

Special Issue

Investigation of the Japanese Classification of Peritoneal Metastasis from Colorectal Cancer Referring to the Correlation with PCI

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Abstract

Objectives: In Japan, there are three grades of peritoneal metastasis from colorectal cancer. The grade depends on the extent and number of lesions (P classification). The P classification is useful for its simplicity but lacks objectivity. On the other hand, the peritoneal cancer index (PCI) objectively indicates the peritoneal metastasis grade. However, the evaluation process is complicated clinically. In this study, we compared these two methods and investigated how to improve the P classification's objectivity by referring to PCI.

Methods: We investigated 150 cases of synchronous peritoneal metastasis from colorectal cancer. We inspected the correlation between the P classification and the PCI and pointed out the problems which prevented objective evaluation when using the P classification. We also estimated new criteria for extent and number in the P classification.

Results: We found the ideal definition for the best alignment between the P classification and the PCI was:

- P1 is metastases confined to one peritoneal region,
- P2 is 19 or fewer peritoneal metastases in two or more regions, and
- P3 is 20 or more metastases in two or more regions.

This revision improved the P classification's objectivity and correlated with the PCI.

Conclusions: Grading using the P classification was both imprecise and subjective. We propose a new standard value of extent and number in the P classification based on the PCI. This improvement would provide an objective, simple method of grading for peritoneal metastasis from colorectal cancer.

Keywords

colorectal cancer, peritoneal metastasis, classification

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Introduction

In Japan, peritoneal metastasis from colorectal cancer is evaluated based on the extent and number of lesions (P classification Table 1)[1]. It is concise since there are only

three grades; however, it is subjective because there are no standard values for the extent and number of lesions. Another evaluation method, the peritoneal carcinomatosis index (PCI)[2], is frequently used worldwide. The PCI, index classifies the degree of peritoneal metastasis into 39 phases, de-

pending on the number of regions in which metastasis exists and the maximum size of the lesions (Figure 1). The PCI is an objective method, but the classification process is complicated clinically. We analyzed the correlation between these two methods and suggested which points required improvement in the P classification by referring to the PCI.

Methods

Patients

Table 1. P Classification.

Degree of peritoneal metastasis is classified into three grades; P1, P2, and P3. Each category is defined by the distance from the primary tumor and metastatic amount (nearly number of lesions) as described on the table. The P classification is established by the Japan Society for Cancer of the Colon and Rectum (JSCCR).

P1: Metastasis localized to adjacent peritoneum
P2: Limited metastasis to distant peritoneum
P3: Diffuse metastasis to distant peritoneum

This multicentric, prospective, observational study included 150 cases of colorectal cancer with synchronous peritoneal metastasis between October 2012 to December 2016 in 28 institutes (see Acknowledgments), who were part of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) project [Grading colorectal cancer peritoneal metastasis]. The JSCCR ethics review board approved the study.

Methods

1. To indicate the current ability of P classification to classify metastatic peritoneal lesions, we investigated the distribution of the extent, the number of lesions, and the maximum size of lesions in every grade (P1, P2, and P3).

2. To inspect the associations between current P classification and the PCI, we calculated the statistical PCI scores for each grade of P classification. We also confirmed the ratio of cases corresponding to the calculated PCI and tried to find out which P classification aspects interfered with objective grading.

3. We attempted to provide standard values for the extent and the number of lesions in the P classification by referring to the PCI as an objective standard.

