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A novel high-risk stage II colon cancer classification method may improve prognosis with patients who receive adjuvant chemotherapy

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Abstract

Purpose: Recent reports have shown that adjuvant chemotherapy (AC) fails to improve prognosis in patients with high-risk stage II colon cancer. Therefore, we examined the method of identifying cases that could benefit from AC.

Methods: The relation between the number of risk factors and the effects of AC was analyzed using definitions of the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC).

Results: The disease-free survival and overall survival of cases with 1 or 2 risk factors, as defined by NCCN or ESMO, were significantly improved by AC. Improved survival was not observed in cases with more than 3 risk factors according to these definitions. There was no relation between the number of risk factors, as defined by ASCO or JFMC, and the effects of AC.

Conclusions: Patients with stage II colon cancer can be categorized into 3 groups as defined by the NCCN or ESMO guidelines: (A) no risk factor cases, (B) 1 or 2 risk factor cases, and (C) more than 3 risk factor cases. This classification may assist in the selection of AC regimens for patients with stage II colon cancer.

Introduction

Although numerous clinical trials of adjuvant chemotherapy (AC) after colon cancer surgery showed that AC improved prognosis for patients with stage III disease, AC did not affect prognosis for patients with stage II [1-4]. Because some patients with stage II disease experience recurrence, the concept of "high-risk stage II" was developed with the aim of suppressing recurrence and improving prognosis by selecting cases where the risk of recurrence was high [5-8]. A retrospective examination of what kinds of cases were likely to relapse found that the presence of T4 staging, perforation, undifferentiated type, mucinous carcinoma, and fewer than 13 searched lymph nodes (LN) were recommended as high-risk cases according to the 2004 American Society of Clinical Oncology (ASCO) guidelines [9]. Thereafter, the definition of high-risk stage II was also applied to the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines. The Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) conducted phase III clinical trials using its own definition of high-risk stage II based on these recommendations [10-12].

A recent clinical study of patients with high-risk stage II disease found that AC did not improve prognosis in patients with stage II disease (some studies reported that there was an effect for T4 cases) [13-16]. Therefore, the research focus shifted to determining recurrence risk biomarkers using a molecular biological technique. Meanwhile, the search for a method that will identify patients with stage II colon cancer who might benefit from AC continues. Although AC cannot suppress all instances of recurrence, there may be certain patients who can benefit from AC. However, to identify these individuals, we require another method of identifying "high-risk stage II" cases.

Patients considered as "high-risk stage II" possess at least 1 risk factor. The defined risk factors of each guideline are similar, but not identical and it is not clear which definition is appropriate. On the basis of these points, we decided to integrate and analyse cases with stage II disease using available data.

In doing so, we developed a novel selection method for patients with high-risk stage II colon cancer for whom AC may improve prognosis.

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Patients and methods

Patient information

We collected data (from 2 facilities: Kumamoto City Ueki Hospital and Kumamoto Regional Medical Center) pertaining to patients with stage II colon cancer, who underwent curative surgery from 2000 to 2013. We excluded cases of surgery-related death, cancer of the appendix, advanced cancer history within 3 years, cases with another active cancer, cases that received chemotherapy other than standard regimens, cases with no information of resected LN number, and cases with insufficient AC information. For cases followed by other institutions, we contacted the relevant medical institution and requested cooperation with the recurrence and the prognosis. Clinical stage classifications carried out according to the Union for International Cancer Control classification method. For pre-2013 cases where the description of perineural invasion (PN) was not obligatory in Japan, we used preserved tissues and asked pathologists to determine the presence or absence of PN.

Patient follow up strategy

Patients were followed up every 3 months for the first year after surgery and every 6 months for the next 4 years. They all underwent colonoscopy once a year, and whole-body computed tomography and/or abdominal ultrasound were performed once every 6 months to monitor for recurrence. The introduction of AC was left to the judgment of the attending physician. The regimen of AC was either an oral 5-fluorouracil (5-FU) formulation or 5-fluorouracil/leucovorin (5-FU/LV).

