

High-risk Stage II Colorectal Cancers Carry an Equivalent Risk of Peritoneal Recurrence to Stage III

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Abstract. *Background/Aim:* Several risk factors for recurrence have been identified in stage II colorectal cancer. However, in contrast to stage III, the benefits of adjuvant chemotherapy for these patients remain controversial. We hypothesized that the different impacts of chemotherapy may be due to different patterns of recurrence between these stages. The aim of this study was to characterize recurrence in high-risk stage II colorectal cancer (CRC) in comparison with stage III. *Patients and Methods:* A total of 442 patients with curatively resected stage III and high-risk stage II CRCs were evaluated. The recurrence site and frequency were compared between these stages. The risk factors of recurrence by site were identified using multivariate analyses. *Results:* During the follow-up (median: 6.4 years), 31% of stage III and 13% of high-risk stage II patients manifested recurrence. Recurrence in the liver, lung, and distant lymph nodes was significantly more frequent in stage III (18%, 12%, 11%) than in high-risk stage II (7%, 6%, 3%). Stage III was independently associated with recurrence in these organs. In contrast, the rate of peritoneal recurrence was 5% in both stages. *Conclusion:* Clinicians should be aware that high-risk stage II CRC has a similar risk of postoperative recurrence in the peritoneum to Stage III CRC.

Colorectal cancer (CRC) is the third most common cancer in the world with approximately 1.4 million new patients being diagnosed annually (1, 2). Stage III CRC needs to be treated surgically and then with adjuvant chemotherapy, as indicated

by the guidelines (3-6). On the other hand, surgical resection is the mainstay of treatments for stage II CRCs that less frequently manifest recurrent disease. The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) previously proposed many risk factors for postoperative recurrence in stage II CRC such as pathological T4, poorly differentiated histology, suboptimal lymph node retrieval, bowel perforation, bowel obstruction, lymphatic and venous invasion, perineural invasion, and positive resection margins (3, 4, 7, 8). After the concept of high-risk stage II CRC emerged, extensive information was obtained on overall recurrence rates; however, recurrence sites have not yet been investigated in detail.

CRC may disseminate *via* lymphatic and hematogenous routes or spread intraperitoneally. In combination with systemic chemotherapy, metastasized site-oriented loco-regional therapies, *e.g.* intraportal chemotherapy for liver recurrence and intraperitoneal chemotherapy for peritoneal recurrence, are considered to be reasonable (9). Previous randomized trials using these combinational therapies reported increased survival rates in CRC patients with high-risk for recurrence in specific organs, even in the adjuvant setting (9), underscoring the importance of comprehending recurrence patterns in more detail in curatively resected CRC.

The aim of the present study, was to characterize recurrence in high-risk stage II CRC in comparison with stage III.

Patients and Methods

Patients. Patients with primary CRC resected curatively (R0 resection) at the Department of Surgical Oncology, the University of Tokyo between January 2005 and 2012 were retrospectively searched. Among these patients, those who were finally diagnosed with stage III or high-risk stage II CRC and were followed-up for at least five years were reviewed. As high-risk stage II, cases of pathological T4, a poorly differentiated histology, less than 12 harvested lymph nodes, bowel obstruction, bowel perforation, or lymphatic/venous invasion were selected according to the major guidelines (3, 4, 7, 8). Perineural invasion was not analyzed because

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Key Words: Colorectal cancer, high-risk stage II, stage III, peritoneal metastasis.

Table I. Clinicopathological factors in stage III and high-risk stage II CRC.

