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Peritoneal lavage cytology in patients with curative resection for stage II and III colorectal cancer: A multi-institutional prospective study

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Abstract

Aim: To clarify the usefulness of intraoperative lavage cytology in patients undergoing curative resection for pStage II-III colorectal cancer in a prospective multicenter study.

Methods: Patients preoperatively diagnosed with stage II-III colorectal cancer between 2013 and 2017 from 20 hospitals were enrolled. Lavage cytology was performed twice during the surgery. The primary endpoint was the effect of lavage cytology on the 5-year relapse-free survival (RFS) in patients with pStage II-III colorectal cancer. The secondary endpoint was the effect of lavage cytology on the 5-year overall survival (OS) and peritoneal recurrence.

Results: A total of 1378 patients were eligible for analysis. The number of patients with pStage II-III colorectal cancer was 670 and 708, respectively. Fifty-four patients (3.9%) had positive cytological results. In pStage II patients, the 5-year RFS rates with positive and negative cytology were 61.1% and 81.6%, respectively ($p = 0.023$). The 5-year OS rates were 67.1% and 91.7%, respectively ($p = 0.0083$). However, there was no difference in RFS or OS between pStage III patients with positive and negative cytology results. The peritoneal recurrence rates were 11.8% and 1.5% in pStage II patients with positive and negative cytology results, respectively ($p = 0.032$). These rates were 10.5% and 2.5% in patients with stage III disease, respectively ($p = 0.022$).

Conclusion: Stage II colorectal cancer patients with negative cytology had better outcomes than those with positive cytology. Peritoneal lavage cytology is useful

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for predicting peritoneal recurrence after curative resection of stage II-III colorectal cancer.

KEYWORDS
colorectal cancer, peritoneal lavage cytology, peritoneal recurrence

1 | INTRODUCTION

Colorectal cancer is the second most common cause of cancer-related deaths in the United States and Japan.[1,2] Furthermore, the incidence of colorectal cancer has been increasing in Japan.[3,4] Even when patients with colorectal cancer undergo curative resection, recurrence develops at a constant rate.[5]

Although various prognostic factors in patients with colorectal cancer have been reported,[6,7] the usefulness of intraoperative lavage cytology in patients with colorectal cancer is controversial.[8–10] Conversely, the usefulness of intraoperative lavage cytology in patients with gastric cancer has been established.[11,12]

Adjuvant chemotherapy has been established for stage III colorectal cancer patients and has been recommended for high-risk stage II patients.[13,14] If the prognostic significance of intraoperative lavage cytology in patients with stage II colorectal cancer is demonstrated, those with positive cytology may be potential targets of adjuvant chemotherapy.

We previously demonstrated that positive lavage cytology was a poor prognostic factor in stage II-III patients.[15] In that study, we used retrospective registry data from the Japanese Society for Cancer of the Colon and Rectum (JSCCR). In this prospective multicenter study, we aimed to clarify the usefulness of intraoperative lavage cytology in patients undergoing curative resection not only for stage II but for stage III colorectal cancer.

2 | METHODS

2.1 | Study design

Twenty hospital members of the JSCCR were involved in this multi-institutional, prospective, observational study. These hospitals joined a committee of the JSCCR, named "Grading of peritoneal metastasis from colorectal cancer." The primary endpoint of this study was the effect of lavage cytology on 5-year relapse-free survival (RFS) in patients with pathological stage (pStage) II-III colorectal cancer. The secondary endpoint was the effect of lavage cytology on the 5-year overall survival (OS) of patients with pStage II-III colorectal cancer. Patients who underwent surgery for clinical stage (cStage) II and III colorectal cancer between 2013 and 2017 were enrolled. Written informed consent was obtained from all patients before enrollment. Because pStage II colorectal cancer patients were the main target of this study, cStage II and III patients were recruited. The estimated number of required pStage II patients with positive cytology was 27, with the probability of a type I error of 0.05 and a type II error of 0.2 from the viewpoint of our previous registry data.[15] Since the assumed positive cytology rate was 5%, the number of required pStage II patients was 540. The surgical procedures were not determined by the study protocol. This study was approved by the Ethics Committees of the Japanese Society of the Colon and Rectum and each institution. This study was registered under UMIN000026070.