Statistical analysis

The relation between disease recurrence and the clinicopathological factors was analysed using the Cox proportional-hazards model. The collected stage II cases were grouped according to the number of risk factors on the basis of the NCCN, ASCO, ESMO and JFMC definitions of high-risk stage II (Table 1). Within these factors, "obstruction" was defined as; cases with symptomatic vomiting, cases where intestinal tract dilation was observed on imaging examination, and cases requiring the insertion of an ileus tube or the construction of a stoma before radical curative surgery. The date of the curative surgery was defined as time zero. The disease-free survival (DFS) and overall survival (OS) curves were calculated using the Kaplan-Meier method and compared by using the log-rank tests. The Cox proportional-hazards model was used for survival analysis. The software R-commander (R-cmdr) was used for all statistical computations. A p-value of < 0.05 was considered significant.

The Ethics Review Committee of Kumamoto City Ueki Hospital (No. 3) and Kumamoto Regional Medical Center (No. 17-035) approved this study. Each case provided general consent and informed consent before surgery. Each participating institution used an "opt-out" method to remove patients' data from examination.

Results

Clinicopathological characteristics of collected stage II CRC cases

We collected 246 cases of stage II colon cancer. Of these, there were 5 surgery-related deaths, 1 case of cancer of the appendix, 2 cases of advanced colon cancer within 3 years, 3 cases with another active cancer at the time of diagnosis, 3 cases who received nonstandard chemotherapy (mitomycin C infusion at days 1 and 2 after surgery), 2 cases with no information pertaining to the number of resected LN, and 4 cases with no information concerning AC. After excluding cases for the above-mentioned reasons, there were 226 cases for further analysis.

The clinicopathological characteristics of these cases are shown in table 2. The median follow-up period was 54 months. There were 26 cases (11.5%) of recurrence. The cecum ($p = 0.034$) and the sigmoid colon ($p = 0.016$) were significantly related to recurrence. Other significant risk factors or high-risk stage II were perforation, T4 staging, fewer than 12 examined LN (LN <12) and residual tumor (R1) (Table 1). AC was introduced in 50 cases (25.0%) of the recurrence (-) group and in 6 cases (23.1%) of the recurrence (+) group. Within these, the oral 5-FU formulation was introduced in 47 cases of the recurrence (-) group and in 5 cases of the recurrence (+) group. The AC regimen of other cases was 5-FU/LV. AC did not improve the DFS and OS of patients with stage II disease, taken as a whole stage II [sFigure 1].

Analysis of the ordinarily high-risk stage II cases

After referring to the risk factors for each guideline (Table 1), we selected high-risk cases using clinical trial methods (even 1 risk factor is regarded as a high-risk case). The number of high-risk cases according to each definition was NCCN, 205 (90.7%); ASCO, 148 (65.5%); ESMO, 205 (90.7%); JFMC, 140 (61.9%). Within these high-risk cases, those that received AC were NCCN, 53; ASCO, 38; ESMO, 54; JFMC, 37. The DFS and OS of these high-risk cases did not significantly differ relative to AC [sFigures 2 and 3]. We further analysed DFS and OS by each risk factor. No factor was associated with improved prognosis by following administration of AC [sTable 1]. These results are similar to those of recent reports [13-16].

Evaluation of cases by the number of risk factors

The relation between the number of risk factors, according to each definition, and the rate of recurrence is shown in table 3. The recurrence rate increased as the number of risk factors increased. The DFS and OS of cases with 1 or 2 risk factors, as per the NCCN or ESMO definition, were significantly improved by AC (Figures 1a,1c,2a,2c). This phenomenon was not observed in cases with 1 risk factor, as per the ASCO or JFMC definition (Figures 1b,1d,2b,2d). In cases with no risk factors, no significant improvement with AC was found in any of the definitions (Figures 3 and 4). Similarly, no significant improvement was found by AC in cases with more than 3 risk factors, as per the NCCN or ESMO definition or more than 2 risk factors, as per the ASCO and JFMC definition (Figures 5 and 6).

