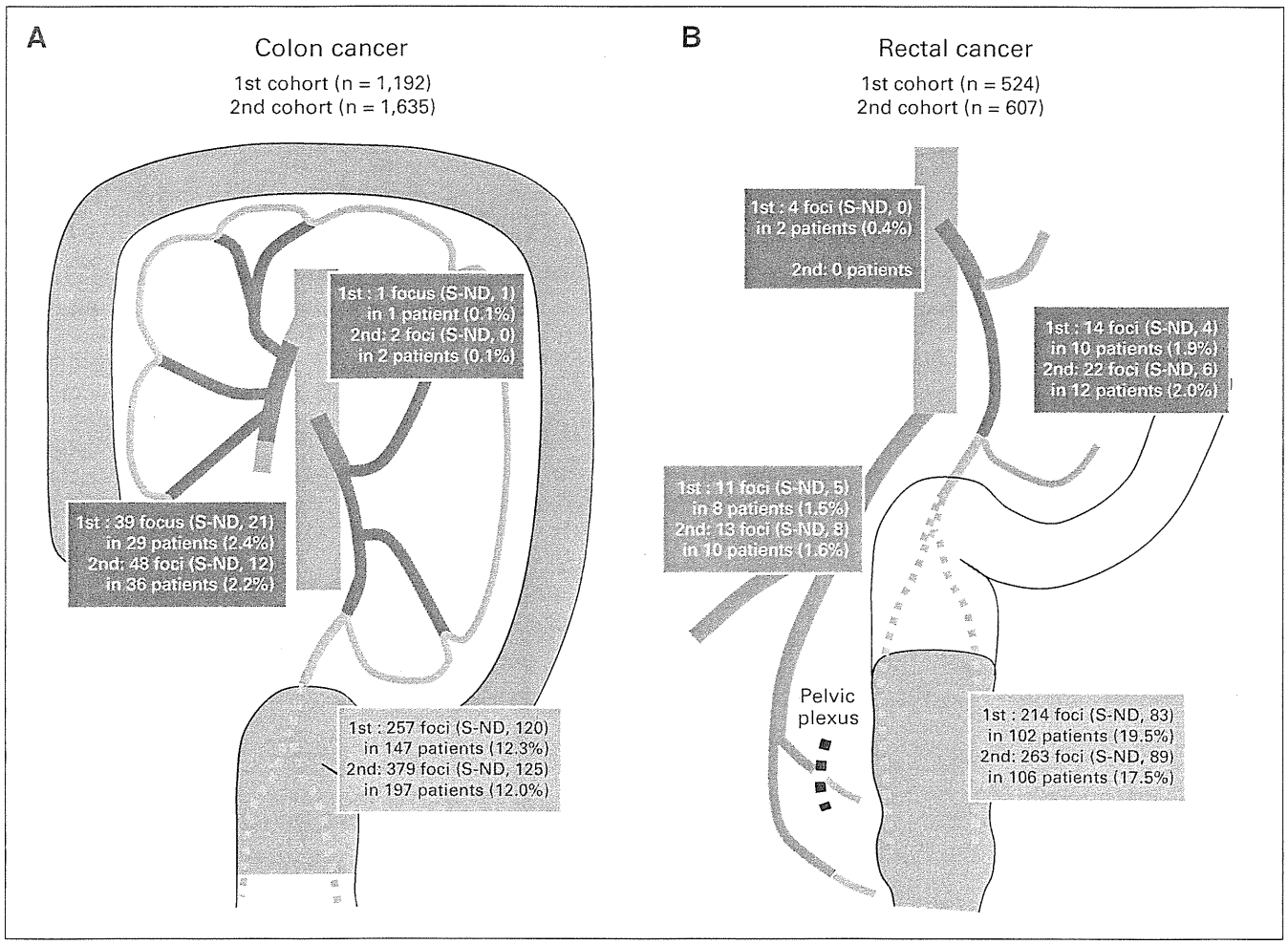

Fig 2. Tumor nodules without residual lymph node structure (ND) distribution in regional lymph node area. (A) Colon cancer; (B) rectal cancer. Gold, pericolic/perirectal region; blue, intermediate lymph node region (region along the branches of the superior/inferior mesenteric artery); red, main lymph node region (region at the origin of each colic artery in right colon cancers and the inferior mesenteric node region in cancers located in the left colon and rectum); dark gold, lateral pelvic node region in rectal cancer. There is a significant difference in the incidence of pericolonic ND between patients with (A) colon cancer and (B) rectal cancer both in the first ($P < .001$) and second cohorts ($P < .001$). S-ND, smooth-contour nodules.

The comparison of the ability to stratify patient prognostic outcome in each edition of TNM classification is presented in Table 3. In the first cohort, both AIC and the c-index showed that the prognostic value of the N stage (N0/N1/N2) was higher in the order of TNM5, TNM7, and TNM6. The prognostic value of T stage was higher in the reverse order. A similar trend was also observed in the second cohort. With regard to tumor staging (I/II/III), in the first cohort, TNM7 had a more favorable prognostic value than TNM6, but not TNM5. In the second cohort, the statistical prognostic power was superior in the order of TNM7, TNM5, and TNM6.

Modified ND Categorization Criteria for TNM

Differences in the prognostic power between the original ND criteria and the modified definition/categorization ND criteria of TNM7 are presented in Table 4. On the basis of the modified ND criteria, all regional NDs are considered as LNM irrespective of their morphology (Table 1). On comparing the N stage (N0/N1/N2a/N2b) based on the original TNM7 criteria and the modified criteria, we found that 4.2% and 4.5% of the patients were classified in different stages in the first and second cohorts, respectively. In both cohorts, AIC and the c-index were better for the modified criteria than for the original criteria.

The modified criteria in both cohorts were also associated with improved prognostic power in regard to the tumor stage as categorized by TNM7 (I/IIA/IIB/IIC/IIIA/IIIB/IIIC; Table 4).

Reproducibility of N Staging

Regarding the reproducibility of judging NDs as N-stage factors, the κ value was 0.91 when judged according to the size rule. On the other hand, the κ value was 0.40 when a nodule was judged as N-stage factor if it was considered by the observer to be a totally replaced lymph node. When determining the reproducibility of N staging, κ value was 0.97 for TNM5 and 0.89 for TNM7; it was 1.00, as a logical result, for the modified ND categorization criteria.

Table 2. Stage Migration in Patients With ND (both cohorts combined)

	Definition and Categorization of ND											
	TNM5–TNM6		TNM5–TNM7		TNM6–TNM7		TNM5–Modified		TNM6–Modified		TNM7–Modified	
T and N Criteria	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
T category												
Unchanged	3,934	99.4	3,954	99.9	3,936	99.4	3,954	99.9	3,936	99.4	3,958	100.0
Changed	24	0.6	4	0.1	22	0.6	4	0.1	22	0.6	0	
T1-T3	6	0.2	0		6	0.2	0		6	0.2	0	
T2-T3	18	0.5	4	0.1	16	0.4	4	0.1	16	0.4	0	
N category												
Unchanged	3,842	97.1	3,856	97.4	3,903	98.6	3,833	96.8	3,783	95.6	3,835	96.9
Changed	116	2.9	102	2.6	55	1.4	125	3.2	175	4.4	123	3.1
N0-N1	51	1.3	37	0.9	55	1.4	52	1.3	67	1.7	15	0.4
N0-N2	2	0.1	1	0.0	0		1	0.0	3	0.1	0	
N1-N2	63	1.6	64	1.6	0		72	1.8	105	2.7	108	2.7

Abbreviations: Modified, modified criteria that considered all regional NDs as lymph node metastasis; ND, tumor nodules without histologic evidence of residual lymph node structure.

DISCUSSION

TNM5 was the first system to categorize tumor nodules without histologic evidence of residual lymph node structure, which had previously been treated differently in tumor staging according to the individual pathologist's interpretation.[1] Considering that such lesions form 15% to 44% of diagnosed CRC[16-24] and offer considerable prognostic information,[7] it is an achievement that the TNM classification had addressed issues regarding treatment of such lesions, which are important elements in stage migration. However, by comparing each TNM revision, we concluded that the TNM staging system may not have progressed favorably after the TNM5 edition.

There are several points that are not clear in TNM classification with regard to the definition of a tumor nodule. These points must be clarified for the use in routine medical practice and for systematic comparison of TNM staging systems. First, TNM7[3,25] uses the term "tumor deposits (satellite)" instead of "tumor nodules" (used in TNM5 and TNM6)[1,2]; however, the difference in the meaning between the terms has not been clarified. In this study, we compared each TNM classification edition on the assumption that there is no fundamental difference between tumor deposits and tumor nodules. These terms represented all lesions with discontinuous spread except for LNM and tumor foci confined within the vascular or perineural spaces.

Because TNM classification has not provided a clear measurement for the length of discontinuous spread that would be used for judging tumor nodules, it is also difficult to objectively determine which of the discrete tumor foci observed at the periphery of the primary tumor corresponds to the tumor nodule.[4] Before histologic review, we decided to use 5 mm of discontinuity as the definition of an ND on the basis of the consensus of members involved in this JSCCR project study. We chose this value because we expected it to avoid interobserver disagreement.