2.2 | Lavage cytology

Lavage cytology was performed twice during the surgery. The first procedure was performed immediately after laparotomy and the second was performed immediately after the specimen retrieval. If ascites were present in the pelvic cavity, cytology was performed for the ascites. The lavage cytology technique was standardized as follows: 50 mL of saline was gently poured into the pelvic cavity (Douglas pouch) and collected. The ascites or lavage fluid was centrifuged at 1500 rpm for 5 min, and the specimens were stained with Papanicolaou and May Giemsa. Cytopathology was performed by pathologists at each institution, and class III-V was diagnosed as positive.

2.3 | Data collection

All data were prospectively collected. Preoperative data included physical information, blood tests, and preoperative diagnoses. Information regarding postoperative chemotherapy and outcomes was collected for at least 5 years after surgery.

2.4 | Statistical analysis

Differences in the continuous variables were compared using the Mann–Whitney *U*-test, while the categorical variables were analyzed using the χ^2 test. The independent risk factors for peritoneal recurrence were analyzed using logistic regression. Actuarial survival after surgery was depicted using Kaplan–Meier curves. The log-rank test and Cox proportional hazard model were used to compare RFS and OS. JMP 13 software (SAS Institute Japan, Tokyo, Japan) was used for data analysis. Data were expressed as medians, ranges, numbers of patients, and percentages (%). Statistical significance was set at $p < 0.05$ for this study.

3 | RESULTS

3.1 | Patients' characteristics

The data flow of this study is illustrated in Figure 1. A total of 1593 patients were enrolled in this study. Thirty patients were diagnosed with stage IV disease during surgery. Five patients underwent an R2 resection. Six patients had missing data. Overall, 174 patients were diagnosed with stage 0-I after surgery. Finally, 1378 patients were included in the analysis. Table 1 shows the patient characteristics. The median patient age was 69 years. The primary tumor was located in the left colon in 64.5% of the patients. The left colon included the descending, sigmoid, and rectal regions. Preoperatively, 563 and 815 patients were diagnosed with stage II and III colorectal cancer, respectively. The final pathological diagnoses were stages II and III in 670 and 708 patients, respectively. Of the 1378 patients, 655 (47.5%) received adjuvant chemotherapy. The percentages of patients with pStage II and III disease who received adjuvant chemotherapy were 19.9% and 73.7%, respectively.

3.2 | Lavage cytology

Among the 1378 patients, 54 (3.9%) had positive cytology results. The number of patients with Class III and V cytology was 33 and 21, respectively. Nine of these 54 patients had positive ascites cytology results. Three of the nine patients showed positive cytological results only for ascites. The association between the timing of lavage cytology and the results is shown in Table 2. Among the 54 patients with positive cytology results, 11 showed positive cytology results at both timepoints. Thirty patients exhibited a change from positive to negative results. However, 13 patients showed negative-to-positive results.

3.3 | Survival

The median follow-up period of the entire cohort was 5.3 (0.001–9.5) years. The 5-year OS rates of patients with stage II and III disease were 91.2% and 82.9%, respectively ($p < 0.0001$). The 5-year RFS rates of patients with stage II and III disease were 81.1% and 67.9%, respectively ($p < 0.0001$).

In the entire cohort, the RFS of patients with negative cytology was better than that of patients with positive cytology ($p = 0.0078$; Figure 2A). In pStage II patients, the 5-year RFS rates with positive and negative cytology were 61.1% and 81.6%, respectively ($p = 0.023$; Figure 2B). In pStage III patients, the 5-year RFS rates with positive and negative cytology were 63.6% and 68.2%, respectively ($p = 0.22$; Figure 2C).