Table 1. High-risk stage II disease risk factors according to various guidelines

NCCN	ASCO	ESMO	JFMC
T4 perforation obstruction por, sig ly+ v+ LN < 12 PN+ positive margin	T4 perforation por, sig, muc LN < 13	T4 perforation obstruction por, sig ly+ v+ LN < 12 PN+	T4 perforation penetration por, sig, muc LN < 12

NCCN: National Comprehensive Cancer Network , ASCO: American Society of Clinical Oncology, ESMO: European Society for Medical Oncology, JFMC: Japanese Foundation for Multidisciplinary Treatment of Cancer, por: poorly differentiated adenocarcinoma, sig: signet ring cell carcinoma, muc: mucinous adenocarcinoma, ly: lymphatic invasion, v: vascular invasion, LN: lymph node examined, PN: perineural invasion

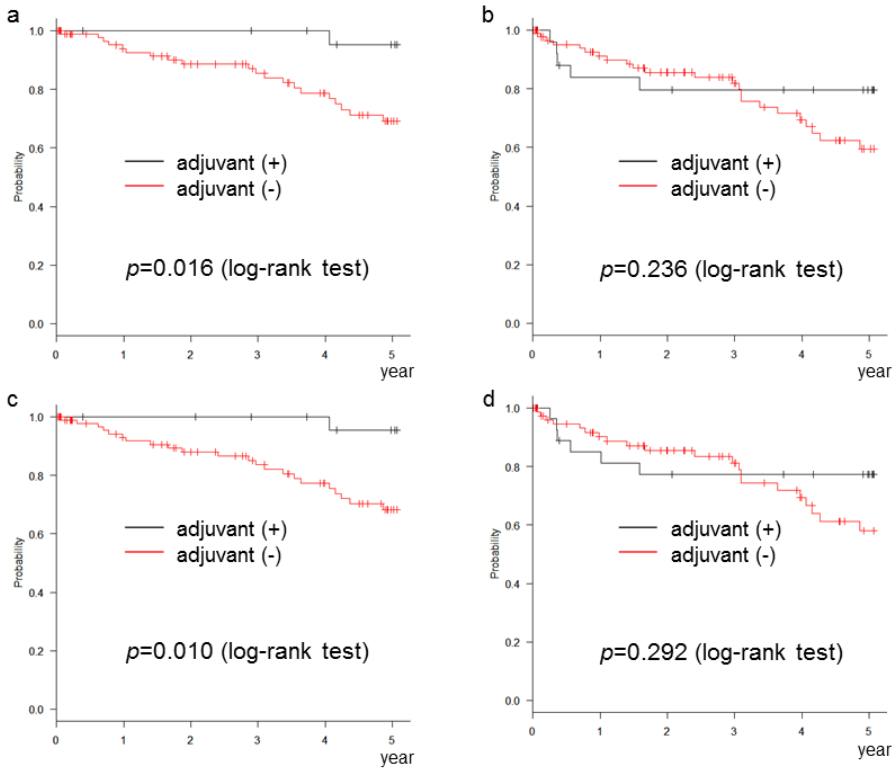

Figure 1. Disease-free survival of cases with (a) 1 or 2 risk factors according to the NCCN definition, (b) 1 risk factor according to the ASCO definition, (c) 1 or 2 risk factors according to the ESMO definition, (d) 1 risk factor according to the JFMC definition

