Indication and Efficacy of Adjuvant Chemotherapy with Oral Fluoropyrimidines for Dukes’ B Colorectal Cancer

KAZUHIKO YOSHIMATSU, ARIHIRO UMEHARA, KEIICHIRO ISHIBASHI, HAJIME YOKOMIZO, KIYOHITO YOSHIDA, TAKASHI FUJIMOTO, KIYO WATANABE and KENJI OGAWA

Department of Surgery, Tokyo Women’s Medical University Medical Center East, 2-1-10 Nishiogu Arakawaku Tokyo, 116-8567, Japan

Abstract. Background: Identifying patients prone to colorectal cancer recurrence is of importance in providing appropriate adjuvant chemotherapy. In this retrospective study on Dukes’ B colorectal cancer, patients at high risk of recurrence were identified by clinicopathological factors, and the efficacy of adjuvant chemotherapy with oral fluoropyrimidines was evaluated. Patients and Methods: The subjects were 229 patients with Dukes’ B colorectal cancer who had undergone curative surgical resection. The relationship between each factor and cancer-related survival was examined. Results: In all the patients, the 5-year cumulative survival rate was 83.5% and the recurrence rate was 20.1%. The multivariate analyses indicated that the depth of invasion was the most significant prognostic factor. The cases with tumor exposed at the serosa or which invaded other organs were considered as a high-risk group. The 5-year survival rate in high-risk patients with adjuvant chemotherapy was significantly better than those without chemotherapy (75.8% and 44.0%, respectively, p=0.0008). The patients who received chemotherapy tended to show a decrease in the recurrence rate, especially in the liver and lung (p=0.0346). Conclusion: In Dukes’ B colorectal cancer, the cases with invasion depth se or si were considered to be at high risk of recurrence or death. Adjuvant chemotherapy was effective for such high-risk patients, especially decreasing recurrence in the liver and lung.

Although the primary curative therapy for colorectal cancer is surgical resection, patients with locally advanced cancer have a significantly increased risk of relapse after surgical resection alone (1). Within the last 15 years, prospectively randomized, appropriately powered clinical trials have convincingly demonstrated that adjunctive postoperative adjuvant chemotherapy is of benefit to all patients with node-positive disease (Dukes’ C) and, arguably, to high-risk node-negative (Dukes’ B) cases (1). Adjuvant chemotherapy for patients with Dukes’ B colon cancer is a controversial subject. Because the available data suggest that Dukes’ B patients benefit from adjuvant chemotherapy, although to a lesser extent than patients with Dukes’ C disease, all patients with Dukes’ C and high-risk Dukes’ B disease should be offered adjuvant treatment (2-10).

A literature-based meta-analysis found no evidence of a statistically significant survival benefit of adjuvant chemotherapy for TNM stage II patients (7, 11). The routine use of adjuvant chemotherapy for medically fit patients with TNM stage II colon cancer is not recommended (7, 11). However, there are populations of patients with TNM stage II disease that could be considered for adjuvant therapy, including patients with inadequately sampled nodes (12), T4 lesions (13), bowel obstruction (14), or poorly-differentiated histology (15). A recent pooled analysis of data from seven trials observed a benefit from adjuvant therapy in a multivariate analysis for both disease-free and overall survival (16). The disease-free survival benefits appeared to extend to TNM stage II patients; however, no p-values were provided. A meta-analysis was conducted using data on TNM stage II patients where data were available (n=4,187). The mortality risk ratio was 0.87 (95% CI, 0.75 to 1.01; p=0.07) (16).

It is important to identify a subgroup of patients with the highest risk of relapse because of the potential benefit of adjuvant chemotherapy (8-10). Many clinical, histopathological (13-15, 18-21) and biomolecular variables (22-25) have been investigated to select high-risk patients (26). However, only a few reports have assessed variables with multivariate analysis.

The aims of this study were to retrospectively examine the prognostic value of routinely assessable clinicopathological factors to identify subgroups of Dukes’ B colorectal cancer patients at high risk of recurrence and death, and to assess...
adjuvant chemotherapy with oral fluoropyrimidines for the high-risk subgroup.

### Patients and Methods

**Patients.** The subjects included 229 patients with Dukes' B colorectal cancer, who had undergone curative resection in our department from 1991 to 2000. The clinicopathological factors, according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (27), obtained at the time of primary surgery were analyzed to evaluate their correlation with disease-related survival.

**Statistics.** The Kaplan-Meier method was applied to examine the effects of the different variables on cancer-related survival. In the univariate analysis, differences in survival were assessed using the log-rank test. Variables found to be univariately associated with survival were evaluated by multivariate analysis using Cox proportional hazard regression. The level for statistical significance was determined at $p=0.05$, and confidence intervals were determined at the 95% level.