Parameter	Stage III (n=234)	High-risk stage II (n=208)	p-Value
Age (years)			
Mean±SD	66.2±11.6	68.3±11.0	0.053
Gender			
Male	139 (59%)	123 (59%)	0.95
BMI (kg/m ²)			
Mean±SD	22.8±3.4	22.9±3.6	0.79
Serum CEA			
Elevated	98 (42%)	97 (47%)	0.34
Serum CA 19-9			
Elevated	39 (17%)	25 (12%)	0.18
Location			
Right-sided colon	83 (35%)	81 (39%)	0.66
Left-sided colon	110 (47%)	96 (46%)	
Rectum	41 (18%)	31 (15%)	
Size (mm)			
Mean±SD	42.4±1.4	50.6±1.4	<0.0001
Obstruction/Perforation			
Present	72 (31%)	83 (40%)	0.045
Histology			
Differentiated	219 (94%)	195 (94%)	0.95
Undifferentiated	15 (6%)	13 (6%)	
Lymphatic invasion			
Present	119 (51%)	35 (17%)	<0.0001
Venous invasion			
Present	187 (80%)	159 (76%)	0.43
Harvested lymph nodes			
<12	41 (18%)	41 (20%)	0.55
Depth			
pT1/pT2	47 (20%)	0	<0.0001
pT3	121 (52%)	155 (75%)	
pT4	66 (28%)	53 (25%)	

CRC: Colorectal cancer; SD: standard deviation; BMI: body mass index; CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9.

this parameter was not systematically evaluated during the aforementioned study period. Patients with multiple primary CRCs and inflammatory bowel disease-associated cancer as well as those who received preoperative chemotherapy and/or radiation therapy were excluded. Patients who had simultaneously other malignancies or were lost to the follow-up before five years were also excluded.

All patient data regarding gender, age, serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 just before surgery, and the pathological parameters of the primary tumor, namely, location, size, and stage in addition to the risk factors described above were retrieved.

The normal upper limits of serum CEA and CA 19-9 are 5 ng/ml and 37 U/ml, respectively. The histopathological description of primary CRC was based on the eighth edition of the American Joint Committee on Cancer and the International Union Against Cancer Tumor-Node Metastasis (AJCC/UICC TNM) grading system (10).

Follow-up. Computed tomography (CT) scans were performed six months after surgery or at the end of adjuvant chemotherapy, and

Table II. Adjuvant chemotherapy and recurrence in stage III and high-risk stage II CRC.

Parameter	Stage III (n=234)	High-risk stage II (n=208)	p-Value
Adjuvant CTX			
Any	157 (67%)	14 (7%)	<0.0001
5-FU (+ LV)	138 (88%) ^a	14 (100%) ^a	0.37
5-FU + oxaliplatin	19 (12%) ^a	0	
Recurrence			
Overall	73 (31%)	28 (13%)	<0.0001
Liver	41 (18%)	15 (7%)	0.0015
Lung	29 (12%)	13 (6%)	0.028
Lymph nodes	26 (11%)	6 (3%)	0.0008
Peritoneum	11 (5%)	10 (5%)	1.00
Local	8 (4%)	2 (1%)	0.12
Bone	2 (1%)	1 (0%)	1.00
Brain	4 (2%)	0	0.13
Others	9 (4%)	2 (1%)	0.067

CRC: Colorectal cancer; CTX: chemotherapy; 5-FU: 5-fluorouracil; LV: levofolinate. ^apercentage in patients who received chemotherapy as the denominator.

every six to twelve months thereafter. When serum tumor marker levels increased in a rapid manner or a new manifestation of symptoms occurred suggesting recurrent disease, CT scans and other imaging modalities such as magnetic resonance imaging and positron emission tomography were additionally performed. Recurrence-free survival (RFS) was defined as the period between the date of surgery and diagnosis of any recurrence. The indication for adjuvant chemotherapy depended on doctors' discretion and patients' conditions and preferences. Dose reductions and the cessation of chemotherapy were considered based on the patient's condition and preference. Basically, adjuvant chemotherapy regimens included oral or infusional 5-FU plus levofolinate (LV), or a 5-FU and oxaliplatin-based regimen such as FOLFOX for six months (3, 4, 11, 12).

Ethical approval. The study protocol was approved by the local ethics committees in the University of Tokyo [reference number: 3252-(5)], and thus meets the standards of the Declaration of Helsinki in its revised version of 1975 and its later amendments.