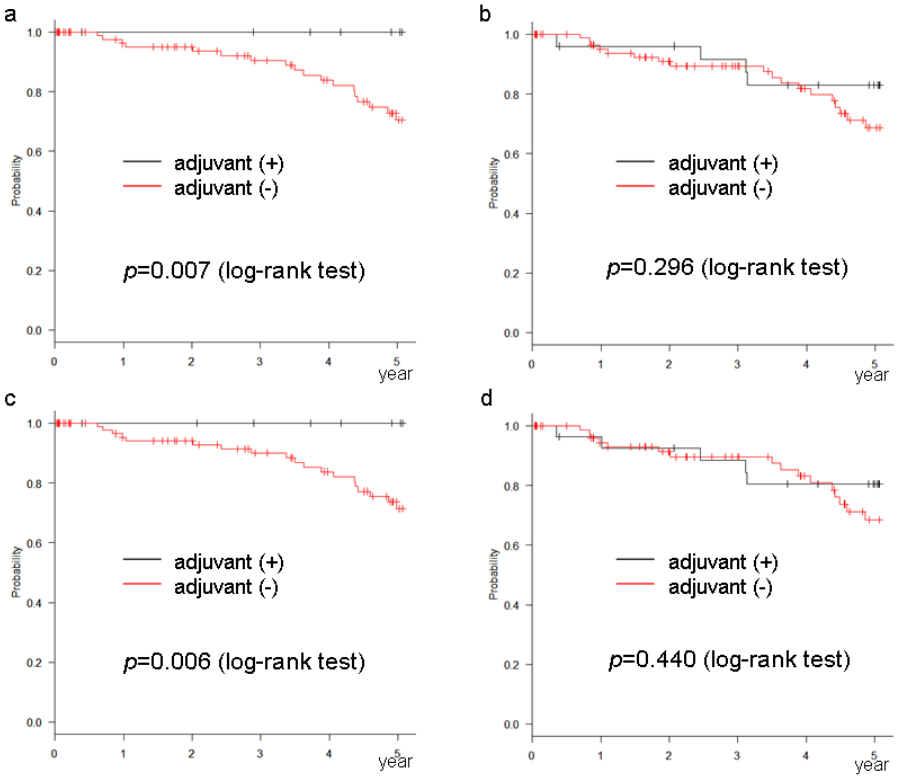

Figure 2. Overall survival of cases with (a) 1 or 2 risk factor according to the NCCN definition, (b) one risk factor according to the ASCO definition, (c) 1 or 2 risk factors according to the ESMO definition, (d) 1 risk factor according to the JFMC definition

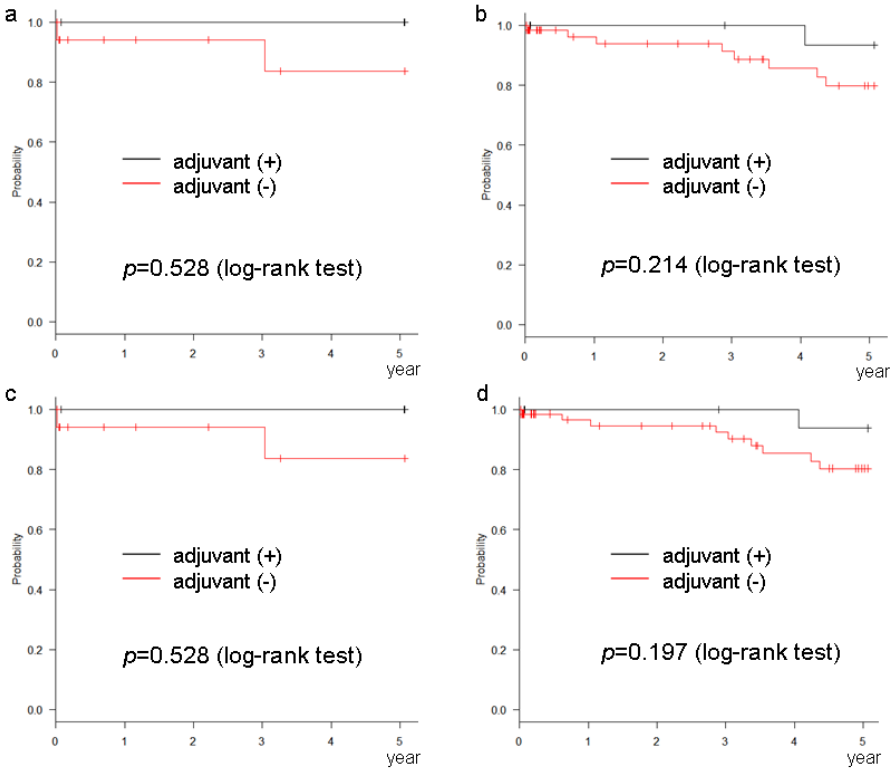

Figure 3. Disease-free survival of cases with (a) no risk factors according to the NCCN definition, (b) no risk factors according to the ASCO definition, (c) no risk factors according to the ESMO definition, (d) no risk factors according to the JFMC definition