4. We proposed new classifications and added clear standard values for the current P classification parameters and

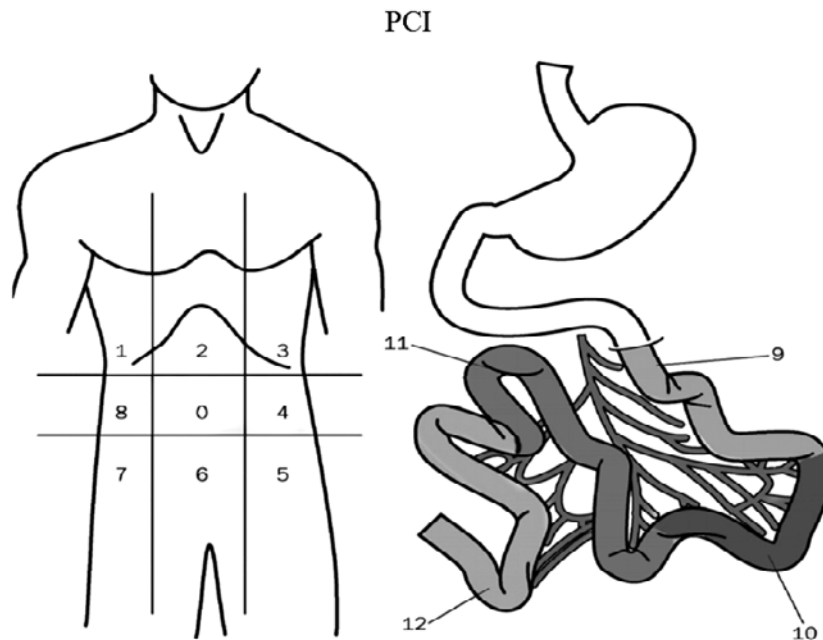


Figure 1. PCI.

Abdominal cavity is divided into 13 regions as a figure. (0 Central, 1 Right upper, 2 Epigastrium, 3 Left upper, 4 Left flank, 5 Left lower, 6 Pelvis, 7 Right lower, 8 Right flank, 9 Upper jejunum, 10 Lower jejunum, 11 Upper ileum, 12 Lower ileum). The size of the maximum lesion in each region is altered to score 0-3 as follows; 0: no lesions, 1: maximum lesion size <0.5 cm, 2: 0.5-5 cm, and 3: >5 cm. The sum of the score in every region becomes PCI (min1 to max39).

then verified their objectivity and accuracy.

Statistical analysis

Various parameters of patient backgrounds were analyzed using Chi-square for independence test, Kruskal-Wallis test, Student’s T test, and Mann-Whitney’s U test. Associations between the P classification and the PCI were estimated with Spearman’s rank correlation coefficient. The calculations for the various cut-off values between each P classification grade were analyzed using logistic regression analysis and Akaike’s Information Criterion (AIC). AIC is a measure of the quality of a statistical model[3]. In brief, the lower the AIC, the better the statistical model. Akaike’s Information Criterion is $AIC = 2\kappa - 2\ln(L)$. The κ represents the number of parameters in the model, and the L represents the maximized value of the likelihood.

All statistical analyses were performed using EZR, a graphical user interface for R[4]. Data are presented as numbers of patients, ratios (%), or means \pm standard deviation.

We indicate the process of analyzing the PCI’s cut-off values between P1-P2 and between P2-P3 (Table 2a, 2b, respectively). We also show an example of how to calculate the cut-off value between P1-P2. First, as shown in Table 2 a, we temporarily put several sample models of two groups divided by the PCI score (as an explanatory variable) in order. Then, we analyzed them, via logistic regression analysis, to determine which method of division would produce

the most suitable sort for P1 or P2. The model showed the lowest AIC with a significant p-value was considered the most suitable. In this case, we found the model that divided the groups at PCI 3 to 4 was the best turning point for P1 and P2. Thus, we concluded that P1 corresponds to PCI 1-3, and P2 corresponds to PCI 4 or more. Using the same method, we analyzed other cut-off values, such as correspondent PCI between P2 and P3 (divided the groups at PCI 8 to 9 was the best turning point for P2 and P3, Table 2b), and every parameter (extent, number of lesions and maximum size) between each P classification grade.

Results

Patient’s backgrounds

All patients were clinically classified by the P classification and evaluated by the PCI simultaneously. Table 3 shows the general patient backgrounds in P1, P2, and P3 cases (Table 3a indicates general parameters, and Table 3b indicates the primary tumor association). P2 included more rectal patients than P3. The ratio having ascites and other distant organ metastases rose as along with the P grade. There were no significant differences in age, sex, performance status, tumor marker, primary tumor size, and pathological types. Table 3c shows the association of every peritoneal metastasis parameter in each grade. As the data indicates, there were

Table 2a. Process for Analyzing PCI Cut-off Values between P1 and P2.