Furthermore, fewer standardized criteria exist for judging lymph nodes completely infiltrated by malignancy; a privileged group of tumor nodules in TNM7. It is assumed that diagnosis varies widely among pathologists. Because TNM7 judges lymph nodes completely infiltrated with malignancy as "generally having a smooth contour,"[3] we analyzed the data by considering all smooth-contour ND, which accounted for 37% of the 1,267 total foci of ND investigated in this study, as "replaced nodes." An interobserver study of the first cohort from 11 separate institutes found that the κ value associated with the judgment of ND with a smooth contour was 0.51.[8]

The location of tumor nodules, used as a staging factor, can also be quite obscure because of different descriptions in International Union Against Cancer and American Joint Committee on Cancer. International Union Against Cancer defines the location as "in the pericolorectal adipose tissue,"[1-3] whereas according to the American Joint Committee on Cancer Cancer Staging Manual (seventh edition),[25] tumor nodules are located "in the pericolic or perirectal fat or in adjacent mesentery (mesocolic fat) away from the leading edge of the tumor." In our analysis, we compared staging systems of TNM classification by counting NDs in the subserosa and pericolic/perirectal lymph node area as a staging factor.

Furthermore, TNM classification indicates that if tumor nodules are observed in lesions that would otherwise be classified as T1 or T2, the T classification is not changed, but the nodule is recorded as N1c[3,25]; however, the interpretation of N1c for tumor nodules in T3/T4 cancer is unclear. The varying interpretations of tumor nodules by different pathologists can be confusing. Some pathologists categorize tumor nodules in T3/T4 node-negative CRC as N1c,[4] whereas some understand the interpretation of such a lesion is left to individual pathologists, reverting to TNM4 staging.[12] In this study, analyses were performed on the basis of the former stance. It should be noted that if tumor nodules in T3/T4 node-negative cancer were not considered as a staging factor, prognostic information of staging systems would certainly decrease considerably.[8]

Objectiveness and simplicity in the process of histologic staging and determination of high prognostic values are necessary for an international cancer staging system such as TNM classification. As a leading criterion for the classification of tumor nodules into T or N categories, the contour rule adopted in TNM6 is highly subjective and is believed to be inferior to the size rule in TNM5 with regard to judgment reproducibility.[9] The categorization of tumor nodules is still at the discretion of pathologists in TNM7, in which those considered as totally replaced lymph nodes are treated

Table 3. Comparison of TNM5, TNM6, and TNM7 Editions by the Proportion of Case Numbers Allocated in Each Category and the Prognostic Value

Stage and Edition	First Cohort (n = 1,716)				Second Cohort (n = 2,242)				Both Populations Combined (N = 3,958)			
	No.	5-Year DSS (%)	AIC	c-Index	No.	5-Year DSS (%)	AIC	c-Index	No.	5-Year DSS (%)	AIC	c-Index
T stage												
TNM5												
T1	239	99.6	3106.4	0.6739	291	98.0	4262.8	0.6729	530	98.8	8077.0	0.6740
T2	278	95.5			373	95.8			651	95.7		
T3	940	86.9			1,116	86.1			2056	86.5		
T4	259	76.5			462	74.5			721	75.4		
TNM6												
T1	237	100	3096.9	0.6756	287	98.3	4253.5	0.6749	524	99.2	8060.0	0.6759
T2	270	95.4			369	95.8			639	95.6		
T3	950	86.9			1,124	86.1			2,074	86.5		
T4	259	76.5			462	74.5			721	75.4		
TNM7/ modified												
T1	239	99.6	3105.9	0.6744	291	98.0	4262.5	0.6731	530	98.8	8076.2	0.6743
T2	281	95.6			374	95.8			655	95.7		
T3	937	86.9			1,115	86.1			2,052	86.5		
T4	259	76.5			462	74.5			721	75.4		
N stage												
TNM5												
N0	1,098	95.1	3034.0	0.7235	1,454	93.9	4207.9	0.7013	2,552	94.4	7955.2	0.7102
N1	433	84.6			586	78.5			1,019	81.2		
N2	185	57.9			202	61.6			387	59.8		
TNM6												
N0	1,102	94.7	3058.1	0.7084	1,467	93.6	4225.8	0.6908	2,569	94.1	7997.5	0.6979
N1	444	84.5			593	77.7			1,037	80.7		
N2	170	58.7			182	63.8			352	61.3		
TNM7												
N0	1,076	95.2	3045.9	0.7209	1438	94.0	4212.7	0.7013	2,514	94.6	7972.3	0.7090
N1	470	83.8			622	77.4			1,092	80.2		
N2	170	58.7			182	63.8			352	61.3		
Modified												
N0	1,067	95.3	3043.0	0.7229	1432	94.2	4192.6	0.7112	2,499	94.7	7948.1	0.7154
N1	430	85.0			569	79.3			999	81.8		
N2	219	62.0			241	62.1			460	62.1		
Tumor stage												
TNM5												
I	451	99.1	3051.6	0.7240	570	98.4	4190.8	0.7157	1,021	98.7	7951.0	0.7189
II	647	92.3			884	90.9			1,531	91.5		
III	618	76.6			788	74.2			1,406	75.3		
TNM6												
I	450	99.1	3063.7	0.7149	568	98.4	4198.7	0.7098	1,018	98.7	7970.8	0.7118
II	652	91.2			899	90.5			1,551	91.0		
III	614	77.3			775	74.5			1,389	75.8		
TNM7												
I	450	99.1	3055.1	0.7215	568	98.4	4189.9	0.7162	1,018	98.7	7953.9	0.7181
II	626	92.4			870	91.2			1,496	91.7		
III	640	77.1			804	74.3			1,444	75.6		
Modified												
I	447	99.1	3056.6	0.7202	568	98.4	4184.6	0.7185	1,015	98.7	7950.4	0.7188
II	620	92.5			864	91.4			1,484	91.9		
III	649	77.2			810	74.2			1,459	75.6		

Abbreviations: AIC, Akaike information criterion; c-index, Harrell's c-index; DSS, disease-specific survival; Modified, modified criteria that considered all regional tumor nodules without histologic evidence of residual lymph node structure as lymph node metastasis.

differently from other types of tumor nodules.[3,25] These difficulties while making objective judgments are likely associated with the loss of tumor staging reproducibility. In addition, the serial sectioning study showed that it was incorrect to assume preexisting histologic structure of tumor nodules, including lymph nodes, according to the contour characteristics of a tumor nodule.[24] However, by considering all tumor nodules equally in the staging system irrespective of their original structure, the objectiveness, reproducibility, and reliability of tumor staging can be improved for routine medical practice.

Table 4. Comparison of the TNM7 Edition and Modified TNM Classification by the Proportion of Case Numbers Allocated in Each Category and the Prognostic Value

Stage and Edition	First Cohort (n = 1,716)				Second Cohort (n = 2,242)				Both Populations Combined (N = 3,958)			
	No.	5-Year DSS (%)	AIC	c-Index	No.	5-Year DSS (%)	AIC	c-Index	No.	5-Year DSS (%)	AIC	c-Index
N stage												
TNM7												
N0	1,076	95.2	3040.6	0.7230	1,438	94.0	4210.1	0.7022	2,514	94.6	7962.6	0.7104
N1	470	83.8			622	77.4			1,092	80.2		
N2a	111	65.4			117	70.3			228	67.7		
N2b	59	45.7			65	52.6			124	49.3		
Modified												
N0	1,067	95.3	3029.4	0.7271	1,432	94.2	4188.5	0.7129	2,499	94.7	7929.4	0.7181
N1	430	85.0			569	79.3			999	81.8		
N2a	142	71.0			135	68.4			277	69.8		
N2b	77	45.2			106	53.7			183	49.9		
Tumor stage												
TNM7												
I	450	99.1	3008.8	0.7566	568	98.4	4156.5	0.7468	1,018	98.7	7875.1	0.7502
IIA	508	93.0			667	92.8			1,175	92.9		
IIB	80	91.0			149	87.9			229	89.1		
IIC	38	86.6			54	80.1			92	83.0		
IIIA	63	86.9			89	89.8			152	88.5		
IIIB	462	81.8			582	75.2			1,044	78.2		
IIIC	115	53.2			133	59.6			248	56.6		
Modified												
I	447	99.1	3003.8	0.7584	568	98.4	4145.1	0.7532	1,015	98.7	7856.2	0.7547
IIA	503	93.2			664	92.9			1,167	93.1		
IIB	79	90.8			148	87.8			227	89.0		
IIC	38	86.6			52	81.3			90	83.7		
IIIA	61	86.6			87	89.6			148	88.3		
IIIB	454	82.8			540	77.0			994	79.7		
IIIC	134	54.7			183	58.4			317	56.8		

Abbreviations: AIC, Akaike information criterion; c-index, Harrell's c-index; DSS, disease-specific survival; Modified, modified criteria that considered all regional tumor nodules without histologic evidence of residual lymph node structure as lymph node metastasis.

Although TNM6 followed the concept originally laid out in TNM5 (ie, tumor nodules should be classified as either belonging to the T or N category), the ability of TNM staging to provide accurate prognostic information was apparently decreased in TNM6 in our study. However, TNM classification improved after the revision from TNM6 to TNM7, in which all types of ND are considered as N category. Despite this, the statistical figures associated with the prognostic information such as AIC and the c-index were not greatly improved in TNM7 as compared with TNM5.