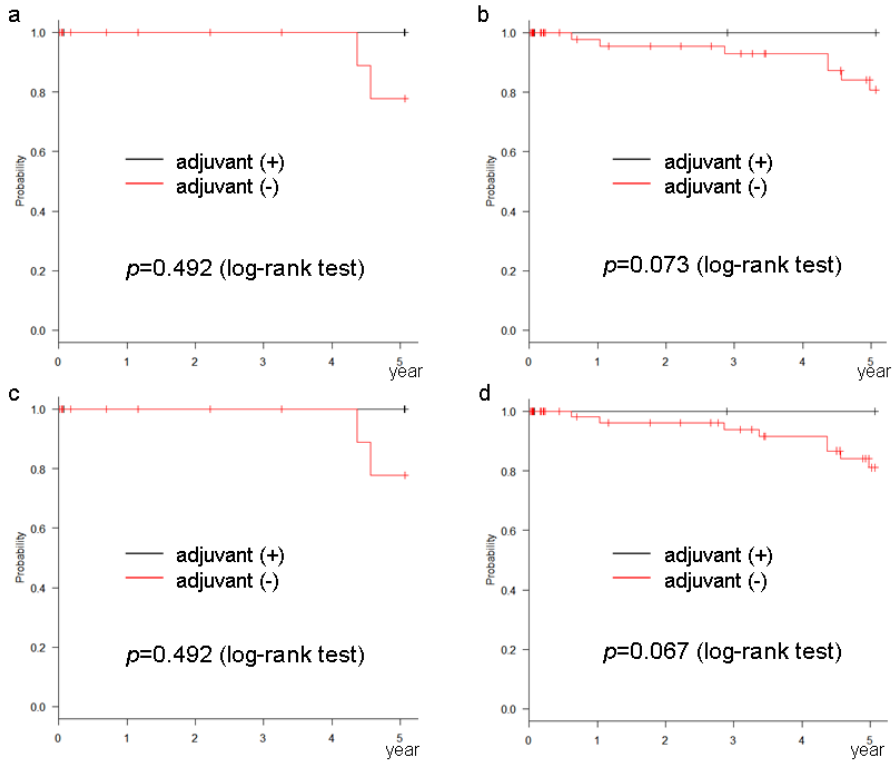

Figure 4. Overall survival of cases with (a) no risk factors according to the NCCN definition, (b) no risk factors according to the ASCO definition, (c) no risk factors according to the ESMO definition, (d) no risk factors according to the JFMC definition

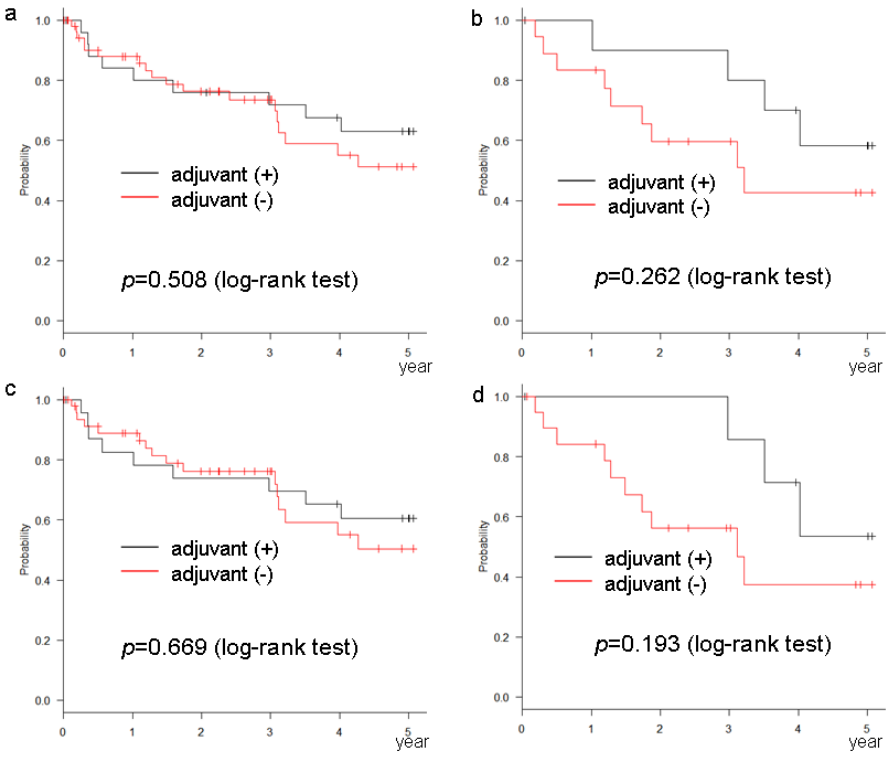

Figure 5. Disease-free survival of cases with (a) more than 3 risk factors according to the NCCN definition, (b) more than 2 risk factors according to the ASCO definition, (c) more than 3 risk factors according to the ESMO definition, (d) more than 2 risk factors according to the JFMC definition