In pStage II patients, positive cytology ($p = 0.023$), left side of tumor location ($p = 0.022$), and T4 cancer ($p = 0.0018$) were identified as adverse prognostic factors for RFS in univariate analysis.

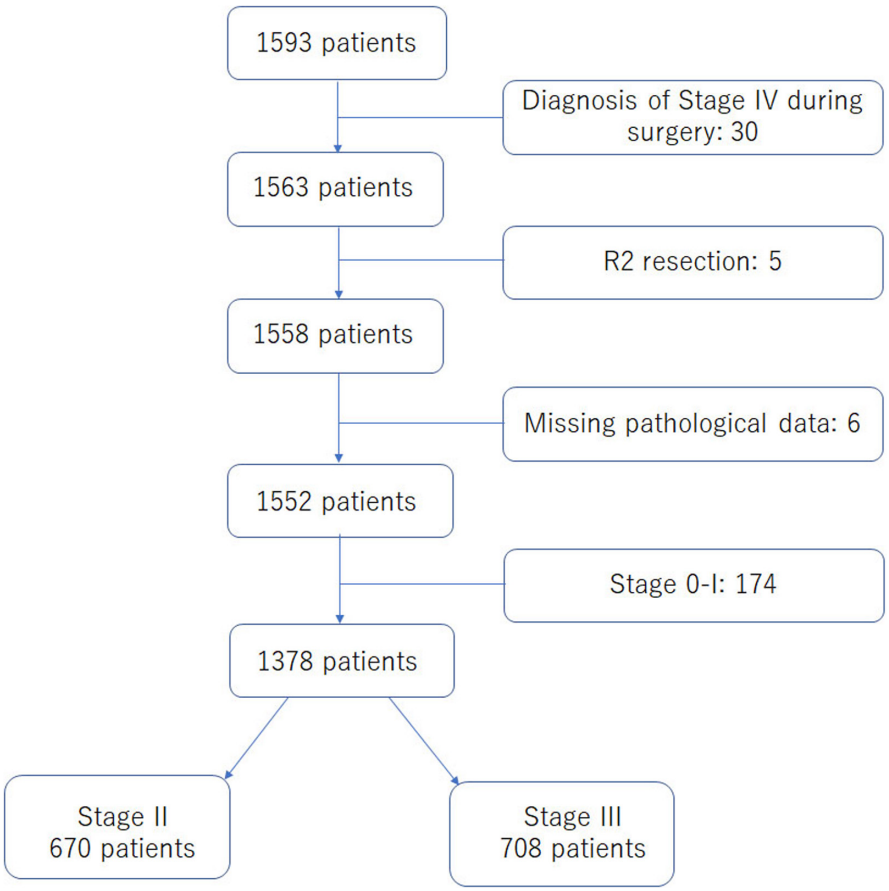

FIGURE 1 Data flow-chart. Finally, 1378 patients participated in this analysis.

TABLE 1 Characteristics of 1378 patients.