Statistical analysis. The Student's *t*-test or Mann-Whitney test was used to compare continuous variables, and the Chi-squared test or Fisher's exact test was employed to compare categorical data. Serum CEA and CA 19-9 were dichotomized by preset cut-off levels as described above. Site-specific recurrence rates were estimated by the Kaplan-Meier method and were compared using the Log-rank test. Cox's proportional-hazard model was performed to evaluate the relationship between perioperative clinicopathological factors and recurrence, in which continuous variables other than tumor markers were dichotomized by their mean values (age, BMI, and tumor size). If factors showed a *p*-value of less than 0.1 in the univariate analysis, these parameters were included in the multivariate analysis as explanatory variables. All statistical analyses of data were performed using JMP Version 13.0.0 (SAS Institute Inc., Cary, NC, USA), with *p*-values less than 0.05 being considered significant.

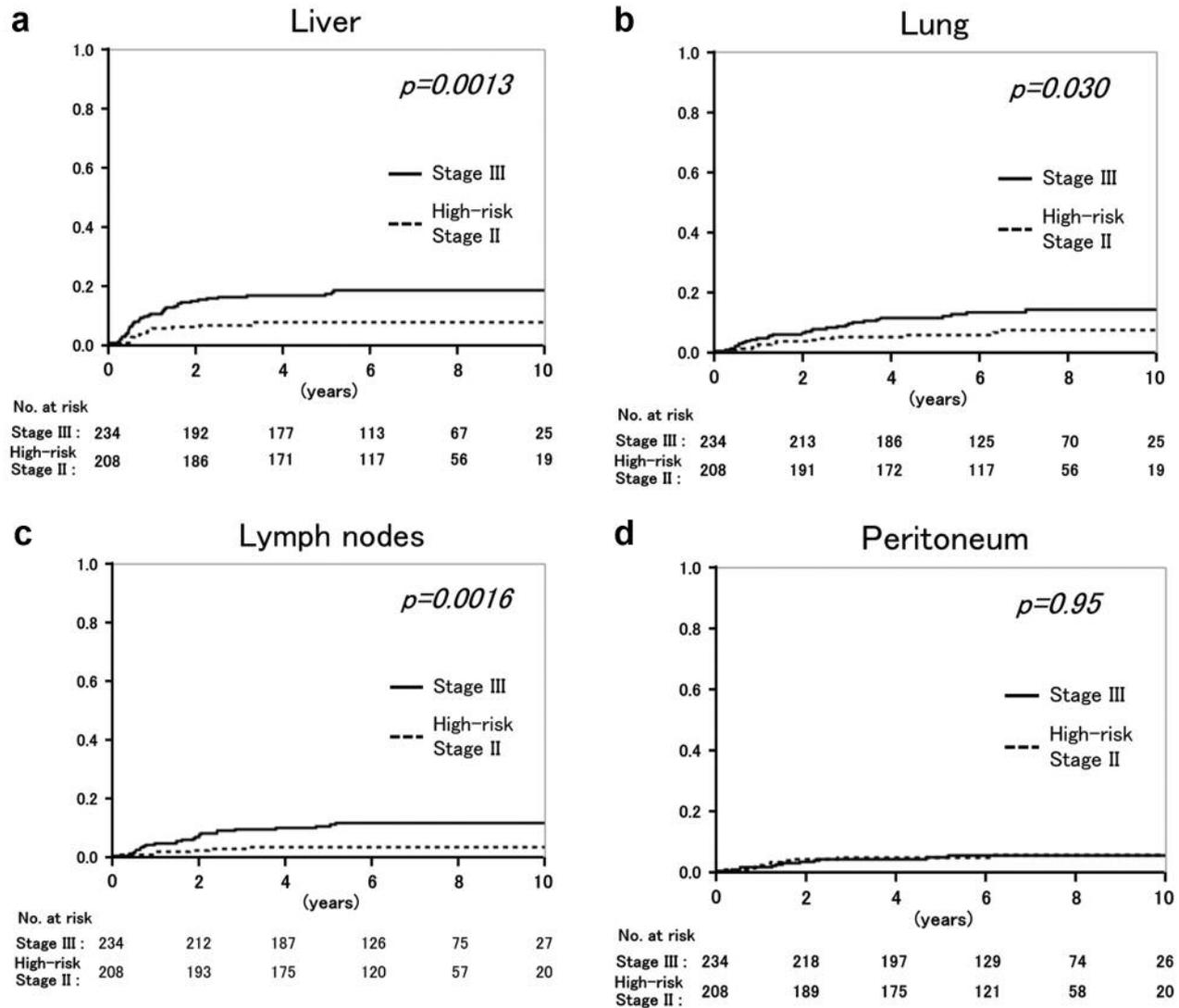


Figure 1. Organ-specific recurrence rate (A) recurrence in the liver, (B) recurrence in the lung, (C) recurrence in distant lymph nodes, and (D) recurrence in the peritoneum.

Results

Patient overview. A total of 442 patients were identified to have stage III or high-risk stage II CRC. In 208 stage II CRCs, obstruction was the leading “high risk” factor (81 patients, 39%), followed by pathological T4 (53 patients, 25%). Table I summarizes the profile of patients examined in the present study. High-risk stage II CRCs were larger than stage III CRCs by 8 mm. Obstructive cancer was also more frequent in high-risk stage II (40%) than in stage III (31%). On the other hand, lymphatic invasion was more frequently observed in stage III (51%) than in high-risk stage II (17%). No significant differences were observed in other background parameters between the stages.

One hundred seventy-one patients (39%) underwent adjuvant chemotherapy after surgery. Most of these patients received 5-FU with or without LV; oxaliplatin was additionally administered to 19 stage III CRC patients (data not shown).