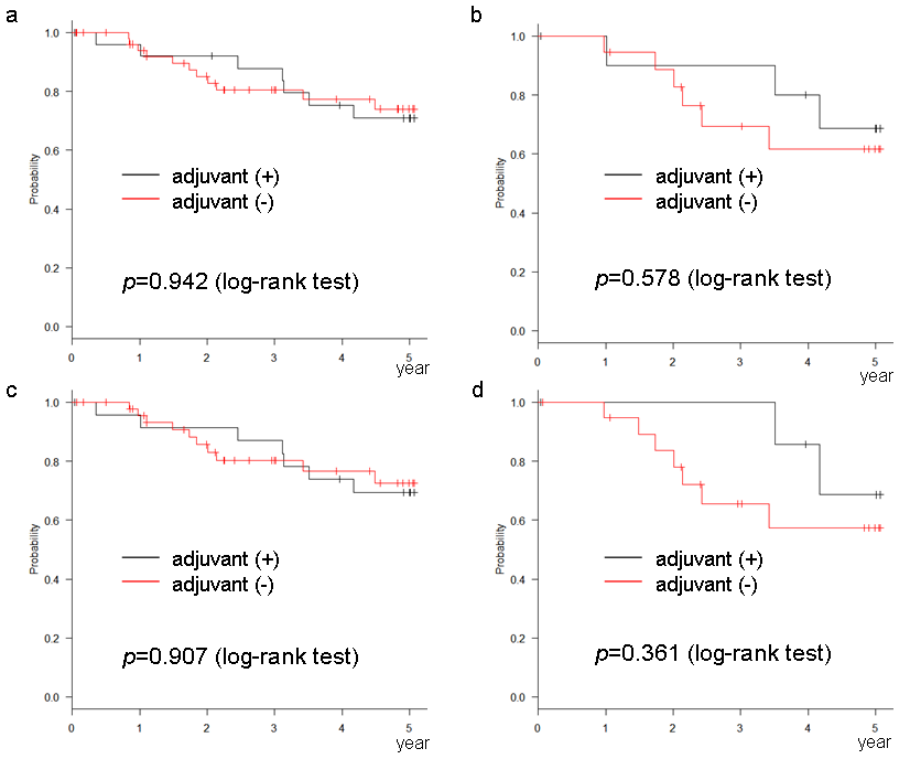

Figure 6. Overall survival of cases with (a) more than 3 risk factors according to the NCCN definition, (b) more than 2 risk factors according to the ASCO definition, (c) more than 3 risk factors according to the ESMO definition, (d) more than 2 risk factors according to the JFMC definition

Table 2. Clinicopathological characteristics of patients with stage II colon cancer

Factors	recurrence (-) n=200	recurrence (+) n=26	*p*-value
Age	72.7 (31-97)	71.7 (52-89)	0.935
Gender			
male	100	13	0.753
female	100	13	
Location			
cecum	14	4	0.034
ascending	53	0	0.997
transverse	32	0	0.996
descending	14	3	0.487
sigmoid	87	19	0.016
Perforation	0	2	<0.001
Obstruction	15	4	0.241
Penetration	5	2	0.070
Tumor marker			
CEA	9.8 (1.1-229.0)	17.2 (1.5-161.4)	0.311
CA19-9	32.2 (1.0-495.0)	32.7 (1.0-160.4)	0.903
Complication	55	7	0.715
Histology			
por/sig	5	0	0.997
muc	12	1	0.724
well/mod/pap	183	25	0.479
T-factor			
T3	177	16	<0.001
T4	23	10	
Examined LN number			
LN< 12	95	18	0.026
LN<13	107	18	0.132
Lymphatic invasion			
ly-	131	10	0.134
ly+	91	16	
Vascular invasion			
v-	45	5	0.751
v+	153	20	
unknown	2	1	
Perineural invasion			
PN-	190	21	0.100
PN+	5	2	
unknown	5	3	
Residual tumor			
R0	181	17	<0.001
R1	14	9	
unknown	5	0	
Adjuvant			
present	50	6	0.368
absent	150	20	
Procedure			
laparo	2	0	0.694
open	198	26	

CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, por: poorly differentiated adenocarcinoma, sig: signet ring cell carcinoma, muc: mucinous adenocarcinoma, well: well differentiated adenocarcinoma, mod: moderately differentiated adenocarcinoma, pap: papillary adenocarcinoma. LN: lymph node. ly: lymphatic invasion, v: vascular invasion, PN: perineural invasion