We believe TNM7 does not use the greatest potential prognostic value that individual tumor nodules offer regarding cancer staging. Firstly, in the TNM7 edition, tumor nodules that were determined not to be LNM by pathologists are considered different from other lymph nodes involved in the staging process. Thus the number of tumor nodules not judged as LNM (ie, tumor nodules with irregular contour) does not affect the subdivisions within stage III; however, the number of tumor nodules had a great deal of prognostic information, and these tumor nodules are quite similar to metastatic lymph nodes in terms of their hazard ratio and impact on recurrence, irrespective of contour characteristics.[7] Second, TNM classification refers only to tumor deposits located in the pericolorectal adipose tissue. Tumor nodules in other regional lymph node areas, such as the area around the inferior mesenteric artery or iliac artery in rectal cancer are not considered relevant for tumor staging. Majority of ND was observed in the pericolorectal area; however, one in five ND-positive patients had ND in more distant sites with a prognostic impact equal to or more than ND in the pericolorectal area.[7]

As might be expected according to the two previously mentioned viewpoints, improved statistical figures associated with the prognostic power of TNM7's N stage (N0/N1/N2a/N2b) were obtained in both cohorts when all tumor nodules in the regional area were counted as metastatic lymph nodes, irrespective of their size or shape (modified ND criteria). An improved prognostic value was also observed in the TNM stages (stages I/IIA/IIB/IIC/IIIA/IIIB/IIIC) with modified ND criteria, which are simpler and less subjective than the original definitions. Our results are consistent with the recent report of Nagtegaal et al, in which they demonstrated, using two independent populations of United Kingdom and Sweden, that TNM5 was superior to TNM6 and the prognostic value of TNM7 was best only when all tumor deposits were included as lymph nodes irrespective of size or contour shape.[9]

In conclusion, the TNM classification revisions do not meet our expectations principally because of the lack of sufficient improvement in their prognostic value. Tumor nodules are the end product of various processes but frequently the process that gave rise to the individual lesion is indistinguishable.[11,16] Categorizing these lesions regarding their initial processes could detrimentally affect the objectiveness of tumor staging. We believe the modified definition and categorization of tumor nodules presented in this study will make

tumor staging simpler and more informative. The accumulation of scientific evidence and their sufficient analyses concerning optimal treatment of tumor deposits in a staging system are necessary in the next revision of TNM classification.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Evaluation of the seventh edition of the tumour, node, metastasis (TNM) classification for colon cancer in two nationwide registries of the United States and Japan

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Abstract

Aim: The new TNM classification is currently being implemented. We evaluated the TNM-7 staging system based on the two nationwide colon cancer registries in the United States and Japan to clarify whether this system better stratifies patients' prognoses than the TNM-6 did and to determine whether stratification can be effectively simplified.

Methods: The *Surveillance, Epidemiology, and End Results* population-based data from 1988 to 2001 for 50 139 colon cancer patients and the multi-institutional registry data from the Japanese Society for Cancer of the Colon and Rectum from 1984 to 1994 for 10 754 patients were analysed. We devised a modified version of the TNM-7 staging system to allow simpler classification of the TN categories and compared the TNM-6, TNM-7, modified TNM-7, and the Dukes staging system based on survival curves and objective statistical tests such as likelihood ratio χ^2 tests, Akaike's information criterion, and Harrell's *c*-index.

Results: The TNM-7 was superior to the TNM-6 in all objective statistical tests in the United States (*c*-index; 0.700 *vs* 0.696, $P < 0.001$) as well as in the Japan data sets (0.732 *vs* 0.729, $P = 0.035$). The modified TNM-7 is much simpler, but it nevertheless showed similar values to those of the original TNM-7 (*c*-index; the United States 0.702, Japan 0.733).

Conclusions: The new TNM-7 is complicated but better at stratifying patients than the TNM-6 in the United States and Japan, and could be effectively simplified.

Keywords Colon cancer, TNM, SEER

What is new in this paper?

We utilized national data from the United States and Japan to assess the prognostic discrimination characteristics of the TNM-7, in comparison to a previous edition, TNM-6, a simplified version of the TNM-7, and the Dukes staging system. This is the first objective statistical evaluation of the TNM-7 staging system.

Introduction

Many staging systems have been proposed to determine treatment options and to predict patient prognosis. The most common and international staging system for colorectal cancer is the TNM staging system of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC). Recently, the seventh edition of the TNM classification of malignant tumors was published [1].

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The new edition for colorectal cancer subdivided the key items of information – tumour depth and nodal involvement – resulting in a more complicated classification [2]. The justification for the changes made under the new staging system from the sixth edition was previously reported by Gunderson *et al.* [3]. However, we need to analyze whether this new staging system effectively stratifies patients without producing confusion due to the complicated stage classification. As a result, the establishment of a modified and simpler staging system may be warranted in future revisions.

TNM staging is also important as a standard tool which allows for comparison across large populations, either within or between countries [4]. Many clinical

trials for colon cancer chemotherapy have been performed and interpreted [5,6], based on the TNM staging system. It should therefore be useful not only within the United States but also in other countries.

According to the worldwide population-based study CONCORD [7], the relative survival rate for colon cancer patients in the United States and Japan is excellent, while ethnic distribution and geographical region are quite different. Therefore, the comparative evaluation of TNM staging systems in nationwide databases in both countries may be useful to elucidate the clinical significance and international versatility of this new staging system.

The current paper is a retrospective study based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry of the National Cancer Institute in the United States and data from the multiinstitutional registry of the Japanese Society for Cancer of the Colon and Rectum (JSCCR). The purpose of the present study is to evaluate the new TNM staging system (TNM-7) to clarify whether this new staging system can stratify patients' prognosis and whether it is useful as an international staging system for colon cancer. We also speculate on the possible simplification of this staging system. As the United Kingdom uses the Dukes staging system, as recommended by the Royal College of Pathologists and the Association of Coloproctology of Great Britain and Ireland, we added this system for comparison. Objective statistical tests for staging systems have thus been introduced to deal with these issues.

Method

Patients

Surveillance, Epidemiology, and End Results, a population-based registry sponsored by the US National Cancer Institute, collects information on cancer incidence and survival from population-based cancer registries, including currently more than 25% of the US population [8,9]. We obtained the SEER November 2008 limited-use data files from nine SEER registries from 1973 to 2006.

A total of 436 281 patients were originally included. We selected those patients who underwent cancer-directed radical surgery for colon cancer (including rectosigmoid junction) who were diagnosed from 1988 to 2001, due to the consistency of data descriptions and sufficient follow-up periods during this time. Our basic policy for patient selection was to include only those patients without distant metastasis, who underwent radical surgery with lymphadenectomy. Exclusion criteria were as follows: rectal cancer, distant metastases, stage IV tumours, tumour *in situ*, appendiceal cancer, unspecified age, synchronous or metachronous cancers, no pathological examination of lymph nodes, survivors with followed-up <3 years, those patients receiving radiotherapy, surgery without curative intent, and incomplete or discrepant records. Tumours were stratified by SEER's 'extent of disease' and 'number of positive nodes' coding schemes. We restricted our analysis to adenocarcinomas, mucinous adenocarcinomas and signet ring cell carcinomas. Finally, a total of 50 139 patients were extracted from the database. Information concerning postoperative adjuvant chemotherapy was not available in the SEER database.

The JSCCR has a registration system which was started in 1980 [10]. The member institutions which are located all over Japan (currently 513 institutions) voluntarily register the clinical and pathological information for patients with colorectal cancer who were treated in each institution. This nationwide database covers approximately 10% of all patients with colorectal cancer in Japan, and has been considered the most reliable source of data which reflects the status of colorectal cancer treatment [11]. A total of 60 160 patients who were operated on between 1984 and 1994 were originally included in the JSCCR database (follow-up data after 2000 are not currently available). The exclusion criteria were essentially the same as those for the SEER data. Additional exclusion criteria used for JSCCR were as follows: receiving preoperative chemotherapy, non-curative resection. Finally, a total of 10 754 patients were extracted from the database. During this time period, adjuvant chemotherapy, such as 5-fluorouracil + leucovorin was not available in Japan.

We only analysed patients with cancer of the colon and rectosigmoid junction because the treatment strategy for rectal cancer tends to be quite different in terms of preoperative radiation therapy and lateral nodal dissection between Japan and Western countries [12].

Staging systems

The staging systems that we analysed were the TNM-6 (2004) [13], the TNM-7 (2009) [1], and the modified TNM-7 staging system that was devised in the present study. The Dukes staging system [14] was only analysed in the JSCCR database. The definition of each staging system in the current study is described in Fig. 1. In the TNM-7 classification, the T4 lesions were subcategorized as T4a (penetrates to the surface of the visceral peritoneum) and T4b (directly invades or is adherent to other organs or structures). N1 is now subdivided as N1a (metastasis in one node) and N1b (metastasis in two to three nodes), and N2 is subdivided into N2a (metastasis in four to six nodes) and N2b (metastasis in seven or

TNM-6 staging system

	N0	N1	N2
T1	I	IIIA	IIIC
T2	I	IIIA	IIIC
T3	IIA	IIIB	IIIC
T4	IIB	IIIB	IIIC

TNM-7 staging system

	N0	N1	N2a	N2b
T1	I	IIIA	IIIA	IIIB
T2	I	IIIA	IIIB	IIIB
T3	IIA	IIIB	IIIB	IIIC
T4a	IIB	IIIB	IIIC	IIIC
T4b	IIC	IIIC	IIIC	IIIC

Modified-TNM-7 staging system

	N0	N1	N2
T1	I	IIIA	IIIB
T2	I	IIIA	IIIB
T3	IIA	IIIB	IIIC
T4a	IIB	IIIB	IIIC
T4b	IIC	IIIC	IIIC

Dukes' staging system

	N (–)	N (+)	
T1	A	C1	C2
T2	A		
T3	B		
T4	B		

Figure 1 Definition of staging systems. The TNM-6 staging system (upper), the TNM-7 staging system (upper middle), the modified TNM-7 staging system (lower middle), and the Dukes' staging system (lower). C1, regional lymph node spread, but apical lymph node not involved; C2, apical lymph node involvement.

more nodes). We did not consider the new N1c (tumour deposits) which requires additional pathological examination. The modified TNM-7 staging system, which was devised in the present study, adopts the previous N-category of TNM-6 while using the new T-category of the seventh edition. The Dukes staging system requires information on the status of the apical lymph node for the subclassification of node-positive patients. This information was not available in the SEER database. Although the JSCCR database does not have specific information on the status of the apical lymph node, we could classify most of the node-positive patients into Dukes C1 (regional lymph node spread, but apical lymph node not involved) or Dukes C2 (apical lymph node involvement) because the database has information on the scope of lymph node dissection and the location of lymph node metastasis according to the Japanese Classification of Colorectal Carcinoma [15].

