Identification of the Risk Factors for Recurrence of Stage II Colorectal Cancer

Sho Sawazaki¹⁾, Manabu Shiozawa¹⁾, Yusuke Katayama¹⁾, Koji Numata¹⁾,
Masakatsu Numata¹⁾, Teni Godai¹⁾, Akio Higuchi¹⁾, Yasushi Rino²⁾,
Munetaka Masuda²⁾ and Makoto Akaike¹⁾

¹⁾Department of Gastrointestinal Surgery, Kanagawa Cancer Center

²⁾Department of Surgery, Yokohama City University

Abstract

Introduction: The use of adjuvant chemotherapy in stage II colorectal cancer patients remains controversial. However, patients with specific clinicopathological features are thought to have a high risk for recurrence. The aim of this study was to identify the subgroup of patients at the greatest risk by investigating the clinicopathological features associated with a poor survival in patients with stage II disease. **Patients & Methods:** A total of 414 patients with stage II colorectal cancer who underwent curative resection between January 1990 and September 2007 at Kanagawa Cancer Center were enrolled. The clinicopathological data of the patients were retrospectively evaluated.

Results: The median follow-up period was 62.5 months. The 5-year disease-free survival rate was 89.6% in the study group as a whole. A univariate analysis of 5-year disease-free survival identified three factors: lymphatic invasion ($p=0.001$), the preoperative serum CEA level (>5 ng/ml) ($p=0.005$) and the CA19-9 level (>37 U/ml) ($p=0.006$). A multivariate analysis of 5-year disease-free survival identified one independent factor: lymphatic invasion (HR: 1.89; 95% CI: 1.02-3.50; $p=0.044$).

Conclusions: Patients with stage II colorectal cancer who exhibit lymphatic invasion are at a high risk for recurrence.

Key words: colorectal cancer, stage II, high risk, disease free survival, adjuvant chemotherapy

Introduction

According to the colorectal cancer treatment guidelines¹⁾, the administration of adjuvant chemotherapy following curative surgical resection in stage III colorectal cancer patients is recommended because it reduces the rate of tumor recurrence and improves disease-free and overall survival^{2,3)}. However, the usefulness of postoperative adjuvant chemotherapy for treating stage II disease has not been verified⁴⁻⁷⁾, and the administration of adjuvant chemotherapy in all patients with stage II disease has not been validated. In other guidelines, groups at a high risk for recurrence of stage II colorectal cancer have been defined, and the use of adjuvant chemotherapy in such groups is recommended. The American Society of Clinical Oncology (ASCO) guidelines⁸⁾ recommend considering the use of adjuvant chemotherapy in patients with stage II colon cancer, such as those with <12 regional lymph nodes examined, T4 lesions, perforation, poorly-differentiated adenocarcinoma, mucinous adenocarcinoma or signet-ring cell carcinoma. The European Society for Medical Oncology (ESMO) guidelines⁹⁾ recommend that adjuvant chemotherapy be considered in patients with the following high-risk factors: T4 lesions, poorly-differentiated adenocarcinoma/undifferentiated carcinoma, vascular invasion, lymphatic vessel invasion, perineural invasion, obstruction or perforation on initial presentation, <12 regional lymph nodes examined or a high carcinoembryonic antigen (CEA) level. The aim of this study was to

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Correspondence to: Sho Sawazaki

Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan

Table 1 Clinicopathological features of patients with stage II colorectal cancer

Factor	Category	Number of patients (n=414)
Gender	Male	267
	Female	147
Age	median	65 (23-91)
Colon or Rectum	Colon	302
	Rectum	112
T stage	T3	246
	T4	168
Number of lymph node examined	median	35
Adjuvant chemotherapy	Absent	269
	Present	142
Recurrence	—	369
	+	45

identify the subgroups of patients at the greatest risk by investigating the clinicopathological features associated with poor survival in patients with stage II disease.

Methods

Patients

Between January 1990 and September 2007, a total of 1,804 patients with colorectal cancer underwent curative resection at Kanagawa Cancer Center. We retrospectively reviewed the following clinicopathological data of 414 patients with stage II disease: clinical characteristics, preoperative tumor staging, details of surgery, postoperative histopathology and the results of follow-up. All patients were staged based on the findings of preoperative colonoscopy, imaging of the chest, abdomen and pelvis with computed tomography and radiographic contrast enemas. Patients with synchronous cancer of other organs or who died due to other causes were excluded.

Treatment and follow-up

All patients underwent standard curative resection at our department. The tumor location was classified into two categories: right colon (cecum, ascending colon and transverse colon) and left colon (descending colon, sigmoid colon, rectum and proctos). The patients received follow-up with computed tomography and measurement of the serum CEA and CA19-9 levels. The median follow-up period was 62.5 months. In each case, after curative surgery, the decision whether to administer adjuvant chemotherapy was left to the clinical discretion of the attending physician. A 5-fluorouracil (5-FU)-based

regimen was used for adjuvant chemotherapy. The duration of treatment was at least six months.