	P1	P2	Odds ratio	95%CI	p value	AIC
PCI ≤ 1	$2 \leq$	21	4.31-103	0.00017	94.484	
≤ 2	$3 \leq$	10	3.31-30.2	0.00005	95.088	
≤ 3	$4 \leq$	26.1	3.33-205	0.00191	94.403	
≤ 4	$5 \leq$	10.4	1.3-82.8	0.0275	107.51	

Table 2b. Process for Analyzing PCI Cut-off Values between P2 and P3.

	P2	P3	Odds ratio	95%CI	p value	AIC
PCI ≤ 6	$7 \leq$	42.9	14.8-124	3.69×10^{-12}	97.871	
≤ 7	$8 \leq$	40.2	13.8-117	1.17×10^{-11}	100.55	
≤ 8	$9 \leq$	69.2	18.6-257	2.52×10^{-10}	92.987	
≤ 9	$10 \leq$	120	15.5-933	4.51×10^{-6}	101.15	

Table 3a. Patient Backgrounds. General Parameters.

	P1	P2	P3	p value		
				P1 vs P2	P2 vs P3	P1 vs P3
Cases	30	57	63			
Age	67.1	63.3	66.7	0.19	0.14	0.13
Sex						
M	17	30	37	0.89	0.62	0.97
F	13	27	26			
Performance Status	0.23	0.4	0.51	0.17	0.38	0.03
CEA (ng/ml)	92.2	506.6	237.4	0.28	0.32	0.31
CA19-9 (U/ml)	798.9	780.1	1422.6	0.97	0.3	0.45
Existence of ascites (%)	36.7	57.9	69.8	0.097	0.241	0.005
Other distant metastasis (%)	36.7	59.6	65.1	0.069	0.67	0.018

Table 3b. Patient Backgrounds. Primary Tumor Findings.

		P1	P2	P3	p value		
					P1 vs P2	P2 vs P3	P1 vs P3
Site	Right colon	19	23	37	0.101	0.013	0.368
	Left colon	6	17	20			
	Rectum	5	17	6			
Size (mm)		56.3	59.3	59.8	0.576	0.924	0.581
Resection	yes	30	52	45	0.235	0.011	0.002
	no	0	5	18			
Depth	T3	4	4	2	0.539	0.716	0.201
	T4a	16	36	37			
	T4b	10	17	17			
Pathology	tub	20	41	34	0.639	0.886	0.907
	others	9	11	11			

Table 3c. Patient Backgrounds. Peritoneal Metastasis Findings.

		P1	P2	P3	p value		
					P1 vs P2	P2 vs P3	P1 vs P3
PCI score		1.8 (1-5)	3.8 (1-10)	14.4 (2-29)	<0.001	<0.001	<0.001
Extent (Number of Regions) (see Figure2a)		1.2 (1-2)	2.4 (1-6)	8.9 (1-13)	<0.001	<0.001	<0.001
Number of Lesions (see Figure2b)		2.7 (1-11)	7.6 (1-40)	71.7 (7-143)	<0.001	<0.001	<0.001
Maximum size (mm) (see Figure2c)		12.3 (2-70)	26.8 (3-345)	46.2 (3-250)	0.038	0.044	<0.001
Residual peritoneal lesions	no	16	15	1	0.023	<0.001	<0.001
	yes	14	42	62			

significant differences between them.

1. Distribution of extent, number and maximum size of lesions in every grade of P classification

Figure 2a shows the distribution of peritoneal metastases extent in each grade. Because digitizing extent in P classification was difficult, we instead substituted the number of regions in which peritoneal metastases existed. The peritoneal regions were defined according to the PCI method that divides the abdominal cavity into 13 parts (Figure 1). As for extent, all P1 cases were in two or fewer regions (1 region: 76.7%, 2 regions: 23.3%), and many P2 cases were also in fewer than two regions (1 region: 31.6%, 2 regions: 29.8%). In Figure 2a, P1 and P2 overlapped in one region. Although the mean number of regions between P1 and P2 was different, the considerable duplication between P1 and P2 suggests that the P classification could not divide them properly in terms of extent. Figure 2b shows the distribution of the number of lesions in each grade. A clear difference was made evident, particularly in the comparison between P2 and P3 (mean 7.6 vs 71.7, $p < 0.001$). Although the data ex-

hibited a clear tendency for the lesion size to increase as the P-grade increased, the distribution showed a lot of overlap between each group (Figure 2c).