Characteristics	Cytology positive		Cytology negative		p value
	Number	%	Number	%	
Gender					
Male	27	50	782	59.1	0.19
Female	27	50	542	40.9	
Age	68 (36–81)		69 (23–98)		0.18
Histologic type					
Well differentiated adenocarcinoma	11	20	303	22.9	0.15
Moderately differentiated adenocarcinoma	36	67	930	70.2	
Poorly differentiated adenocarcinoma	3	6	41	3.1	
Mucinous adenocarcinoma	3	6	42	3.2	
Others	1	2	8	0.6	
Tumor location					
Left side	33	61	856	64.7	0.6
Right side	21	39	468	35.3	
Preoperative stage					
Stage II	16	30	547	41.3	
Stage III	38	70	777	58.7	
Neoadjuvant therapy					
Present	1	2	34	2.6	0.98
Absent	53	98	1290	97.4	
Laparoscopic surgery					
Present	18	33	493	37.2	0.31
Absent	33	61	804	60.7	
Unknown	3	6	27	2.0	
Depth of tumor invasion					
T1	0	0	15	1.1	0.0009
T2	0	0	44	3.3	
T3	28	52	963	72.7	
T4	26	48	302	22.8	
Lymph node metastasis					
N0	17	31	653	19.3	0.018
N1	21	39	466	35.2	
N2a	8	15	126	9.5	
N2b	8	15	79	6.0	
Postoperative stage					
Stage IIA	13	24	531	40.1	0.0015
Stage IIB	4	7	90	6.8	
Stage IIC	0	0	32	2.4	
Stage IIIA	0	0	50	3.8	
Stage IIIB	23	43	486	36.7	
Stage IIIC	14	26	135	10.2	
Adjuvant chemotherapy					
Present	32	59	623	47.1	0.14
Absent	22	41	701	52.9	
Recurrence					

TABLE 1 (Continued)

Characteristics	Cytology positive		Cytology negative		p value
	Number	%	Number	%	
Present	19	36	281	21.2	0.021
Absent	35	65	1043	78.8	
Peritoneal recurrence					
Present	6	11	27	2.0	0.0014
Absent	48	89	1297	98.0	

TABLE 2 Results of cytology according to the timing.

First cytology		Second cytology	Number of patients
Positive	→	Positive	11
Positive	→	Negative	30
Negative	→	Positive	13
Negative	→	Negative	1324

Multivariate analysis revealed that positive cytology ($p=0.049$), left side of tumor location ($p=0.015$), and T4 cancer ($p=0.0050$) were independent prognostic factors of RFS (Table 4).

The OS rate of pStage II patients with negative cytology was better than that of patients with positive cytology ($p=0.0083$; Figure 3A). However, there was no difference in OS between pStage III patients with positive and negative cytology results ($p=0.96$, Figure 3B).

In pStage II patients, positive cytology ($p=0.0083$), age 66 or older ($p=0.039$), and T4 cancer ($p=0.0050$) were identified as adverse prognostic factors for OS in univariate analysis. Multivariate analysis further revealed that positive cytology ($p=0.030$), age 66 or older ($p=0.030$), and T4 cancer ($p=0.015$) were independent worse prognostic factors of OS (Table 3).

In patients with stage II-III colorectal cancer who tested positive on cytology, no differences were observed in RFS and OS based on the presence or absence of adjuvant chemotherapy.

3.4 | Recurrence to peritoneum

Among the 1378 patients, 300 (21.8%) experienced recurrence after curative resection for colorectal cancer. Thirty-three patients experienced peritoneal recurrences. The peritoneal recurrence rates according to stage are shown in Table 4. The peritoneal recurrence rates were 11.8% and 1.5% in pStage II patients with positive and negative lavage cytology results, respectively ($p=0.032$). This was 10.8% and 2.5% in pStage III patients with positive and negative lavage cytology results, respectively ($p=0.022$). In total, 11.1% of patients with positive lavage cytology experienced peritoneal recurrence in this cohort. The rate of peritoneal recurrence in patients with Class III and V cytology was 6.1% and 19.1%, respectively. However, there was no statistically significant difference ($p=0.14$). Only one patient, whose cytology changed from negative, to positive, had peritoneal recurrence. The sensitivity and specificity of cytology for peritoneal recurrence were 18% (6/33 patients) and 96.4% (1297/1345 patients), respectively. Additionally, the accuracy was 94.6% (1303/1378 patients).

3.5 | Risk factors for peritoneal recurrence

Table 5 shows the risk factors for peritoneal recurrence. T4 cancer ($p<0.0001$) and positive lavage cytology ($p=0.0014$) were risk factors for peritoneal recurrence in the univariate analysis. Among these factors, both T4 cancer ($p<0.0001$) and positive lavage cytology ($p=0.0045$) were independent risk factors in the multivariable analysis.

