

## Risk Factors of Stage II Colon Cancer : A Comparison between the Right-Side and Left-Side Colon

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**Abstract :** Aims : Although approximately 25-35% of all patients with stage II colon cancer experience a tumor relapse, so far no specific therapy has been established. In this retrospective study, we attempted to identify the characteristics predictive of a poor prognosis in stage II colon cancer patients. Patients and Methods : From 1991 to 2000, 123 stage II patients underwent surgery at our institution. Using the Cox proportional hazards model, we divided patients into two groups (groups R and L). Results : An analysis revealed no differences in the sex, gross appearance, tumor depth, lymphatic invasion, and venous invasion between the two groups. However, regarding the pathological grade, a significant difference was seen between the two groups ( $p=0.005$ ), and the rate of group R was significantly lower than that of group L (80.8%, 96%,  $p=0.027$ , log-rank test). Conclusions : Right-side colon cancer patients with a high tumor grade were thus found to have a poor prognosis in stage II. These patients should therefore receive chemotherapy.

**Key words :** Colon cancer, Risk factors, Poor prognosis, Stage II

### Introduction

Colorectal cancer is a worldwide public health concern and it is a frequently occurring disease with increasing incidence. Its prognosis has recently improved because of progress in both diagnostic and therapeutic procedures. However, optimal surgery with a curative intent may also often be followed by an unfavorable course of the disease, primarily due to the occurrence of distant metastasis during follow-up. The prognosis of the newly diagnosed colon cancer patient is determined by the clinicopathologic stage of the disease. Approximately 25-35% of patients with stage II disease experience a tumor relapse, usually within 5 years of surgery,<sup>1)</sup> and the overall survival in this group of patients is 70% to 80% at 5 years after surgery.<sup>2)</sup>

In 1990, a review by the National Institutes of Health indicated that adjuvant therapy with FU and levamisole was recommended for patients with stage II colon cancer because clinical trials had shown that disease relapse and mortality decreased by 30-40% at 5 years, but they did not recommend any specific therapy outside of a clinical trial for patients with stage II disease.<sup>3)</sup> However, a substantial number of patients tend to develop recurrence within 5 years in stage II.

The aim of this retrospective study was to identify the characteristics predictive of a poor prognosis in stage II colon cancer patients.

### Materials and Methods

Between January 1991 and April 2000, 402 patients with histologically confirmed adenocarcinoma of the colon underwent surgery at our institution.

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A colon resection was performed with a formal regional lymph node dissection. This group comprised 123 stage II patients. Patient staging was determined according to the International Union Against Cancer (UICC) TNM classification system. The patients with rectal cancer were excluded from this study, and there were no patients with hereditary nonpolyposis colon cancer. First, to determine the risk factors for stage II colon cancer, we calculated the risk ratios using a Cox proportional hazards model. Our results showed only tumor location to be a risk factor for stage II colon cancer survival (Table 1). According to this finding, we divided the patients into two groups (groups R and L).

The right colon (group R) was defined as the cecum, ascending colon, and transverse colon. The left colon (group L) was defined as the descending colon and sigmoid colon. In these two groups we investigated any differences between the groups. Clinicopathological variables including age, sex, tumor gross appearance, pathological findings, and long-term survival were analyzed. In the tumor gross appearance, patients were divided into 2 groups, namely less than 2 tumors or more than 3. As for the tumor depth, the patients were divided also into 2 groups, a depth less than the subserosa or greater. In the pathological findings, the patients were divided into two groups less than poorly differentiated adenocarcinoma or more than moderately differentiated adenocarcinoma.

A statistical analysis was performed using the

**Table 1** Risk ratios using a Cox proportional hazards model

Factor	Relative risk	P value
Sex	1.094	0.839
Location	5.144	0.046
Appearance	4.525	0.072
Tumor depth	2.020	0.522
Age	1.004	0.886
Pathology	2.198	0.243

Location : Two groups were distributed at the splenic fracture.  
 Appearance : The patients were divided into groups with less than 2 or more than 3  
 Tumor depth : The patients were divided into groups with less than subserosa or not  
 Pathology : The patients were divided into a less than moderate group or a poor group

software program SAS version 5.0. The distribution age was compared using a two-sample t-test. The Pearson chi-square test was used for a comparison of sex, tumor appearance, and pathological findings. The survival curves were generated by the Kaplan-Meier method. Differences in the survival rate were determined using the logrank test.

## Results

From 1991 to 2000, 402 patients with histologically confirmed adenocarcinoma of the colon underwent surgery at our institution. A colon resection was performed with a formal regional lymph node dissection. There were 123 stage II patients in this group. Initially, Cox's regression hazard model was used to assess the influence on survival. As shown in Table 1, we analyzed 6 factors, including sex, tumor location, tumor gross appearance, tumor depth, age and pathological findings. In the results, the tumor location was only found to be independent of the prognostic factors for long-term survival. Consequently, we divided the patients into two groups (right side and left side).