2. The associations between current P classification and the PCI

The PCI corresponding to each P-grade was calculated as follows: P1: 1-3, P2: 4-8, P3: 9 or more (Figure 3 shows the distribution). We evaluated the correlation between the P classification and the PCI using Spearman's rank correlation coefficient (Figure 4). The correlation coefficient for both classifications was $r = 0.815$ ($p = 6.41 \times 10^{-37}$). The correlation was good in general, but the ratios of each grade corresponding to each calculated PCI were not (shown at the upper row of Table 4). We found that the P classification could not classify precisely, especially in P2.

As shown above, a problem with the P classification was that it could not evaluate the precise extent of the lesions. On the other hand, we confirmed this classification was able to classify the number of lesions with high precision. Also, using size as a parameter was difficult in the P classifica-

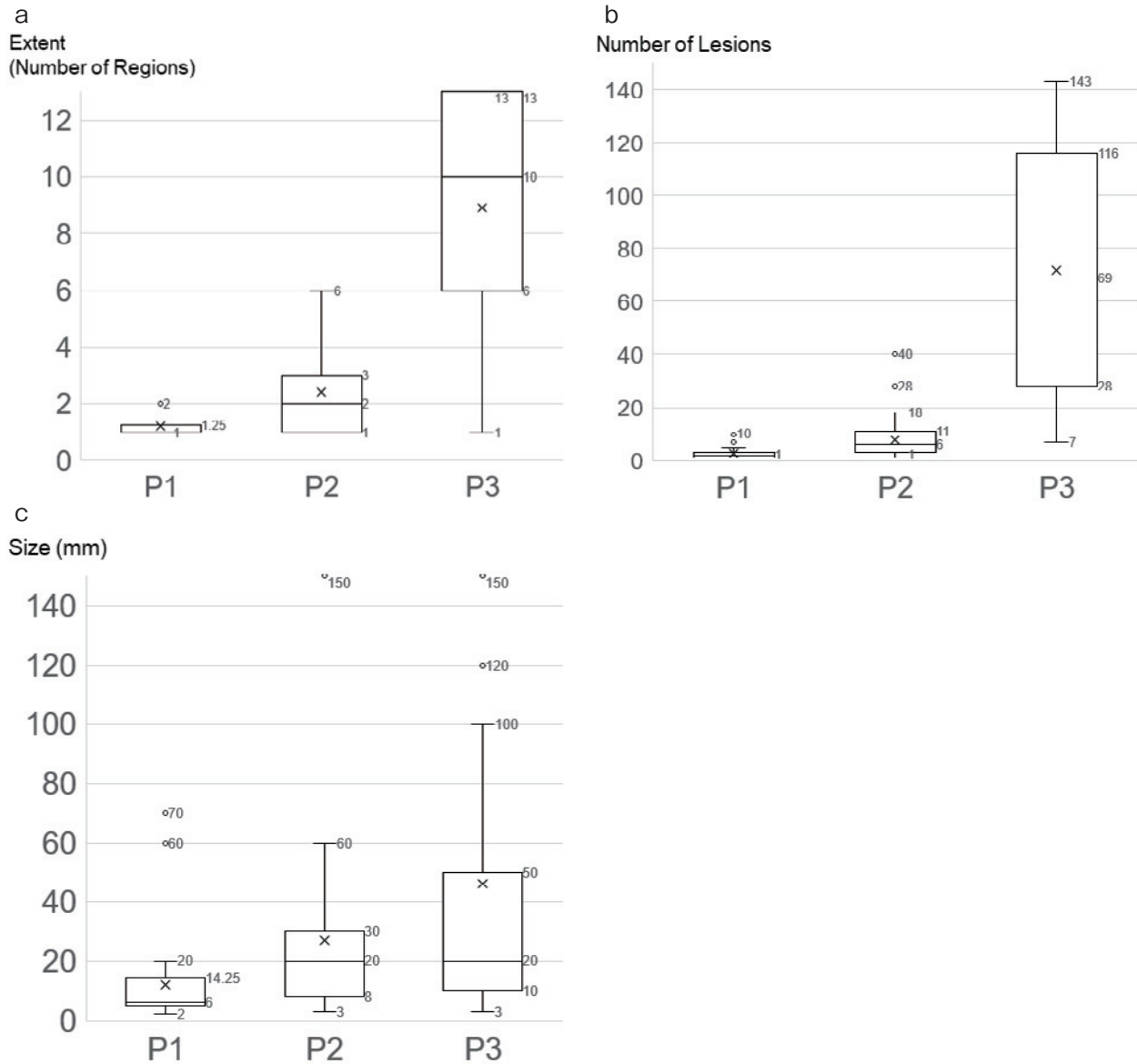


Figure 2. Distribution of parameter for each P grade.
 a. Peritoneal metastasis extent (Number of Regions).
 See the Number of Regions row in Table3c for detailed values.
 b. Number of Lesions.
 See the Number of Legions row in Table3c for detailed values.
 c. Maximum Lesion size.
 See the Maximum size row in Table3c for detailed values.