4 | DISCUSSION

This study demonstrates that positive lavage cytology is a poor prognostic factor in patients with pStage II colorectal cancer. However, the utility of lavage cytology in patients with colorectal cancer remains controversial.

Nishikawa et al reported the results of lavage cytology in colorectal cancer patients with serosal invasion.[9] In their study, 7.6% of 410 patients had positive lavage cytology, which was associated with a lower OS rate. In the multivariable analysis, positive lavage cytology was an independent prognostic factor, as well as liver metastasis, histologic type of the primary tumor, and depth of tumor invasion. Yamamoto et al reported lavage cytology results in 189 patients with T3-T4 colorectal cancer. In their study, the positivity rate of lavage cytology was 5.8%. Positive lavage cytology is associated with poor cancer-specific survival and is an independent prognostic factor for lymph node metastasis.[10]

In several studies the usefulness of lavage cytology in patients with colorectal cancer could not be demonstrated. Fujii et al reported the results of lavage cytology in 298 patients with colorectal cancer.[8] In their study, the positivity rate of lavage cytology was 6%. Kanellos et al reported the results of 110 patients who underwent lavage cytology.[16] The authors reported a positivity rate of 20%. Positive cytology was associated with higher rates of local recurrence and peritoneal carcinomatosis. However, in their study there

