	<0.001
IIIB	371	75 (20.2)	296 (79.8)	
IIIC	167	83 (49.7)	84 (50.3)	
JSCCR-based N status				
N1	297	0 (0)	297 (100)	<0.001
N2a	78	0 (0)	78 (100)	
N2b/N3(L)	233	173 (74.3)	60 (25.7)	
Number of lymph nodes examined				
≤ 11	15	3 (20.0)	12 (80.0)	0.46
≥ 12	593	170 (28.7)	423 (71.3)	

Data are *n* (%). JSCCR, Japanese Society for Cancer of the Colon and Rectum.

Table 7 Prognostic significance of clinicopathological factors in patients receiving adjuvant chemotherapy

	5-year cancer-specific survival (Kaplan–Meier method; %)	*P*
Age (years)		
≤ 59	78.8	0.088
60–69	83.8	
≥ 70	74.1	
Sex		
Male	78.9	0.75
Female	81.1	
T status		
T1	100	<0.001
T2	93.4	
T3	78.5	
T4b	67.6	
TNM-N status		
N1	91.1	<0.001
N2a	73.3	
N2b	53.0	
Lateral lymph node metastasis		
Negative	85.1	<0.001
Positive	66.1	
JSCCR-based N status		
N1	91.4	<0.001
N2a	76.6	
N2b/N3(L)	65.3	
Number of lymph nodes examined		
≤ 11	85.7	0.50
≥ 12	79.7	

JSCCR, Japanese Society for Cancer of the Colon and Rectum.

studies, the adaptability across varied stage III patients should be studied. According to the present results, metastasis in the internal iliac area was found most frequently among all lateral areas; moreover, a comparable prognosis in patients with this type of metastasis and in patients without lateral metastasis was documented. Clinically, this represents one of the key findings of the present study, and it could be hypothesized that the dissection of this area in addition to total mesorectal excision could produce survival benefits under certain conditions. Actually, indications for lateral node dissection and the appropriate dissection area have been considered as essential clinical questions; however, these retrospective data could not specifically address these issues. Future prospective studies are required to investigate the indications focusing on the appropriate dissection areas based on the differential prognostic benefit. Nevertheless, there were some potential limitations. Firstly, this was a non-randomized retrospective study. Selections of the lymph node dissection type and subsequent therapies may have been affected by age and performance status even in stage III patients. Analyses of big data have drawbacks. During the selection of condition-matched patients, several patients were eliminated, which may result in inaccurate conclusions. However, in the present study, the results of cohort 1 were validated in a consecutive case study of cohort 2. Thirdly, the characteristics of Japanese patients (e.g. age, sex, and BMI) could be different from other cohorts. However, a modified N classification system was created where the N status was upgraded in L-stage-high-risk patients judged according to the number and extent of lateral lymph node metastases. AIC and c-index analyses implied that the TNM-N and JSCCR-based N classification systems could not stratify patients according to the survival outcome as the modified N classification system. L-stage and modified N classification system could be useful for precise risk stratification, which will be helpful in decision-making for patient-adjusted post-operative treatment.

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References

1. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma: the 3d English Edition (secondary publication). *J Anus Rectum Colon* 2019;**3**:175–195
2. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K *et al.* Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg* 2012;**255**:1129–1134
3. Kanemitsu Y, Komori K, Shida D, Ochiai H, Tsukamoto S, Kinoshita T *et al.* Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on prognoses and local control: a comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery* 2017;**162**:303–314
4. Sugihara K, Kobayashi H, Kato T, Mori T, Mochizuki H, Kameoka S *et al.* Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum* 2006;**49**:1663–1672
5. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T *et al.* Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020;**25**:1–42
6. Brierley J, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumors* (8th edn). Hoboken, NJ: Wiley-Blackwell, 2017
7. Akaike H. Information theory and extension of the maximum likelihood principle. In: Kotz S and Johnson NL (eds), *Breakthroughs in Statistics Volume 1. Foundations and Basic Theory*. New York: Springer-Verlag, 1973, 610–624
8. Harrell FE J, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387
9. Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y *et al.*; Colorectal Cancer Study Group of Japan Clinical Oncology Group. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. *Lancet Oncol* 2012;**13**:616–621