Comparison of staging systems

The criteria for assessing the performance of the prognostic systems were homogeneity, discriminatory ability and predictive accuracy [16].

1 Homogeneity: homogeneity within the same group (small differences in survival among patients with the same stage). The likelihood ratio χ^2 test (LR test) was used to assess the homogeneity within each classification system [16].

2 Discriminatory ability: the relative differences in the survival times among patients classified into different groups, as compared with the differences within the group. The Akaike information criterion (AIC) within a Cox proportional hazard regression model were used to demonstrate the discriminatory ability of the given staging system. The AIC can be used to compare systems with different combinations of numbers of stages, as a statistical estimate of the trade-off between the likelihood of a model against its complexity [17].

3 Accuracy of prediction: whether the patient with the higher prognostic score (i.e. a longer expected survival time according to the model) also had a longer survival time than patients with a lower prognostic score, as tested by all possible pairs of patients. A Harrell's *c*-index [18,19] was calculated to verify the prediction accuracy of each staging system. The *c*-indices were compared using the 'somersd' STATA (Stata Corporation, College Station, TX, USA) command which calculated the confidence interval for Harrell's *c*-index using jackknife variance estimation.

These statistical values suggest the rank order of the desirability of the models. A larger LR test and *c*-index, and a smaller AIC indicate a more desirable model for predicting the outcome. There is no available test to evaluate the statistical significance of the difference in AIC between models.

Statistical analyses

We selected cause-specific survival because the difference in survival rates between SEER and JSCCR patients was much smaller in cause-specific survival than in overall survival. The cause-specific survival was computed as the time from diagnosis or primary surgery to death due to primary colon cancer. The cumulative survival rates were calculated using the Kaplan–Meier method and were

compared with the log-rank test. Differences between the groups were analysed using the χ^2 test. Differences were considered to be statistically significant for P-values <0.05 with a two-tailed test. Statistical calculations were performed using the STATA statistical software, release 10 program (Stata Corporation).

We used SEER Program (http://www.seer.cancer.gov) limited-use data (1973–2006) (National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2007 submission). The institutional review board of the National Defense Medical College approved the study protocol.

Results

Characteristics of the patients

The characteristics of the patients are shown in Table 1. The SEER patients were older and included more women. There were more patients with cancer of the rectosigmoid junction and T4a cancer in the JSCCR data set. The proportion of patients withT4b tumours in patients with T4 tumours was 36% in the SEER data set, but only 14% in the JSCCR data set. The number of lymph nodes involved was higher in the SEER patients, while the number of lymph nodes examined was higher in the JSCCR patients.

Analyses among 25 TN categories

In the TNM-7 system, localized tumours with tumour depth of greater than Tis could be classified with five degrees of T (T1, T2, T3, T4a, T4b) and five degrees of N (N0, N1a, N1b, N2a, N2b), which resulted in 25 possible TN categories. The TNM classification condensed these categories into seven TNM stage groups (Stage I, IIA, IIB, IIC, IIIA, IIIB and IIIC) as indicated in Figs. 1 and 2. The number of patients, and the cause-specific survivals for the TN categories, were analysed and are shown in Fig. 2.

The 5-year cause-specific survivals for node-negative patients in categories classified as Stage I, IIA, IIB, IIC were 91.6–94.5, 82.1, 77.7 and 54.5% in SEER, but 97.1–98.5, 92.8, 87.2 and 81.1% in JSCCR. The survivals for node-positive patients in categories classified as Stage IIIA, IIIB and IIIC were 72.7–88.6, 40.0–67.7 and 11.3–38.9% in SEER, and 93.5–100, 66.4–85.7 and 16.3–58.8% in JSCCR, without notable overlaps.

The log-rank tests for cause-specific survival for all of these categories within each T and N degree were statistically significant ($P < 0.0001$) for the SEER data.

Table 1 Characteristics of the patients in Surveillance, Epidemiology, and End Results (SEER) and Japanese Society for Cancer of the Colon and Rectum (JSCCR) studies.

Registry	SEER	JSCCR
Years	1988–2001	1984–1994
Patients	50 139	10 754
Node-positive patients	18369 (36.6%)	3933 (36.6%)
Age (median)	70.6 (72.0)	64.4 (65.0)
Gender		
Male	22855 (45.6%)	5922 (55.1%)
Female	27284 (54.4%)	4832 (44.9%)
Race		
White	42107 (84.0%)	3 (0.0%)
Black	4088 (8.2%)	1 (0.0%)
Asian	2803 (5.6%)	10728 (99.8%)
Others (including unknown)	1141 (2.2%)	22 (0.2%)
Site of disease		
Right colon	27219 (54.3%)	3962 (36.8%)
Left colon	18312 (36.5%)	5165 (48.0%)
Rectosigmoids	4608 (9.2%)	1627 (15.1%)
Tumour depth (TNM-7)		
T1	3241 (6.5%)	1135 (10.6%)
T2	7688 (15.3%)	1311 (12.2%)
T3	32090 (64.0%)	5105 (47.5%)
T4a	4535 (9.0%)	2809 (26.1%)
T4b	2585 (5.2%)	394 (3.7%)
Nodal status (TNM-7)		
N0	31770 (63.4%)	6821 (63.4%)
N1a	6279 (12.5%)	1699 (15.8%)
N1b	6155 (12.3%)	1374 (12.8%)
N2a	3646 (7.3%)	563 (5.2%)
N2b	2289 (4.6%)	297 (2.8%)
Number of lymph nodes involved	1.25	0.98
Number of lymph nodes examined (median)	12.1 (10.0)	17.5 (14.0)

In contrast, the JSCCR patients with T1 tumours did not show statistically significant prognostic differences with respect to the N categories ($P = 0.0907$). There was a significant difference in the cause-specific survival between patients in T1N2a and T1N2b only in the SEER data ($P = 0.0253$). However, it is noteworthy that there were only 24 and 5 patients categorized as T1N2a and T1N2b in the SEER database, and 7 and none in the JSCCR database, respectively.

SEER

$n = 50\,139$

Number of patients

	N0	N1a	N1b	N2a	N2b	Total	
T1	2925	198	89	24	5	3241	6.5%
T2	6397	671	427	133	60	7688	15.3%
T3	18 909	4385	4503	2687	1606	32090	64.0%
T4a	2363	660	699	481	332	4535	9.0%
T4b	1176	365	437	321	286	2585	5.2%
Total	31770	6279	6155	3646	2289	50139	
	63.4%	12.5%	12.3%	7.3%	4.6%	100%	

5-year cause-specific survival

	N0	N1a	N1b	N2a	N2b	Total	p-value
T1	94.5±0.4	88.6±2.3	79.7±4.4	72.7±9.5	40.0±21.9	93.5±0.5	<0.0001
T2	91.6±0.4	84.3±1.5	82.3±1.9	64.3±4.3	64.2±6.4	89.7±0.4	<0.0001
T3	82.1±0.3	67.7±0.7	58.9±0.8	48.4±1.0	32.4±1.2	71.5±0.2	<0.0001
T4a	77.7±0.9	62.9±2.0	51.7±2.0	38.9±2.4	23.3±2.5	63.4±0.8	<0.0001
T4b	54.5±1.5	37.9±2.8	28.3±2.3	17.9±2.3	11.3±2.0	38.5±1.0	<0.0001
Total	83.9±0.2	68.1±0.6	57.9±0.7	45.3±0.9	29.4±1.0		<0.0001
p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

JSCCR

$n = 10\,754$

Number of patients

	N0	N1a	N1b	N2a	N2b	Total	
T1	1007	90	31	7	0	1135	10.6%
T2	1042	156	78	28	7	1311	12.2%
T3	3198	821	682	271	133	5105	47.5%
T4a	1357	554	524	231	143	2809	26.1%
T4b	217	78	59	26	14	394	3.7%
Total	6821	1699	1374	563	297	10754	
	63.4%	15.8%	12.8%	5.2%	2.8%		

5-year cause-specific survival

	N0	N1a	N1b	N2a	N2b	Total	p-value
T1	98.5±0.3	96.6±1.9	93.5±4.4	100		98.2±0.4	0.0907
T2	97.1±0.5	95.2±1.8	93.6±2.8	78.4±7.8	85.7±13.2	96.2±0.5	<0.0001
T3	92.8±0.4	84.2±1.3	79.1±1.6	66.4±3.0	58.6±4.4	87.3±0.5	<0.0001
T4a	87.2±0.9	75.5±1.9	70.1±2.1	58.8±3.3	39.4±4.2	76.9±0.8	<0.0001
T4b	81.1±2.7	58.3±5.9	54.0±6.8	45.3±10.6	16.3±10.5	68.2±2.4	<0.0001
Total	92.9±0.3	81.9±1.0	75.8±1.2	63.3±2.1	48.2±3.0		<0.0001
p	<0.0001	<0.0001	<0.0001	0.0048	<0.0001	<0.0001	

Figure 2 Distribution and prognosis for patients in TN categories of the TNM-7 staging system. Dark columns are for Stage IIIB patients. SEER, Surveillance, Epidemiology, and End Results; JSCCR, Japanese Society for Cancer of the Colon and Rectum.