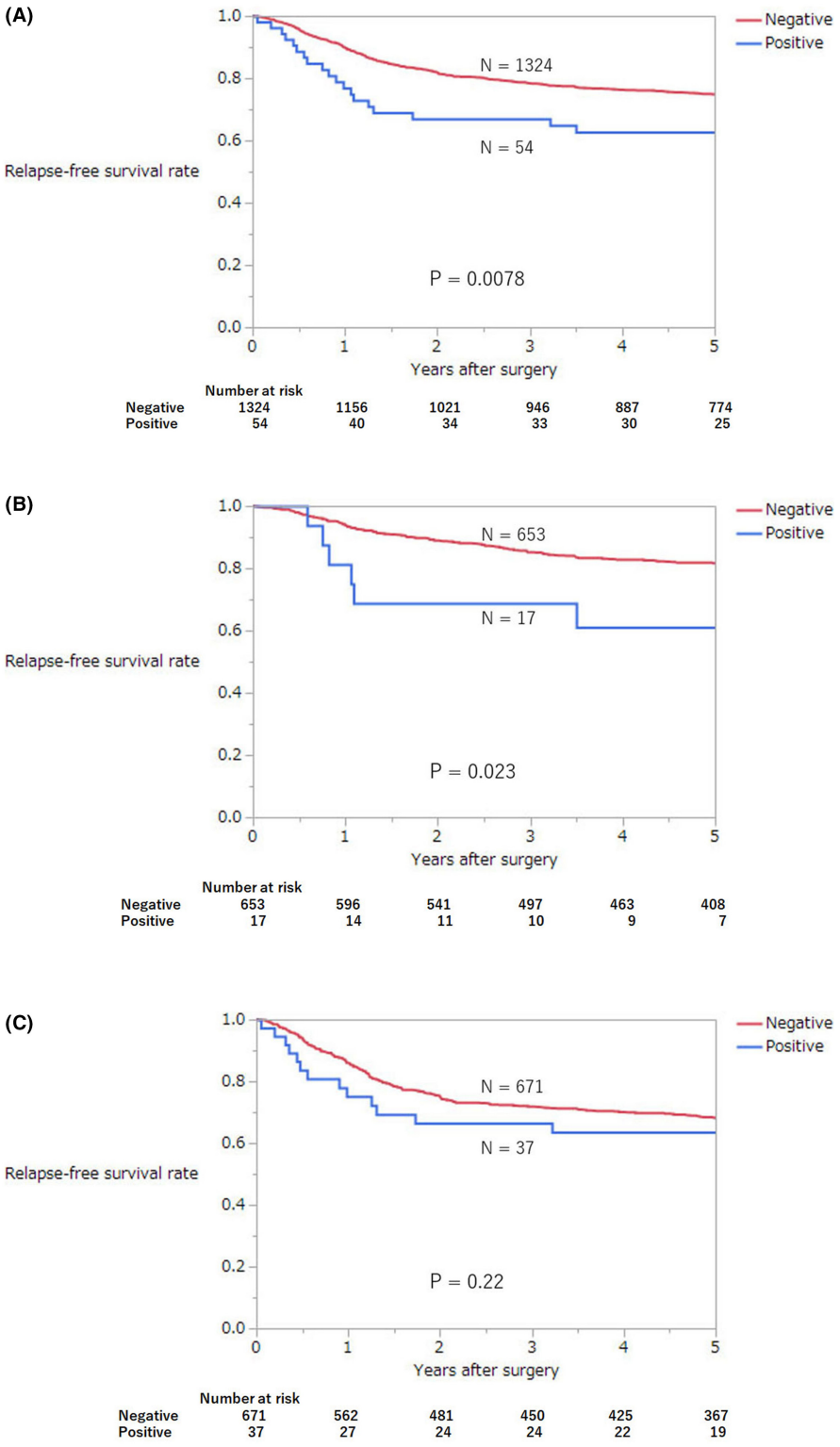

FIGURE 2 Relapse-free survival curves of entire cohort (A), stage II patients (B), and stage III patients (C).

was no difference in survival between patients with positive and those with negative cytological results.

One reason for these controversial results is the small number of patients. In most studies, the number of patients with positive cytological results was less than 30. The present study was performed prospectively on the largest scale and demonstrated the usefulness of lavage cytology in patients with pStage II colorectal cancer. Adjuvant chemotherapy has been recommended for patients with high-risk stage II colorectal cancer by some guidelines.[13,14] These guidelines indicate some risk factors for stage II colorectal cancer. However, positive lavage cytology findings have not yet been identified as risk factors. The present study reports that patients with pStage II cancer patients with positive cytology could be potential targets for adjuvant chemotherapy.