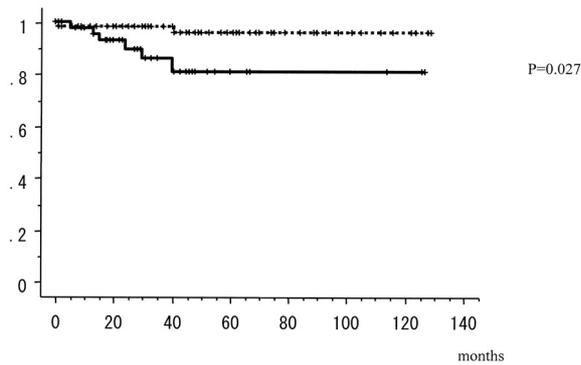
Fifty-six patients belonged to group R and 67 patients to group L. The patient characteristics are summarized in Table 2. There was no significant difference in the sex, gross appearance, tumor depth, lymphatic invasion, or venous invasion. Regarding age, the patients of group R were older than those of group L.

Regarding the pathological grade, a significant difference was seen between the two groups

**Table 2** Characteristics of 123 patients who belonged to stage II

	Group R	Group L
Age	69.6±11.6	63.6±11.9
male/female	33/23	31/36
Appearance	49/5	62/7
Tumor depth	40/8	41/13
Pathology	29/26	52/16

Appearance : The patients were divided into groups with less than 2 or more than 3  
 Tumor depth : The patients were divided into groups with less than subserosa or not  
 Pathology : The patients were divided into a less than moderate group or a poor group



**Fig. 1** The overall 5-year survival rate was 90.5%. The rate of group R was significantly lower than that of group L (80.8%, 96%,  $p=0.027$ , log-rank test).  
(Solid line=group R dotted line=group L)

( $p=0.005$ ). In group R, 6 patients died, including 2 cecal and 4 transverse patients. In group L, 2 sigmoid colon patients died.

The overall survival rate was 90.5%, with the rate of group R being significantly lower than that of group L (80.8%, 96%,  $p=0.027$ , log-rank test) (Fig. 1).

### Discussion

Many trials have continued to show benefits for adjuvant therapy in patients with stage III disease, whereas its value has remained doubtful for stage II patients. In addition, none of the individual trials reviewed showed a significant benefit in the overall survival for the adjuvant treatment of stage II colon cancer in comparison to other observations.<sup>4)-14)</sup>

In 2004, the American society of clinical oncology indicated that it did not recommend the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer, but that there are populations of patients with stage II disease that could be considered for adjuvant therapy, including patients with inadequately sampled nodes, T4 lesions, perforation, or a poorly differentiated histology.<sup>15)</sup>

Although patients with stage II colon cancer are generally considered to have a good prognosis after surgery alone, approximately one-quarter will experience recurrence within 5 years. More complete knowledge regarding the prognosis and predictive

factors will allow clinicians to identify those patients at higher risk of recurrence who are more likely to benefit from adjuvant chemotherapy as opposed to those at lower risk for recurrence and death, and thus are unlikely to derive any benefit.

Rectal cancer is sometimes different from colon cancer regarding the site of recurrence and the survival rate. Patients with rectal cancer were therefore excluded from this study.

The survival rate of group R was found to be lower than that of group L. This result is the reverse of that reported by Merkel.<sup>16)</sup> Merkel indicated that patients with hereditary nonpolyposis colorectal carcinoma, who tend to have tumors located in the right colon, have a lower stage at the time of diagnosis and they also have a better prognosis. In our study, there were no patients with hereditary nonpolyposis colon carcinoma, which may have influenced the survival rates. It appears, however, that patients with left-side colon in which feces become hard tend to have lower-stage lesions at the time of diagnosis and therefore have a better prognosis.

Right-side colon cancer patients were significantly younger than left-side patients. It is possible in this study that the age influenced the survival rate, but no significance was shown by a Cox regression analysis for survival ( $p=0.886$ ). Elderly patients with colon cancer do not have an inferior disease-free survival in comparison to younger patients.<sup>17)18)</sup> It is therefore thought that age might not influence the survival rate.

Sharlene et al<sup>19)</sup> have reported that the nodal status, T stage, and tumor grade are prognostic factors that are independently significant for both the disease-free survival and overall survival, and that treatment benefits are consistent across sex, location, age, T stage, and tumor grade.

As also suggested in the results mentioned above, only the tumor grade was found to be an independent factor in the present study. Our results suggest that right-side stage II colon cancer patients with a high tumor grade have poor prognosis. These patients should therefore receive chemotherapy.

In stage II colon cancer patients, a large group of patients who may remain disease-free without adjuvant therapy may thus be overtreated, whereas

a second group may develop disease recurrence despite adjuvant therapy. However, there may well be a third group of patients who would indeed benefit from adjuvant chemotherapy, thus helping them to remain free of recurrence. As a result, only certain subgroups of patients with stage II carcinoma are likely to benefit from adjuvant chemotherapy. In the future, a large-scale study should be designed to identify such patients.

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(Received on December 20, 2005,

Accepted on April 3, 2006)