Comparison of recurrence rates between stage III and high-risk stage II. During the median follow-up of 6.4 years, recurrence was observed in 31% of stage III CRC and 13% of high-risk stage II ($p<0.0001$). As shown in Table II, the liver, lung, and distant lymph nodes were metastasized more frequently in stage III (18%, 12%, and 11%) than in high-risk stage II (7%, $p=0.0015$, 6%, $p=0.028$, and 3%, $p=0.0008$, respectively). In contrast, metachronous peritoneal dissemination occurred in stage III and high-risk stage II with

Table III. Univariate and multivariate analyses of predictive factors for each organ recurrence.

Organ	Parameter	Univariate	Multivariate	
		p-Value	HR (95%CI)	p-Value
Liver	Lymphatic invasion (vs. no)	0.085		
	Venous invasion (vs. no)	0.035	2.37 (1.09-6.21)	0.028
	Stage III (vs. high-risk stage II)	0.0019	2.44 (1.33-4.69)	0.0035
Lung	Elevated CEA (vs. normal)	0.064		
	Elevated CA 19-9 (vs. normal)	0.0004	2.60 (1.27-5.09)	0.010
	Venous invasion (vs. no)	0.023	3.35 (1.21-13.93)	0.017
Lymph nodes	Stage III (vs. high-risk stage II)	0.028	1.91 (1.01-3.82)	0.046
	Male (vs. female)	0.041		
	Elevated CA 19-9 (vs. normal)	<0.0001	4.70 (2.26-9.65)	<0.0001
	Undifferentiated histology (vs. differentiated)	0.035		
	pT4 (vs. pT1-3)	0.067		
	Lymphatic invasion (vs. no)	0.016		
Peritoneum	Venous invasion (vs. no)	0.059		
	Stage III (vs. high-risk stage II)	0.0010	3.23 (1.32-9.10)	0.0089
	Elevated CA 19-9 (vs. normal)	0.0059		
	Undifferentiated histology (vs. differentiated)	0.038	3.96 (1.10-11.33)	0.037
	pT4 (vs. pT1-3)	0.0025	3.42 (1.41-8.59)	0.0068
	Obstruction/Perforation (vs. no)	0.015		

HR: Hazard ratio; CI: confidence interval; CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9.

the same frequencies (5% and 5%, $p=1.00$). Figure 1 shows site-specific recurrence rates over time according to stage. Stage III CRC showed a markedly higher rate of recurrence in the liver, lung, and distant lymph nodes than high-risk stage II. However, the recurrence rate curves of the peritoneum were superimposed for both stages.