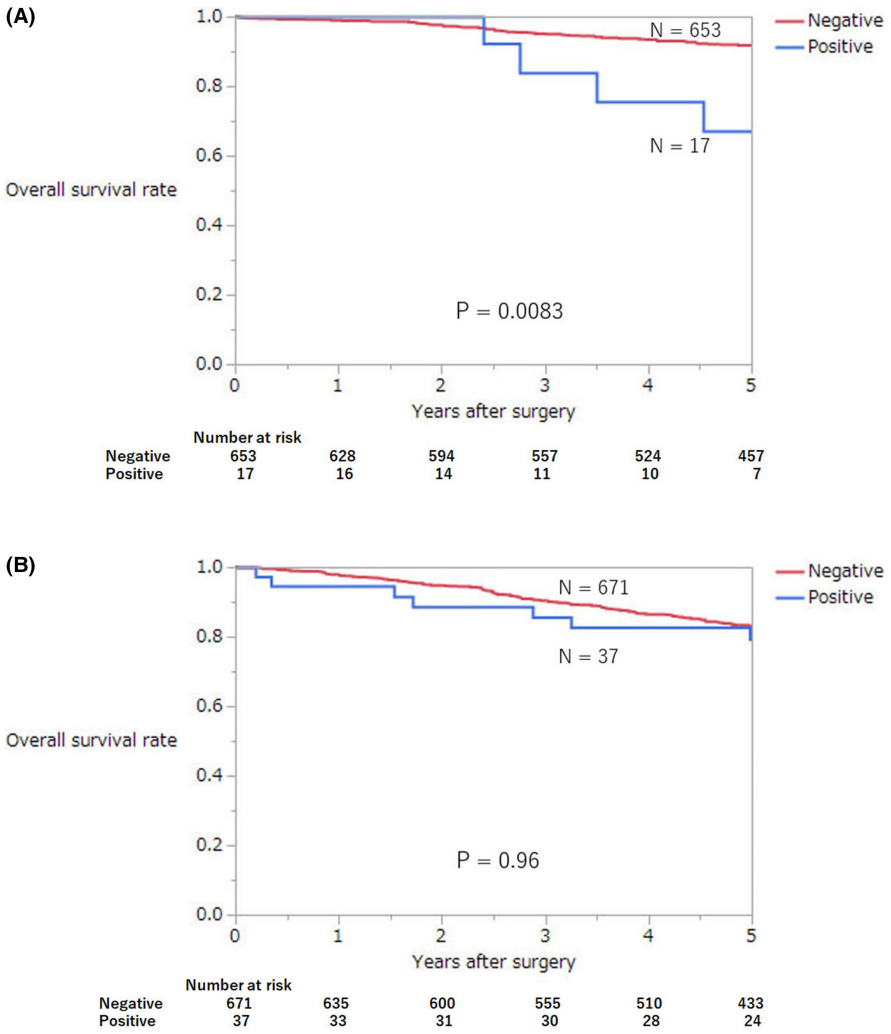

FIGURE 3 Overall survival curves of stage II (A) and III (B) patients.

TABLE 3 Lavage cytology and peritoneal recurrence according to the stage.

Stage	Cytology	Number of patients	Peritoneal recurrence		*p* value
pStage II	Positive	17	2	(11.8%)	0.032
	Negative	653	10	(1.5%)	
pStage III	Positive	37	4	(10.8%)	0.022
	Negative	671	17	(2.5%)	
Total	Positive	54	6	(11.1%)	0.0014
	Negative	1324	27	(2.0%)	

In the present study, there was no difference in survival between pStage III patients with positive and those with negative cytology. One of the reasons might be the impact of lymph node metastasis. The impact of lymph node metastasis on the prognosis in pStage III colorectal cancer patients might be much larger than the positive cytology.

There are several reports on the timing of the lavage cytology. In the present study we performed lavage cytology twice during surgery. Among the 54 patients with positive cytology results, 40 tested positive immediately after laparotomy. In contrast, 26 patients had positive cytology results after specimen retrieval. In particular, 14 of 26 patients had negative cytology results immediately after laparotomy. Thus, there was a possibility of cancer cell dissemination during surgery in these 14 patients. The cancer cell dissemination rate was 1.0% (14/1338 patients). Although not very high, we should try not to provoke this phenomenon.

The peritoneal recurrence rate in the patients with positive cytology was 11.1%. Positive lavage cytology and T4 cancer are independent risk factors for peritoneal recurrence. Because the outcomes of patients with peritoneal metastasis from colorectal cancer, especially those with unresectable peritoneal metastasis are unsatisfactory,[17,18] we should pay attention to the patients with positive cytology so as not to miss peritoneal recurrence during the postoperative follow-up.

This study had some limitations. First, because this was a multi-institutional observational study, the treatments depended on the institution. Therefore, differences in the treatment strategies may have affected the results of this study. Although the treatments were not regulated by the protocol, all the institutions were members of the JSCCR. The quality of the treatments used in this study was maintained above a certain level according to the JSCCR guidelines for the treatment of colorectal cancer.

TABLE 4 Prognostic factors in pStage II patients.