In the TNM-7 staging system, T3N2a was situated in the prognostically marginal zone of Stage IIIB and Stage IIIC. There were statistically significant differences in cause-specific survival for patients in the T3N1b, T3N2a and T3N2b categories in the SEER study ($P < 0.0001$), while the difference was only significant between the T3N1b and T3N2a categories ($P < 0.0001$) in the JSCCR system.

Survival curves according to the staging systems

The survival curves for each staging system are shown in Fig. 3 (SEER) and Fig. 4 (JSCCR). In the TNM-6 staging systems, the order of the cause-specific survival curves of each group was the same in both the SEER and JSCCR studies.

In the TNM-7 staging system and the modified TNM-7 staging system, the order of the 5-year cause-specific survival curves was different between the SEER and JSCCR studies. The cause-specific survivals among substages within node-negative or node-positive patients were significantly different in all staging systems.

Comparison of staging systems by objective statistical tests

In a comparison of the TNM-6 and TNM-7 staging systems (Table 2), the TNM-7 system was better according to all tests for the SEER and JSCCR patients. When we compared the TNM-7 and the modified TNM-7 staging systems in the SEER study, the TNM-7 system was superior according to the LR-test and the AIC but significantly inferior according to the c-index. Interestingly, in JSCCR patients, the TNM-7 staging system was almost identical to the modified TNM-7 according to all tests.

When we compared the TNM-7 system and the Dukes staging system in JSCCR patients, the TNM-7 system was superior according to the LR-test and the c-index but inferior according to the AIC.

Discussion

We evaluated the new TNM-7 staging system based on the two nationwide colon cancer registries in the United States and Japan. This is the first objective statistical evaluation of the TNM-7 staging system. The main point of this study was to analyse the new staging algorithm, not to compare these two databases.

We evaluated the appropriateness of the new grouping of elements of the 25 TN categories in the TNM-7 staging system (Fig. 2). Each TN category appears to have been appropriately condensed to homogeneous groups with different prognoses in the SEER and JSCCR studies, as far as node-negative and node-positive patients are considered.

In the TNM-7 staging system, T4 tumours are subdivided into T4a and T4b tumours. The patients with T4b tumours had worse outcomes than those with T4a tumours in both SEER and JSCCR subjects. The T4 subdivisions were useful to identify patients with very poor prognoses regardless of patient N status among both the SEER and JSCCR patients.

In contrast to the new T-category, the new N-category of the TNM-7 system is not well utilized in the new staging algorithm. The differences between N1a

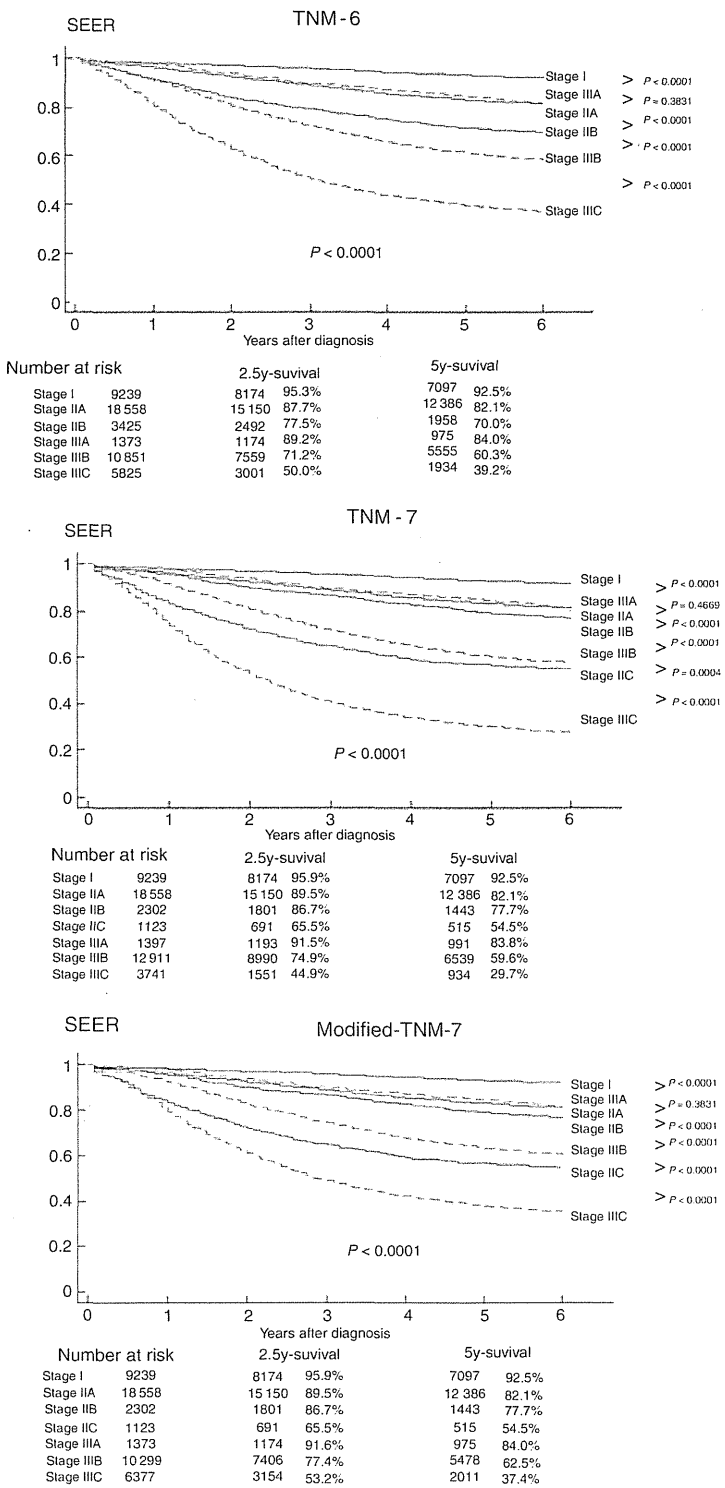

Figure 3 Cause-specific survivals of Surveillance, Epidemiology, and End Results (SEER) patients stratified by the TNM-6 (upper), the TNM-7 (middle), and the modified TNM-7 staging system (lower). Continuous lines are for node-negative patients and broken lines for node-positive patients.

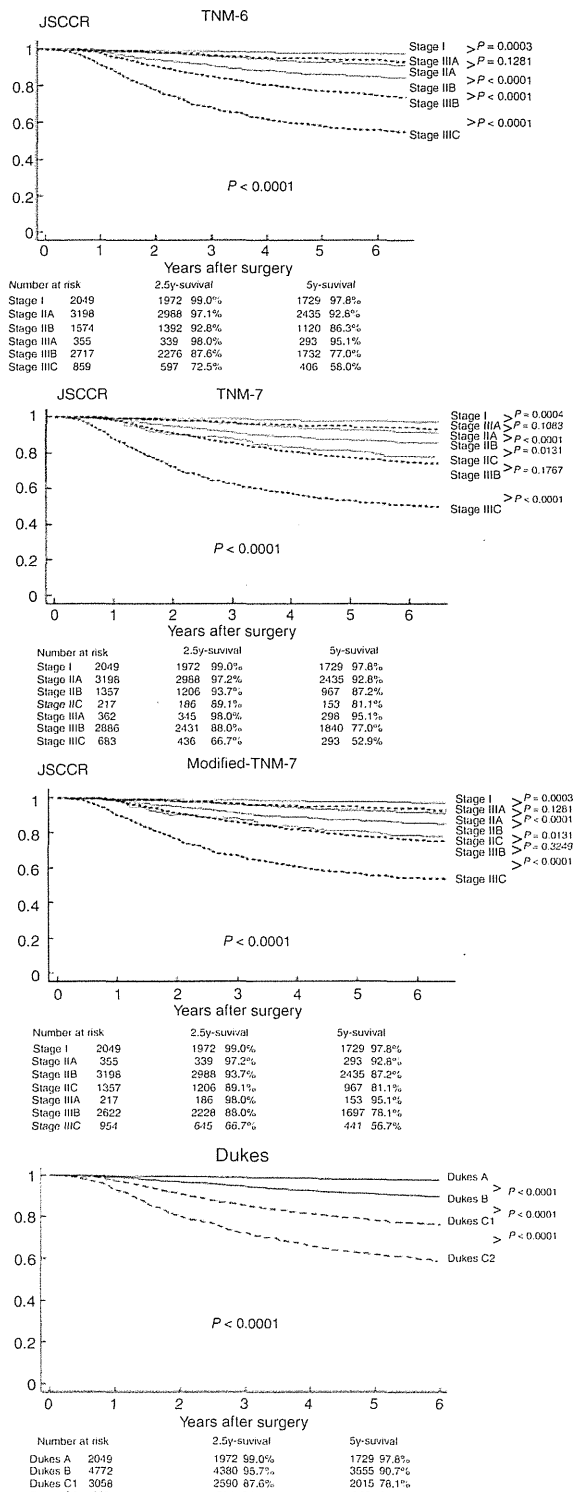

Figure 4 Cause-specific survivals for Japanese Society for Cancer of the Colon and Rectum (JSCCR) patients stratified by the TNM-6 (upper), the TNM-7 (upper middle), the modified TNM-7 staging system (lower middle) and the Dukes staging system (lower). Continuous lines are for node-negative patients and broken lines for node-positive patients.