tion. From these results, we provided the following solution to improve the P classification. First, when classifying in P1 and P2, it is necessary to alter the parameter of extent in a way that makes it a more objective measure. It should not be like the current, subjective method of evaluation, based on one’s intuition. Instead, a new concept is required. Second, for a clear distinction of classification between P2 and P3, a clear, standard value for the number of lesions is necessary.

3. Creation of the standard value for the extent and number of lesions in the P classification

We attempted to digitize these two parameters by referring to the PCI as an objective index. We redefined P1 as cases in which metastases were limited to only one abdominal region. Part of the reason for this change is that peritoneal metastasis localized in one region is akin to the JSCCR concept that defines P1 as adjacent to the primary tumor. As for the number of lesions, we based the cut-off value between P2 and P3 on the data obtained via logistic regression

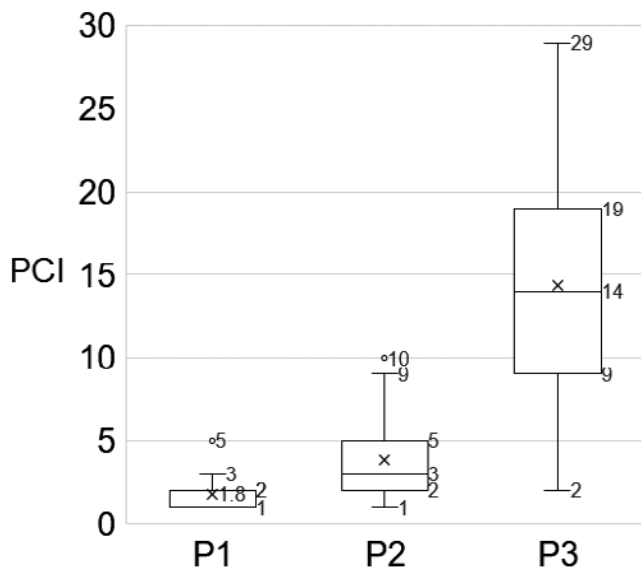


Figure 3. PCI corresponding to each P grade.

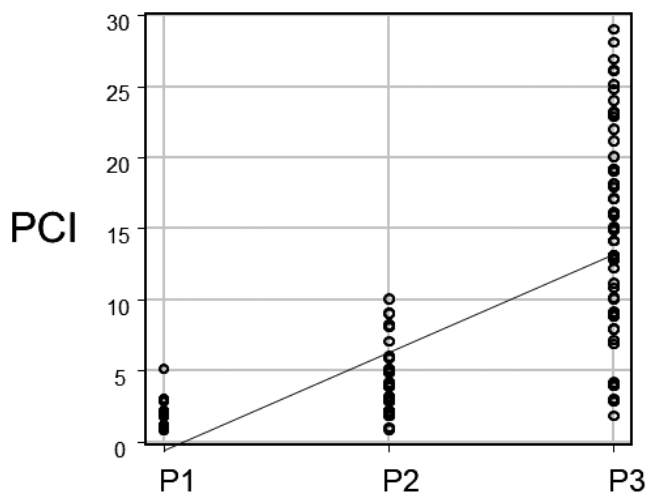


Figure 4. Correlation between P classification and PCI.

analysis, as previously mentioned. As a result, we determined the standard objective value to be “a few (referring to P2) is 19 or less” and “diffuse (referring to P3) is 20 or more.”