	Relapse-free survival					Overall survival			
	Log-rank test		Cox proportional hazards model			Log-rank test	Cox proportional hazards model		
Characteristics	Number	*p* value	Hazard ratio	95% CI	*p* value	*p* value	Hazard ratio	95% CI	*p* value
Age									
65 or younger	216 (32.2)	0.13				0.039	1	1.1–3.4	0.03
>65	454 (67.8)						1.9		
Gender									
Male	406 (60.6)	0.12				0.22			
Female	264 (39.4)								
Location of primary tumor									
Left	416 (62.1)	0.022	1	0.42–0.91	0.015	0.68			
Right	254 (37.9)		0.63						
Histologic type									
High-grade	34 (5.1)	0.83				0.66			
Others	636 (94.9)								
T-category									
-T3	544 (81.2)	0.0018	1	1.2–2.6	0.005	0.005	1	1.1–3.3	0.015
T4	126 (18.8)		1.8				2.0		
Cytology									
Negative	17 (2.5)	0.023	1	1.0–5.4	0.049	0.0083	1	1.2–9.6	0.03
Positive	653 (97.5)		2.6				3.9		
Adjuvant chemotherapy									
Present	133 (19.9)	0.57				0.33			
Absent	537 (80.1)								

Note: High-grade: poorly differentiated and mucinous adenocarcinoma.

Second, the positivity rate of lavage cytology was lower than expected. We expected a positivity rate of 5%–6% using the protocol. This percentage was only 3.9%. As the positivity rate may vary among pathologists, there may be bias. However, the results of this study can provide real-world data. Nevertheless, the development of more accurate lavage cytology with higher sensitivity is desirable to benefit more patients. In gastric cancer, molecular detection has been reported for the diagnosis of peritoneal metastases and the prediction of peritoneal recurrences.[19] Molecular markers such as CEA mRNA might be useful in improving the positive rate of cytology in patients with colorectal cancer as well as gastric cancer.

In conclusion, intra-abdominal lavage cytology was associated with both overall and RFS in patients with pStage II CRC. Simultaneously, patients with stage II and III colorectal cancer with positive cytology had more peritoneal recurrences. Peritoneal lavage cytology should be performed to predict peritoneal recurrence in patients with curative resection for stage II and III colorectal cancer.

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TABLE 5 Risk factors for peritoneal recurrence.

	Univariate analysis					Multivariate analysis		
	Recurrence	(%)	No recurrence	(%)	*p* value	OR	95% CI	*p* value
Gender								
Male	15	1.9	794	98.2	0.12			
Female	18	3.2	551	96.8				
Age								
<66	16	3.2	487	96.8	0.15			
≥66	17	1.9	858	98.1				
Tumor location								
Left	17	1.9	872	98.1	0.12			
Right	16	3.3	473	96.7				
Laparoscopic surgery								
Absent	25	3.0	812	97.0	0.11			
Present	8	1.6	503	98.4				
Unknown	0	0	30	100				
Histologic grade								
High grade	5	5.6	84	94.4	0.08			
Others	28	2.2	1261	97.8				
Depth of tumor invasion								
-T3	12	1.1	1038	98.9	<0.0001	1	2.5–11.0	<0.0001
T4	21	6.4	307	93.6		5.3		
Lymph node metastasis								
Absent	12	1.8	658	98.2	0.15			
Present	21	3.0	687	97.0				
Cytology								
Negative	27	2.0	1297	98.0	0.0014	1	1.5–10.6	0.0045
Positive	6	11.1	48	88.9		4.0		

Note: High grade, poorly differentiated adenocarcinoma or mucinous carcinoma.
Abbreviations: CI, confidence interval; OR, odds ratio.

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CONFLICT OF INTEREST STATEMENT

Hideki Ueno, Ichiro Takemasa, and Yusuke Kinugasa are editorial board members of the *Annals of Gastroenterological Surgery*.

ETHICS STATEMENT

Approval of the research protocol: The study protocol followed the ethical guidelines of the 2008 Declaration of Seoul and was approved by the Institutional Review Boards of the JSCCR and each institution.
Informed Consent: Written informed consent was obtained from all the patients.
Registry and the Registration No. of the study/trial: UMIN000026070.
Animal Studies: N/A.

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