Table 2 Objective comparisons among the staging systems for cause-specific survival.

	Cohort	Number of patients	Number of categories	Likelihood-ratio χ^2 test (*P*-value)	Akaike information criterion	Harrel's *c*-index	Harrel's *c*-index 95% CI	Harrel's *c*-index *P*-value *vs* TNM6	Harrel's *c*-index *P*-value *vs* TNM7
TNM-6	SEER	50 139	6	6721 (<0.0001)	28 7991	0.6958	0.6916–0.7000	–	<0.001
TNM-7	SEER	50 139	7	7367 (<0.0001)	28 7348	0.7001	0.6959–0.7044	<0.001	–
Modified-TNM-7	SEER	50 139	7	7242 (<0.0001)	28 7474	0.7019	0.6977–0.7061	<0.001	<0.001
TNM-6th	JSCCR	10 754	6	1119 (<0.0001)	28 263	0.7292	0.7179–0.7405	–	0.035
TNM-7th	JSCCR	10 754	7	1168 (<0.0001)	28 216	0.7318	0.7205–0.7432	0.035	–
Modified-TNM-7	JSCCR	10 754	7	1167 (<0.0001)	28 216	0.7332	0.7219–0.7446	<0.001	0.110
Dukes*	JSCCR	10 704	4	916 (<0.0001)	28 083	0.7021	0.6907–0.7135	<0.001	<0.001

A larger likelihood-ratio χ^2 test, Harrell's *c*-index, and a smaller Akaike information criterion indicate a more desirable model for predicting outcome.
SEER, Surveillance, Epidemiology, and End Results; JSCCR, Japanese Society for Cancer of the Colon and Rectum.
*Fifty cases could not be classified by Dukes staging.

and N1b were not reflected in the new staging system, as shown in Fig. 1. Furthermore, the differences between N2a and N2b were only reflected in the separation of T1N2a (Stage IIIA) and T1N2b (Stage IIIB) as well as T3N2a (Stage IIIB) and T3N2b (Stage IIIC). However, T1N2 may not warrant a separate classification, considering the very small number of T1N2 patients in both databases. When we compared the T1N1 (n = 287) and T1N2 (n = 29) patients in the SEER data set, there was a significant difference in 5-year cause-specific survival (85.8% *vs* 66.7%, respectively, P = 0.0029). The original stratification could be simplified to the classification of T1N2 (T1N2a + T1N2b) to represent Stage IIIB.

The prognostic difference between the T3N2a and T3N2b patients was significant in SEER, but the prognosis for these two patient types was identical among JSCCR patients. Because the prognoses of T3N1b and T3N2a patients were significantly different in both the SEER and JSCCR data sets, the original classification could be simplified to the classification of T3N2 (N2a + N2b) to represent Stage IIIC. This modification seems particularly reasonable for JSCCR patients. By changing the attribute of T1N2b from Stage IIIC to Stage IIIB as well as that of T3N2a from Stage IIIB to Stage IIIC, we can change the stair type classification of the TNM-7 staging system to a much simpler modified TNM-7 staging system (Fig. 1). This classification does not require a new subdivision of the N-category, and it could be a simple substitution for the TNM-7 staging system.

We performed a comparison of the survival curves for the TNM-6, TNM-7 and modified TNM-7 staging systems. In the TNM-7 staging system, the prognosis of patients with Stage II or Stage III tumours significantly overlapped, as shown in Figs. 3 and 4. Furthermore, the order of the cause-specific survival at 5 year differs between the databases for Stages I, IIIA, IIA, IIB, IIIB, IIC and IIIC for SEER patients and Stages I, IIIA, IIA, IIB, IIC, IIIB and IIIC for JSCCR patients. In SEER dataset the 5-year survival for patients with Stage IIIB cancer (59.6%) was significantly better than that for patients with Stage IIC tumours (54.5%). In contrast the 5-year survival for Stage IIC patients (81.1%) was better than that for Stage IIIB patients (77.0%) in the JSCCR dataset. Kim *et al.* [20] recently performed a validation of TNM-7 for Korean patients with Stage II or III colorectal cancer and reported the order of the overall survival at 5 years as Stage IIA, IIIA, IIB, IIC, IIIB and IIIC. They reported a better 5-year overall survival for patients with Stage IIC cancer (83.5%) than for those with Stage IIIB tumours (81.8%), which is similar to the survival for JSCCR patients in these stages. Because the inclusion of the TN categories into groups may not be allowed across

node-negative and node-positive patients under the basic concept of TNM classification, such overlapping substages between the node-positive and node-negative patients may be supposed to be inevitable and the order may vary among databases. Such inconsistencies may be a cause for confusion. Considering the overlapping of survival curves between Stage II and Stage III patients, it seems difficult to justify the indication of postoperative chemotherapy for Stage IIIA patients, while excluding patients with Stage IIC tumours.

We performed an objective comparison of the staging systems using several statistical tests. These analyses offered a significant advantage over the traditional method of comparing staging systems by estimating the curves, and these statistical tests have been used in several studies [16,21]. As the statistical values of the objective tests can suggest the rank order of the desirability of the models, we can decide which model is more desirable. The objective comparison shows that the TNM-7 staging system is better than that of the TNM-6 in all the objective tests, for SEER as well as JSCCR data. The improved discriminatory ability and the homogeneity of each substage in the TNM-7 staging system should be emphasized for the purpose of stratifying patients for therapeutic trials, thereby reducing any overly optimistic results caused by patient selection or the large heterogeneity among studies.

The differences in survival curves for the TNM-7 and modified TNM-7 staging systems are not easily recognizable. Although the TNM-7 system showed slightly better values than those of the modified TNM-7 system in homogeneity and discriminatory ability in SEER patients, there was little difference between the two systems in any of the objective tests in the JSCCR data set. Furthermore, the predictive accuracy of the modified system as represented by the c-index was significantly better than that of the original TNM-7 system in SEER patients ($P < 0.001$) and was identical in JSCCR patients ($P = 0.110$). Thus, the modified TNM-7 staging system is considered to be easier to learn, while also providing sufficient predictive accuracy.

The TNM-7 staging system stratified both SEER and JSCCR patients well. Furthermore, the predictive accuracy (c-index) of the TNM-7 system was even better for JSCCR patients than for SEER patients, supporting its feasibility as an international standard for colon cancer staging.

The Dukes staging system, which utilizes the concept of apical lymph node involvement, is by far the simplest of the systems analysed in this study. The discriminatory ability of the Dukes system represented by AIC was even superior to that of the TNM-7 staging system, partially because AIC is a statistical estimate of the trade-off between the likelihood of a model and its complexity. Although simplicity is its strength, its prognostic value represented by the c-index is limited by not being able to distinguish several subgroups such as T3N0, T4aN0 and T4bN0 as defined by the TNM-7 staging system.

This study has several limitations. As this is a retrospective study, the treatments for patients including postoperative chemotherapy are not controlled. The data collection time periods of the two databases were not identical. We observed several disparities in characteristics of patients between the databases including differences in the number of lymph nodes involved and examined. Therefore, direct comparisons of the survival data between these two databases are not relevant. We could not discriminate the new N1c (tumour deposits) category, which requires additional pathological examination. Nonetheless, the new N1c category is important for precise evaluation of the TNM-7, although the current TNM at that point may not be optimal as we previously reported [22]. Further investigation is required with respect to N1c and the new T categories of the TNM-7 staging system.

In conclusion, the new TNM-7 staging system is complicated but is better at stratifying patients than is the TNM-6 system, and it could be simplified to a modified TNM-7 staging system without losing its discriminatory ability. Although the TNM-7 staging system seemed to be useful both in the United States and in Japan, it may be possible to be effectively simplified for clinical use in future revision.

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Commentary

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In the Editorial of this issue of *Colorectal Disease*, Chapuis and colleagues [1] discuss the important question of standardization of the numerous, currently six, existing staging systems for large bowel cancer. They do so with authority, since they have been closely involved with the development of the Australian Clinicopathological Staging System, which was the first to propose that clinical factors should be added to purely histopathological information for the purpose of staging. As readers will know, the introduction by Dukes of a staging system for rectal cancer in the 1920s [2] was followed by some modifications in the 1940s and 1950s, for example by Astler and Coller [3]. These, however, were concerned only with attempts to refine pathological staging and were therefore inevitably focused on the examination of the excised surgical specimen and its relation to survival rather than the whole patient and the incidence of local recurrence and disease-free survival.

The Australian Clinicopathological Staging System, originally proposed by Davis and Newland of the Princess Alexandra Hospital, Brisbane in 1983 [4], was further developed at the Concord Hospital, Sydney [5]. It included the concept of the completeness of surgical removal. It is now generally accepted that local recurrence is *the* relevant endpoint of the adequacy of any locoregional treatment such as surgery and radiotherapy. Thus the measure of their cancer-specific success is the incidence of local recurrence.

Over the last 20 years the TNM staging system [6,7] has emerged as the most used. Its definitions are regularly updated by new editions of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual based on carefully considered evidence. In the present issue of *Colorectal Disease* Hashiguchi and colleagues [8] have compared the TN definitions of the sixth edition with those of the seventh edition. They conclude that

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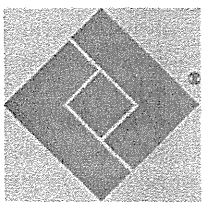

Prospective Longitudinal Evaluation of Quality of Life in Patients With Permanent Colostomy After Curative Resection for Rectal Cancer

A Preliminary Study

Naomi Ito ■ Megumi Ishiguro ■ Mitsuko Uno ■ Syunsuke Kato ■ Sayaka Shimizu ■ Riri Obata ■ Makoto Tanaka ■ Keiko Tokunaga ■ Midori Nagano ■ Kenichi Sugihara ■ Keiko Kazuma

PURPOSE: The aim of this study was to evaluate health-related quality of life in patients with a colostomy immediately before and during the first year after surgery.