Thus, we prescribed a new definition for P classification as follows: “P1: Within only one abdominal region (distance from the main tumor does not matter),” “P2: In two or more regions, and with 19 or fewer lesions,” “P3: In two or more regions, and with 20 or more lesions” (new P classification).
 4. Assessment of the accuracy of the peritoneal metastasis evaluation by new P classification

The result of this new P classification meant many instances of changed categorizations between P1 and P2 (23% of P1 changed to new P2 and 31.6% of P2 were changed to new P1). By using the PCI score of each new P1, P2 and P

Table 4. Conformity Rate between Each P Grade and the PCI (%).

	P1	P2	P3
Current P classification	96.7	42.1	79.4
New P classification	92.9	86.6	76.8

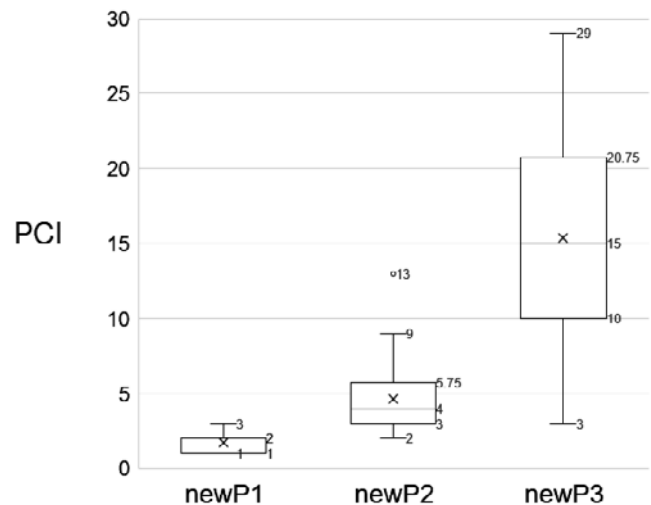


Figure 5. PCI corresponding to each new P grade.

3 cases that were classified and determined according to the new definition, the PCI corresponding to each new P-grade was recalculated to be newP1: 1-2, newP2: 3-9, NewP3: 10 and more respectively. Figure 5 shows the distribution of the PCI corresponding to each new P-grade and the overlap between P1 and P2 decreased. The new P2 grade’s conformity rate with the PCI improved a lot (shown at the bottom row of Table 4), and the Spearman’s rank correlation coefficient was also improved to $r = 0.884$, more than that of the current classification $r = 0.815$.

Discussion

Most colorectal cancer patients with synchronous peritoneal metastasis show poor prognosis[5]. However, resection is useful for some lesions limited to a small region like in P 1 or low PCI cases[6-8]. The Japanese Classification of Colorectal Cancer, P classification, defines peritoneal metastasis findings using two parameters: distance from the main tumor and number of peritoneal lesions[1]. P classification sorts metastatic grade into three categories: P1, P2 and P3. In that, P2/P3 is classified as P1 by distance, and P3 is classified as P2 by a number of lesions. In the 2019 Japanese Guidelines for the Treatment of Colorectal Cancer, the treatment strategy for peritoneal metastasis is described as follows: complete resection is strongly recommended for P1, complete resection is recommended for P2 when easily re-

sectable and the efficacy of resection for P3 has not been demonstrated[9]. Because many peritoneal metastases can be detected intraoperatively, surgeons prefer simple classification by which lesions can be evaluated in a short period. In this way, P classification can indicate treatment strategy quickly, so it is helpful for surgeons in a clinical setting. And more, a previous study showed 5-year survival rate of P1: 26%, P2: 12% and P3: 7%, $p < 0.0001$ [10]. This indicates that P classification can reflect the prognosis even though a simple method.