Histopathological analysis

All resected specimens underwent standard histopathological analyses. After surgery, the disease was pathologically staged according to the 7th UICC TNM classification¹⁰⁾. Complete tumor resection was performed in all patients. Well-differentiated, moderately-differentiated, poorly-differentiated and mucinous adenocarcinomas were evaluated histopathologically. The presence of local and distant recurrence was confirmed clinically, radiologically and/or histopathologically.

Statistical analysis

Disease-free survival rates were calculated using the Kaplan-Meier method, and survival curves were compared with the log-rank test. A Cox regression analysis was used for the univariate and multivariate analyses. The variables that reached statistical significance ($p < 0.05$) were entered into a multivariate analysis. In all cases, p values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the Dr. SPSS II software program, version 11.0. 1J for Windows (SPSS, Inc., Chicago, IL).

Results

The clinicopathological features of the 414 patients with stage II colorectal cancer are shown in **Table 1**. Forty-five patients developed recurrence. Local recurrence was defined as intrapelvic recurrence and anastomotic recurrence. The recurrent sites includ-

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Table 2 Univariate analysis of prognostic factors for 5-year disease-free survival

Factor	Category	Number of patients (n=414)	Hazard ratio	95% C.I.*	p-value
Gender	Male	267	1		
	Female	147	0.901	0.485-1.675	N.S.**
Age	≤65	208	1		
	>65	206	1.262	0.701-2.273	N.S.**
Colon or Rectum	Colon	302	1		
	Rectum	112	1.706	0.934-3.117	0.082
Tumor location	Right	126	1		
	Left	288	1.370	0.694-2.704	N.S.**
Tumor diameter(cm)	≤5	209	1		
	>5	204	0.606	0.331-1.106	N.S.**
Pathological type	Wel, Mod	363	1		
	Por, Muc	51	1.348	0.602-3.018	N.S.**
T stage	T3	246	1		
	T4	168	1.456	0.812-2.612	N.S.**
Lymphatic invasion	Absent	271	1		
	Present	143	2.460	1.366-4.429	0.001
Venous invasion	Absent	204	1		
	Present	210	1.030	0.574-1.848	N.S.**
Number of lymph node examined	<12	22	1		
	≥12	392	0.433	0.171-1.098	0.078
Preoperative serum CEA (ng/ml)	≤5	325	1		
	>5	81	2.450	1.303-4.606	0.005
Preoperative serum CA19-9 (U/ml)	≤37	347	1		
	>37	52	2.632	1.319-5.253	0.006
Adjuvant chemotherapy	Absent	269	1		
	Present	142	0.792	0.414-1.514	N.S.**

*C.I.: Confidence Interval **N.S.=Not Significant

Table 3 Multivariate analysis of prognostic factors for 5-year survival

Factor	Hazard ratio	95%C.I.*	p-value
Lymphatic invasion(Present/Absent)	1.887	1.018-3.496	0.044
CEA(>5/≤5)	1.951	0.979-3.889	0.057
CA19-9 (>37/≤37)	1.910	0.902-4.045	0.091

*C.I.: Confidence Interval

ed the liver (15 patients, 29.4%), lungs (14 patients, 27.5%), peritoneum (9 patients, 17.6%) and local sites (9 patients, 17.6%).

The 5-year disease-free survival rate was 89.6% and the overall survival rate was 96.1%. Clinico-pathological features, including age, gender, tumor location, tumor diameter, pathological type, T stage, presence of lymphatic invasion, presence of venous invasion, number of lymph nodes examined, use of adjuvant chemotherapy and the preoperative serum levels of CEA and CA19-9, were analyzed. The Cox univariate regression analysis showed that the recurrence rate was significantly related to the presence of lymphatic invasion and the preoperative serum levels of CEA (>5 ng/ml) and CA19-9 (>37 U/

ml) (**Table 2**). Features such as age, gender, tumor location, tumor diameter, pathological type, T stage, presence of venous invasion, number of lymph nodes examined and use of adjuvant chemotherapy were not found to be significant recurrent factors. The Cox multivariate analysis showed that the presence of lymphatic invasion ($p=0.044$) was the only independent prognostic factor significantly related to recurrence in patients with stage II colorectal cancer (**Table 3**).

The 5-year disease-free survival rates differed significantly between the patients without this prognostic factor (93.0%) and those with this prognostic factor (83.2%, $p=0.0019$; **Fig. 1**). Among the patients with this prognostic factor, the 5-year disease-free

Fig. 1 Disease-free survival of patients with stage II colorectal cancer: 271 patients without lymphatic invasion, and 143 with it.

survival rates differed between the patients who received adjuvant chemotherapy (89.2%) and those who did not (77.6%, $p=0.068$), although the 5-year overall survival rates did not differ significantly (93.8% vs 89.5%, $p=0.35$).