Table 3. Relation between the number of risk factors and recurrence

Guideline	factors	cases	recurrence	rate (%)
NCCN	0	21	1	4.76
	1-2	123	8	6.50
	≥ 3	82	17	20.73
ASCO	0	78	4	5.13
	1	119	13	10.92
	≥ 2	29	9	31.03
ESMO	0	21	1	4.76
	1-2	131	10	7.63
	≥ 3	74	15	20.27
JFMC	0	86	4	4.65
	1	112	13	11.61
	≥ 2	28	9	32.14

NCCN: National Comprehensive Cancer Network, ASCO: American Society of Clinical Oncology, ESMO: European Society for Medical Oncology, JFMC: Japanese Foundation for Multidisciplinary Treatment of Cancer

Discussion

We sought to identify patients with high-risk stage II disease to identify those at high-risk of recurrence and improve prognosis by introducing AC [5-8]. As the high-risk factors related to recurrence in stage II differ for each guideline, there is no list of established factors that are monitored in clinical settings. This leads to difficulty in judging the indications for AC. In addition, if at least 1 risk factor is placed in the category of the high-risk group, most cases become "high-risk" cases. Because AC does not improve prognosis for all patients with stage II disease, it is no wonder that there is no prognostic effect if most cases fall within the same category as the high-risk group [13-16]. The methods of identifying high-risk stage II patients require reconsideration. We therefore examined the relation between the number of risk factors and the effects of AC.

There are 3 possible prognostic categories for patients with stage II colon cancer. Group 1: some cases are cured only by surgical therapy. These cases do not experience recurrence, regardless of whether AC is introduced or not. The prognosis of these cases is good, and there is no prognostic difference due to the introduction of AC. Group 2: in some cases, recurrence is suppressed by AC. These patients' prognosis will vary, depending on the presence or absence of AC. Group 3: some patients experience recurrence even after AC is introduced. These patients have a poor prognosis, and there is no prognostic value to introducing AC.

In this study, the prognosis of patients with stage II colon cancer worsened as the number of risk factors included in each case increased. Kim et al. also reported this phenomenon [17]. Cases where a cure is obtained only by surgical therapy might be those with no risk factors: in other words, a 'low-risk group'. Most patients where recurrence is suppressed by AC might be included in the group with 1 or 2 risk factors according to the NCCN or ESMO definition. Most cases with recurrence despite AC might be included in the group with more than 3 risk factors according to the NCCN or ESMO definition.

Although the cases analysed in this study spanned a relatively long period, they all had stage II disease and their AC regimen was either an oral 5-FU formulation or 5-FU/LV. Therefore, the AC regimen used appeared not to change prognosis [18]. Therefore, results generalizability might be limited to patients who only received oral 5-FU or 5-FU/LV. This suggests that cases with 1 or 2 risk factors according to the NCCN or ESMO definition, may benefit from oral 5-FU or 5-FU/LV. Stated differently, oral 5-FU or 5-FU/LV may be insufficient to suppress recurrence in cases with 3 or more risk factors according to the NCCN or ESMO definition. The effect of adding oxaliplatin against stage II colon cancer is controversial [19-22]. However, in these reports, the authors did not extract and evaluate populations with recurrence rates equivalent to those of patients with stage III colon cancer. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [23], the 5-year OS of patients with colon cancer with any T N1 (JSCCR defines these cases as stage IIIa) is 76.1%. In this study, the OS values of cases with more than 3 risk factors, according to the NCCN and ESMO definitions were 78.0% and 77.0%, respectively. This is considered comparable to stage IIIa. This suggests that the prognosis of patients with more than 3 risk factors according to the NCCN or ESMO guidelines, can be improved when oxaliplatin is added to the AC regimen.

These results led us to consider classifying patients with stage II colon cancer into 3 categories instead of into 2 types (low and high -risk). Referring to the NCCN and ESMO guidelines, the following treatment methods may be considered: follow-up observation without AC for cases with no risk factors, AC with oral 5-FU or 5-FU/LV for

cases with 1 or 2 risk factors, an oxaliplatin augmented regimen for cases with 3 or more risk factors. As expected, accurate verification is impossible without a prospective clinical trial. However, if possible, recent clinical trial should be reviewed when considering this method of stratification.

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