Predictive factors of recurrence in each organ. A univariate analysis was performed using Cox's proportional hazards model in order to identify clinicopathological predictors of recurrence in each organ. As shown in Table III, stage III correlated with recurrence in the liver (hazard ratio (HR)=2.44, $p=0.0035$), lung (HR=1.91, $p=0.0046$), and lymph nodes (HR=3.33, $p=0.0089$). In contrast, peritoneal recurrence correlated with an undifferentiated histology (HR=3.96, $p=0.037$) and pT4 (HR=3.42, $p=0.0068$), whereas stage III was not an independent predictor for peritoneal recurrence. Adjuvant chemotherapy was not associated with recurrence at any site.

Discussion

Previous studies reported the overall frequency of postoperative recurrence and predictive factors in stage II and III CRCs (13-19). However, limited information is currently available on recurrence rates in terms of metastasized organs. Russell *et al.* analyzed the pattern of recurrence of colon cancer according to the lymph node

status; no significant differences were observed in local, peritoneal, or distant metastases between node-negative and -positive cases (20). Sadahiro *et al.* reported the number of stage II and III CRC patients who relapsed in a follow-up period of more than 10 years according to the recurrent site. Based on their data, we calculated the rates of metastases in the liver and lung in stage II as 6% and 3%, respectively, which were significantly lower than those in stage III (14% and 11%, respectively). Peritoneal and local recurrence rates were slightly lower in stage II than in stage III patients (1% vs. 2%, and 4% vs. 8%) (21). However, these studies were published more than a decade ago when the concept of high-risk stage II was not established. The present study is the first to analyze the site distribution of recurrence after surgery using the largest number of patients with stage III and high-risk stage II CRCs.

The liver, lung, lymph nodes, and peritoneum were identified as the most common organs of recurrence in stage III and high-risk stage II CRCs. Recurrence rates in the liver, lung, and lymph nodes were significantly higher in stage III. In contrast, peritoneal recurrence rates were similar in stage III and high-risk stage II CRCs (Table II and Figure 1). The stage III and high-risk stage II cohorts comprised almost the same percentages of T4 cancers (Table I), which are known risk factors for peritoneal dissemination (22, 23). Although the absence of a significant difference may be due to the lack of power, we need to be aware of the similar risk of peritoneal recurrence between high-risk stage II and stage III.

Adjuvant chemotherapy was not associated with recurrence in the common sites. This is partly due to the potential bias of the indication for chemotherapy and/or insufficient statistical power due to the small number of patients. Although clinicians currently consider adjuvant chemotherapy for patients with any high-risk factor, recent studies reported that survival outcomes were influenced by features not suggested in the guidelines (13, 14). On the other hand, Kumar *et al.* demonstrated that T4 may be the only risk factor for which stage II CRC may obtain survival benefits from adjuvant chemotherapy (24). In this regard, adjuvant chemotherapy oriented towards peritoneal targets such as intraperitoneal chemotherapy in combination with intravenous chemotherapy or hyperthermia might be promising in pT4 CRC (25, 26).

Our study had several limitations due to its retrospective nature and single institute experience. As mentioned above, the application and regimen of adjuvant chemotherapy was not based on pre-determined criteria. In addition, a relatively small number of stage III and high-risk stage II patients received adjuvant chemotherapy because the study period spanned a long time period, during which guidelines regarding chemotherapy were repeatedly revised.

In conclusion, the potential for recurrence in the peritoneum was similar between high-risk stage II and stage III CRCs. A larger number of patients should be examined to confirm the finding, and further studies are needed in order to clarify how to prevent recurrence in these patients using adjuvant chemotherapy.

Conflicts of Interest

The Authors report no potential conflicts of interest regarding this study.

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