Discussion

Many trials have shown that the administration of adjuvant chemotherapy in patients with stage III colorectal cancer is beneficial, whereas the benefits in patients with stage II disease remain controversial. In the QUASAR (Quick And Simple And Reliable) trial⁵⁾, chemotherapy with fluorouracil and folinic acid was found to improve the survival rates of patients with stage II colorectal cancer, although the absolute improvements were small. Sargent D. et al.¹¹⁾ compared the use of surgery alone with surgery and FU-based adjuvant chemotherapy and found adjuvant chemotherapy to be associated with a significant improvement in 8-year overall survival (72.2% versus 66.8%; $p=0.026$). Lin BR et al.¹²⁾ compared the use of surgery alone with surgery and oral uracil and tegafur (UFT) adjuvant chemotherapy and found adjuvant chemotherapy to be associated with a significant improvement in 5-year overall survival (89.1% versus 84.2%; $p=0.018$).

On the other hand, a literature-based meta-analysis by an ASCO panel working in collaboration with the Cancer Care Ontario Practice Guideline Initiative⁸⁾ found no evidence of any statistically significant survival benefits for adjuvant chemotherapy in stage II patients. The authors concluded that the

routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended, although it can be considered in high-risk patients (those with inadequately sampled nodes, T4 lesions, perforation or poorly-differentiated histology). Using the Surveillance, Epidemiology and End Results (SEER) -Medicare database¹³⁾, either with or without poor prognostic features, adjuvant chemotherapy was not found to substantially improve overall survival among patients with stage II colon cancer.

In the American Joint Committee on Cancer study¹⁴⁾, T4aN0 and T4bN0 in stage II were found to be associated with a poorer prognosis than T1-2N1a and T1-2N1b in stage III in terms of 5-year relative survival rates. Therefore, administering adjuvant chemotherapy is thought to be necessary in groups at a high risk for recurrence of stage II colorectal cancer. The National Comprehensive Cancer Network (NCCN) guidelines¹⁵⁾ recommend that the use of adjuvant chemotherapy be considered in patients with stage II colorectal cancer, such as those with <12 regional lymph nodes examined, T4 lesions, perforation, peritumoral lymphovascular involvement, poorly-differentiated adenocarcinoma or perineural invasion.

In the MOSAIC trial¹⁶⁾, the use of LV5FU2 in addition to oxaliplatin (FOLFOX4) was compared with LV5FU2 alone in patients with stage II disease. The probabilities of surviving to six years were 86.9% and 86.8% in the FOLFOX4 and LV5FU2 groups, respectively (HR=1.00; 95% CI, 0.70 to 1.41; $p=0.986$). In an exploratory analysis, the probabilities of OS at six years in high-risk stage II patients (at least one of the following: T4 disease, tumor perforation, bowel obstruction, poorly-differentiated tumors, venous invasion or less than 10 lymph nodes examined) were 85.0% and 83.3% in the FOLFOX4 and LV5FU2 groups, respectively (HR=0.91; 95% CI, 0.61 to 1.36; $p=0.648$). This trial did not demonstrate any effectiveness of adding oxaliplatin.

Our study showed that the presence of lymphatic invasion was an independent prognostic factor in patients with stage II colorectal cancer. We evaluated lymphatic invasion using Hematoxylin-Eosin (HE) staining. Because evaluating lymphatic invasion is frequently difficult by means of HE staining alone, the additional use of D2-40 immunostaining, which is useful for evaluating lymphatic invasion, is

therefore considered to be essential in order to accurately evaluate colorectal cancer specimens. Developing objective criteria based H-E staining alone may therefore be difficult. However, the use of D2-40 staining is not standard for most general hospitals, and its high cost and the need for a pathological analysis make its use problematical. Yet, it is not necessary to use D2-40 staining for all patients. D2-40 staining should therefore be considered when lymphatic invasion cannot be fully evaluated by some pathologists.

We identified patients with stage II colorectal cancer with lymphatic invasion as being at high risk. Adjuvant chemotherapy might offer survival benefits in such patients. However, the administration of adjuvant chemotherapy in the patients with high risk factors did not improve the 5-year overall survival rates. In addition, our study is associated with some limitations. This study retrospectively examined the risk factors for recurrence of stage II colorectal cancer and the usefulness of adjuvant chemotherapy. The decision whether to administer adjuvant chemotherapy was not standardized in our department and was left to the clinical discretion of the attending physician. The drugs used for adjuvant chemotherapy and the duration of therapy differed. Various genetic and molecular biomarkers, including microsatellite instability (MSI), loss of heterozygosity at chromosome 18q (LOH18q) and thymidylate synthase¹⁷⁾, were not investigated. However, we identified the subgroup of patients at high risk by investigating the clinicopathological features of 414 patients who underwent standard curative resection at the same institution. Furthermore, this study examined many regional lymph nodes (median N=35); therefore, the results are credible. Considering the usefulness of various genetic and molecular biomarkers, adjuvant chemotherapy should be aggressively administered to stage II colorectal cancer patients with lymphatic invasion.

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