SUBJECTS AND SETTING: Patients (aged ≥20 years) who were diagnosed with rectal cancer and scheduled to undergo curative surgery with a permanent colostomy were recruited for this study. Data were collected at 2 university hospitals in Tokyo.

METHODS: Participants were asked to complete a self-administered questionnaire regarding health-related quality of life before surgery and a mailed or hand delivered questionnaire to evaluate quality of life at 2, 6, and 12 months after surgery using the Short Form–36 version 2. For patients who responded at all 4 time points, the scores at each time point were compared using paired *t* tests to examine longitudinal changes in quality of life after surgery.

RESULTS: Mean quality-of-life scores in most domains before surgery and during the first year after surgery were lower than the normal control in the norm-based scoring method. Scores at 2 months after surgery were lower than those before surgery. At 12 months after surgery, however, quality-of-life scores improved almost to the level observed before surgery, with the exception of the score in the social functioning domain. Statistical differences in scores between the time points of the survey were observed in the role-physical, bodily pain, and mental health domains.

CONCLUSIONS: These results suggest that patients with permanent colostomy after curative resection for rectal cancer need additional medical support and care before surgery and during the first year after surgery.

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The authors declare no conflict of interest.

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Introduction

The proportion of colorectal cancer patients who require permanent colostomy is hypothesized to be decreasing because of improvements in techniques of sphincter-preserving surgery, including intersphincteric resection. However, the number of patients who require a permanent colostomy for locally advanced carcinoma has not changed. Health-related quality of life (QOL) in patients may be influenced by a permanent colostomy. Therefore, evaluation of QOL in these patients could be useful for planning and improving care for patients after surgery for rectal cancer.

Quality of life is increasingly used as an important subjective measure of medical care.[1] The early period after surgery during the first year with permanent colostomy is especially important for patients since they have to learn effective stoma care and often have to receive adjuvant therapy. Health-related QOL may also be challenged in this patient population because of the risk for recurrence. Therefore, understanding the QOL status during the early period after surgery is important.

Many researchers have reported on QOL in patients with colostomy during the first year after surgery. Using the European Association for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and CR-38, Gervaz and colleagues[2] reported that patients after abdominoperineal resection (APR) demonstrated a significant improvement in global QOL and tumor-related symptoms within 12 months of surgery, while body image remained significantly impaired. Using the same instrument, Tsunoda and associates[3] reported that QOL scores in some domains in 100 colorectal cancer patients improved within 3 months of surgery. However, the number of patients with a colostomy in their study was limited; it included 6 patients with a permanent colostomy and 5 with a temporarily diverting colostomy. Sharma and coworkers[4] stated that preoperative QOL is one of the predictors of QOL within 6 to 10 weeks of surgery.

Some studies have compared QOL of patients with and without stomas. No consistent conclusion was drawn from these studies regarding the comparison of QOL between patients who had undergone APR and those who had undergone anterior resection.[5-12]

Some instruments have been used to evaluate QOL in patients with colostomy, but few studies[13] have used the generic Short Form–36 (SF-36) scale[14] for this purpose. The SF-36 is widely used to evaluate health-related QOL in various health-related fields, and it has been translated into various languages including Japanese. The generic SF-36 scale allows comparison of health-related QOL in patients with a colostomy with other populations by norm-based scoring (NBS). Norm-based scoring is a standardized scoring method that assumes the national norm data to be 50 points and the standard deviation to be 10 points.

Moreover, the use of the instrument allows comparison of health-related QOL before surgery with that measured following ostomy surgery for each of the 8 domains. We intended to investigate when the QOL of patients with permanent colostomy recovered to the preoperative level during the postoperative period. However, to the best of our knowledge, no studies have examined the longitudinal changes in QOL in patients with a colostomy before and during the first year after surgery for each domain of SF-36.

The objective of this study was to examine the longitudinal changes in health-related QOL in patients scheduled for surgery including creation of a permanent colostomy at 4 time points: before surgery and 2, 6, and 12 months after surgery. These data provide detailed explanation of the QOL of patients with a colostomy. Therefore, it is very helpful for medical staff caring for patients.

Methods

Patients fulfilling the following criteria were enrolled in this study: (1) diagnosed with rectal cancer, (2) scheduled to undergo curative surgery with a permanent colostomy, (3) ≥20 years of age, and (4) capable of completing the questionnaire at the University of Tokyo Hospital and Tokyo Medical and Dental University Hospital. Participants were recruited between February 2005 and March 2008. The study protocol was approved by the institutional review board at the University of Tokyo Hospital and Tokyo Medical and Dental University Hospital. All patients provided written informed consent.

Instrument

Health-related QOL was evaluated using the Japanese language version of the SF-36 version 2, which comprises 8 domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health, vitality (VT), social functioning, role-emotional, and mental health (MH).[14] Higher scores indicate a better level of QOL in each domain. Demographic and medical variables were collected from medical records and the self-administered questionnaire before surgery. The following parameters were considered demographic and medical variables: sex, age, occupational status, marital status, diagnosis, clinical stage of cancer, surgical procedure, and comorbidity.

Data Collection

An investigator explained the study protocol to the patients before surgery. Once they agreed to participate in the study, participants were asked to complete the self-administered questionnaire before surgery. After surgery, the questionnaires were mailed or hand delivered at 2, 6, and 12 months after surgery. The time points of the survey after surgery were chosen based on perceptions of clinical relevance.[15] Participants were requested to complete the questionnaires for a total of 4 time points until the end of the study (12 months after surgery). Data collection was discontinued

when a patient died or a recurrence of colorectal cancer was detected. The participants regularly attended all follow-up appointments. A member of the research team monitored patients for recurrence of colorectal cancer.

Statistical Analyses

Scoring was performed according to the directions in the manual for SF-36 version 2,[14] and NBS was used for each SF-36 domain. A mean QOL score was calculated at each time point of the survey (before surgery and 2, 6, and 12 months after surgery). For patients who completed the questionnaires at all 4 time points of the survey, the scores at each time point were compared using paired *t* tests to examine the longitudinal changes in QOL after surgery. All inferential statistical analyses were 2-tailed; $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.1 for Windows (SAS Institute, Cary, North Carolina).

Results

Twenty patients were deemed eligible for inclusion, and 18 agreed to participate. One patient refused to participate in the study after giving consent and another was excluded when it was subsequently found that the individual did not meet inclusion criteria. Seven patients completed the questionnaires at all 4 time points (before surgery and 2, 6, and 12 months after surgery), 4 completed them at 2 time points, and 5 completed them at 3 time points.

Table 1 summarizes the characteristics of the patients analyzed. Eleven were men; their mean age was 65.3 ± 11.1 years (mean ± SD). Twelve patients underwent APR, and 2 underwent Hartmann's procedure. One participant had ultra-low anterior resection, resulting in permanent colostomy, and 1 underwent total pelvic exenteration. Figure 1 shows longitudinal changes in QOL scores of the 16 patients. In most domains included in SF-36, QOL scores were lower than the control NBS point of 50 before surgery and during the first year after surgery for each of the 8 domains, except at 6 and 12 months for the BP domain, 6 months for the VT domain, and 12 months for the MH domain.

Quality-of-life scores at 2 months after surgery were lower than those before surgery. However, QOL scores improved at 6 months after surgery, and they recovered almost to the level observed before surgery at 12 months after surgery. In the BP, VT, and MH domains, health-related QOL scores 6 and/or 12 months after surgery were higher than those before surgery.

Seven patients completed the questionnaires at all 4 time points. This group included 6 men, with mean age of 62.3 ± 9.8 years. Five patients underwent APR. Figure 2 shows the longitudinal changes in QOL scores of the 7 patients. Quality-of-life scores in the RP domain significantly improved from 2 to 12 months after surgery (25.6 ± 16.8 vs 42.1 ± 10.3, $P = .01$). The QOL scores in the BP domain significantly improved from before surgery to 6 months after surgery (43.7 ± 14.0 vs 49.9 ± 11.3, $P = .02$) and from before surgery to 12 months after surgery (43.7 ± 14.0 vs 51.2 ± 11.8, $P = .02$). Quality-of-life scores in the BP domain also significantly improved from 2 months to 6 months after surgery (34.6 ± 10.9 vs 49.9 ± 11.3, $P = .02$) and from 2 months to 12 months after surgery (34.6 ± 10.9 vs 51.2 ± 11.8, $P = .01$). Health-related QOL scores in the MH domain significantly improved from 2 months to 12 months after surgery (43.8 ± 15.5 vs 55.1 ± 9.4, $P = .03$) and from 6 months to 12 months after surgery (51.0 ± 12.0 vs 55.1 ± 9.4, $P = .04$).

TABLE 1.

Characteristics of Patients (N = 16)

Variable	n (%)
Gender	
Men	11 (68)
Women	5 (31)
Age, mean (SD), y	65.3 ± 11.1
Occupational status	
Employed full or part time	8 (50)
Unemployed	8 (50)
Marital status	
Married	11 (69)
Other	5 (31)
Diagnosis	
Rectal cancer	14 (88)
Fistula cancer	2 (12)
Clinical stage (tumor node metastasis)	
I	1 (6)
II	10 (63)
IIIa	3 (19)
IIIb	1 (6)
IV	1 (6)
Surgical procedure	
APR	12 (75)
Hartmann's procedure	2 (12)
U-LAR resulting in permanent diverting colostomy	1 (6)
TPE	1 (6)

Abbreviations: APR, abdominoperineal resection; TPE, total pelvic exenteration; U-LAR, ultra-low anterior resection.