However, a clear standard value for extent and number in peritoneal metastasis is not shown in P classification, so surgeons must judge the degree of the lesions subjectively. On the other hand, the PCI is evaluated for its objectivity and it seems to be the international standard[11]. However, in the process of PCI evaluation, it is necessary to measure the size of each metastatic lesion. If we encounter many lesions in laparoscopic surgery, for example, it demands much labor. Considering those situations, we attempted to improve the objectivity of P classification while maintaining its benefit, simplicity. And to make the problems with P classification clearer, we investigated its association with the PCI as an objective model.

In general, the P classification had a high correlation with the PCI; however, when examining each grade's correlation with the PCI, the precision of the P2 grade was very poor. In fact, P1 and P2 were not clearly sorted, and we thought this was one of the most important points to improve P classification. The overlap of P1 and P2 is attributed to the lack of a clear standard value about the extent of peritoneal metastasis. In terms of the extent, the P classification uses ambiguous wording to explain the difference between P1 and P2. So, for instance, if there are very few peritoneal metastases only on Douglas foramen from transverse colon cancer, the lesions can be evaluated as P2. Indeed, 31.6% of cases categorized in P2 contained peritoneal metastasis confined to only one region, and their PCI scores were low. It is necessary to change this criterion of distance to correct such sensory gaps. However, defining a clear standard for distance from the primary tumor is challenging. By examining the correlation with the PCI, which is an objective evaluation method, we expected that the PCI could be used as an index of the objective criteria for the P classification.

The distance criterion in the P classification and region numbers of the PCI are slightly different. However, as a realistic means of evaluation, we attempted to introduce the PCI method into the P classification by, in short, dividing the abdominal cavity into 13 regions and counting the number of regions in which peritoneal metastasis existed. Moreover, because the word "adjacency" is akin to "being localized in a small area" we briefly defined P1 as being within only one region case to avoid judgments based on a subjective sense of distance. As a result, the overlap of P1 and P2

improved, and the PCI correlation to each of them became more consistent.

The P classification also does not have a standard value for the number of metastatic lesions. However, there was only a little overlap between P2-P3 in terms of those numbers shown in this examination. This matter indicated that the current intuitive evaluation of the P classification was able to sort them so that we could define the standard value for the number of lesions as the cut-off value calculated statistically between P2 and P3. As a result, we acquired an objective standard to assume P2 and P3.

The maximum size of peritoneal metastasis plays an important role in the PCI evaluation. However, the size could not classify each grade of the P classification clearly in this study. Also, the measurement of lesion size is a complicated procedure and seems to be a disadvantage of the PCI. Thus, as is the case in conventional P classification, we decided not to require lesion size for the new classification.

Referring to the concept of the PCI, we produced a new P classification that classifies peritoneal metastasis into three grades using two parameters, extent and number of lesions, in the same way as the conventional method. The objectivity improved with a clear standard value of the extent between P1-P2 and of the number of lesions between P2-P3. The correlation with the PCI improved, and the conformity rate of each grade to the PCI also improved.

The goal of JSCCR project [Grading colorectal cancer peritoneal metastasis] is to establish a new classification that can indicate treatment strategies based on prognoses, and our research group is collecting the prognostic data. On the other hand, the main purpose of this study is to clarify the problems of current P classification and to find further improvements. In this study, we suggested a new P classification which has objectivity equal to that of the PCI while keeping the same level of handiness, and we also showed the usefulness of the P classification.

Of course, it will be necessary to further inspect with prognostic information in the future. The prognosis will be announced in future study. When prognostic plasticity is shown, we will be able to consider this classification to be a new grading method for providing treatment strategies based on prognostic prediction.

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Conflicts of Interest

There are no conflicts of interest.

Author Contribution

All authors meet authorship the ICMJE recommends.

Approval by Institutional Review Board(IRB)

This study [Grading colorectal cancer peritoneal metastasis] was approved by the ethics review board of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) on July 5th, 2012.

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