Discussion

We assessed health-related QOL before surgery and during the first postoperative surgery in patients with colorectal cancer managed by surgical resection and a permanent colostomy. Although our sample was small, this is among the

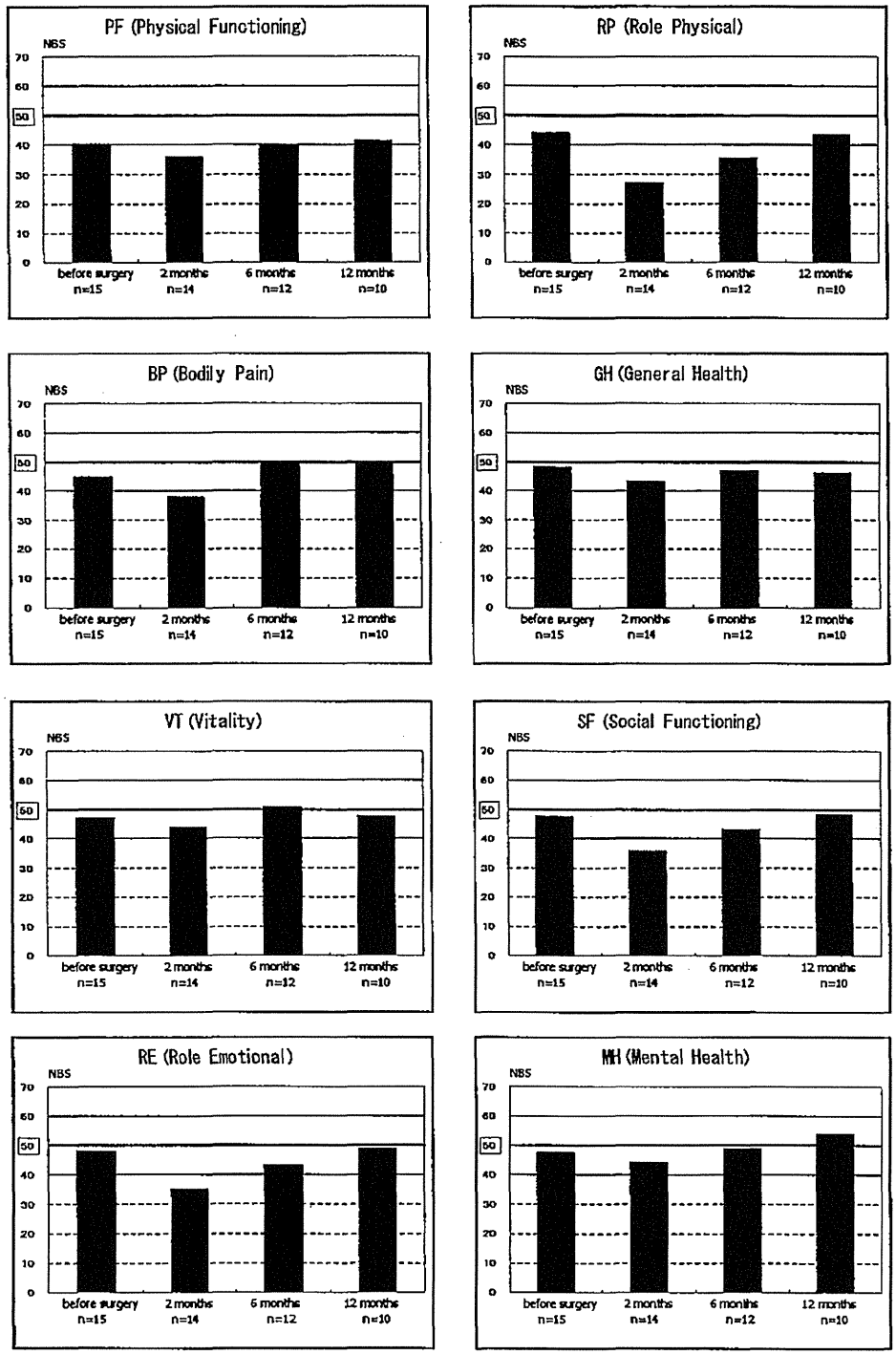

FIGURE 1. Changes in quality-of-life scores of all patients (N = 16). Abbreviation: NBS, norm-based scoring.

first studies to look at longitudinal changes in QOL in patients with a colostomy before surgery and during the first year after surgery based on QOL domains identified in the SF-36. We also compared health-related QOL in respondents by comparing their SF-36 scores with population-based controls. We found that QOL scores were lower than the population-based score of 50 before surgery and during the first year after surgery for each of the 8 domains, except at 6 and 12 months for the BP domain, 6 months for the VT domain, and 12 months for the MH domain. Our findings suggest that the health-related QOL of patients with a permanent colostomy are lower than the QOL among

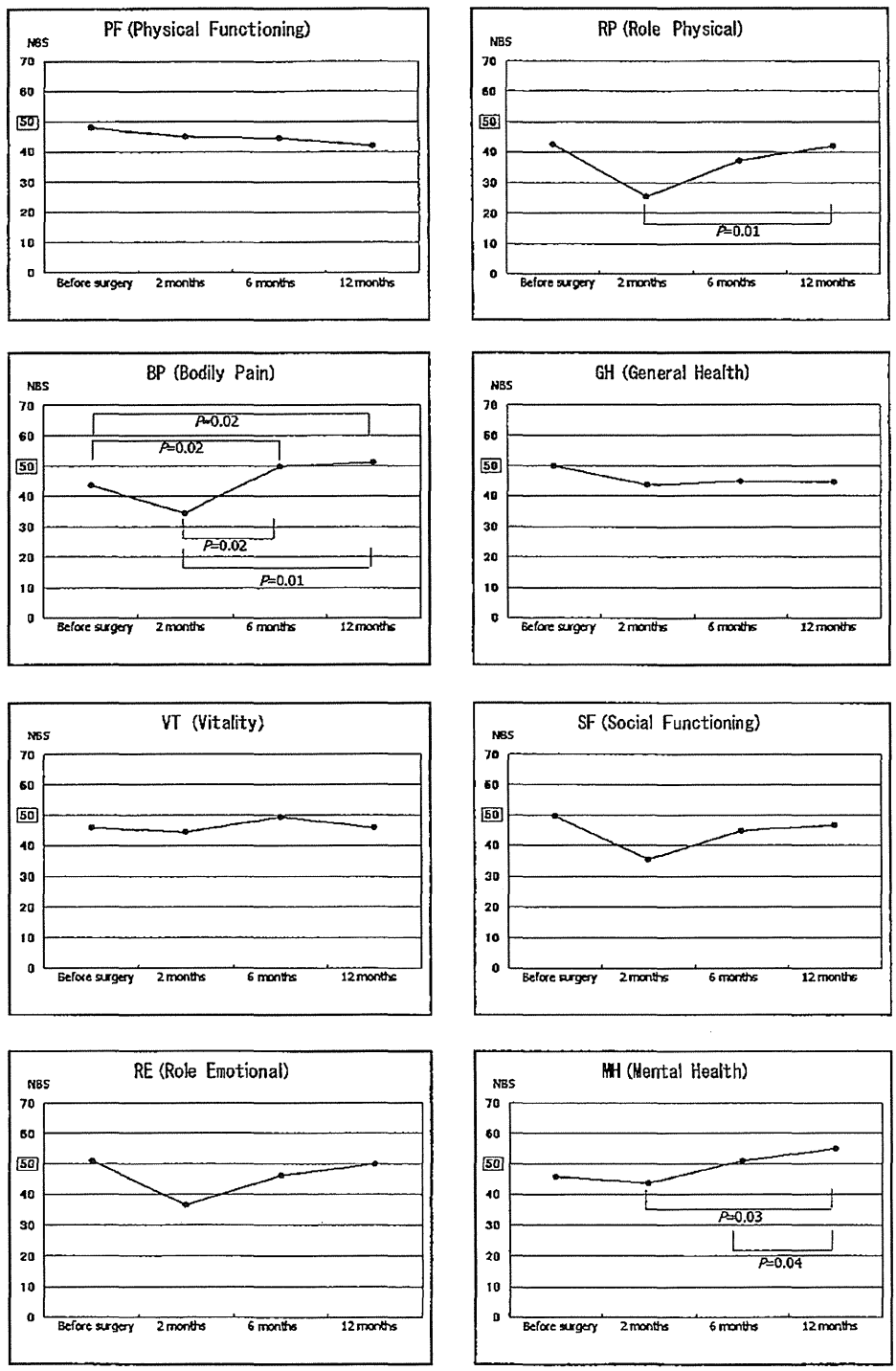

FIGURE 2. Changes in quality-of-life scores of 7 patients completed the questionnaires at all 4 time points (N = 7). Abbreviation: NBS, norm-based scoring.

healthy controls. The lower scores we found in the physical functioning, RP, social functioning, and role-emotional domains may reflect the physical burden caused by the surgery and permanent surgery, and the uncertainty patients perceive when attempting to integrate ostomy-related self-care skills into their daily activities.

Quality-of-life scores declined at 2 months and improved at 6 months after surgery and recovered almost to the level observed before surgery at 12 months. Our results support those of Gervaz and colleagues,[2] who also found that health-related QOL after APR improves within 12 months of surgery. Pittman and colleagues[16] reviewed literature and