### Results

The average age of the all patients was 64.8 (range 29-93 years). There were 127 males and 102 females. The 5-year cancer-related survival rate was 83.5% and recurrence rate was 20.1% (Figure 1).

Univariate analysis for cancer-related survival is summarized in Table I. CEA, CA19-9, histological type, lymphatic invasion, venous invasion, depth of invasion, number of dissected nodes and adjuvant chemotherapy were significantly correlated with cancer-related survival.

The multivariate analysis was subsequently performed for selection of factors in cancer-related survival. The depth of invasion, number of dissected nodes and adjuvant chemotherapy were identified as prognostic factors in Dukes' B (Table II). Because the depth of invasion was the most significant factor for cancer-related survival (hazard ratio: 2.826, $p=0.0186$), the 64 patients with tumor exposed at the serosa or invasion of other organ (se, si) were identified as a high-risk group. The 161 patients with

![Figure 1. Overall survival and recurrence rates in Dukes' B patients.](image)
tumor invasion under the subserosa (ss) were considered to be the low-risk group.

Adjuvant chemotherapy with oral fluoropyrimidines such as UFT was administered to 114 patients in the low-risk group and 44 patients in the high-risk group. In the low-risk group, the 5-year survival rates with or without adjuvant chemotherapy were 91.8% and 87.9%, respectively (Figure 2). On the other hand, the 5-year survival rate in the high-risk patients with adjuvant chemotherapy was significantly better than those without chemotherapy (75.8% and 44.0%, respectively, \( p = 0.0008 \)) (Figure 3).

The recurrence site in the high-risk group with or without chemotherapy was investigated regarding the effect of adjuvant chemotherapy. Recurrence in the liver or lung was observed in two cases with adjuvant chemotherapy, but in five cases without therapy (Table III). The patients treated with chemotherapy showed a significant decrease in the recurrence rate, especially in the liver and lung (patients with chemotherapy: 4.5%, without chemotherapy: 25.0%, \( p = 0.0346 \)).

Discussion

Burdy et al. (14) examined the clinical and pathological findings associated with tumor recurrence in T3-T4 node-negative colon cancer patients. In multivariate analysis, male gender \( (p = 0.005) \), bowel obstruction \( (p = 0.002) \), pericolic organ invasion \( (i.e., \) T4 tumor; \( p = 0.02 \)) and less than 14 uninvolved nodes on a specimen \( (p = 0.01) \) were found to be independent factors. On the other hand, CEA, size and tumor location, blood transfusion and mucin production were not associated with a higher risk of tumor recurrence. Swanson et al. (12) examined data from the National Cancer Data Base (NCDB) to determine whether the number of examined lymph nodes was prognostic for T3N0 colon cancer and concluded that the prognosis of T3N0 colon cancer was dependent on the number of lymph nodes examined. A minimum of 13 lymph nodes should be examined to label a T3 colon cancer as node-negative.

Table II. Multivariate analysis for survival of Dukes' B patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (positive/negative)</td>
<td>2.342</td>
<td>0.3990</td>
</tr>
<tr>
<td>CA19-9 (positive/negative)</td>
<td>1.302</td>
<td>0.5397</td>
</tr>
<tr>
<td>Histological type (poor/others)</td>
<td>1.905</td>
<td>0.2107</td>
</tr>
<tr>
<td>ly (positive/negative)</td>
<td>1.302</td>
<td>0.2827</td>
</tr>
<tr>
<td>v (positive/negative)</td>
<td>1.656</td>
<td>0.2435</td>
</tr>
<tr>
<td>Depth (se, si/ss)</td>
<td>2.826</td>
<td>0.0186</td>
</tr>
<tr>
<td>Dissected lymph nodes (≤11/12≤)</td>
<td>2.211</td>
<td>0.0480</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>2.974</td>
<td>0.0286</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

ly, lympatic invasion; v, venous invasion.

Table III. Recurrent site in high-risk group with or without chemotherapy.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>performed (n=44)</th>
<th>not performed (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver/lung</td>
<td>2 (4.5%)</td>
<td>5 (25.0%)</td>
<td>0.0346</td>
</tr>
<tr>
<td>Lymph node</td>
<td>1 (2.3%)</td>
<td>1 (5.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Local/peritoneum</td>
<td>7 (15.9%)</td>
<td>6 (30.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.5%)</td>
<td>0 (0.0%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns, not significant.
Fabio et al. (13) reported that multivariate analysis showed that T4 stage and age (>70) significantly affected cancer-related survival. In our study, the depth of invasion, number of dissected nodes and adjuvant chemotherapy were identified as prognostic factors in Dukes’ B cases, these results being similar to those previously reported.

In Japan, oral fluoropyrimidines have been widely used for long-term adjuvant chemotherapy since two immunochemotherapy clinical trials demonstrated a significant effect against minimal residual disease in colorectal cancer (28, 29). One of the advantages of oral fluoropyrimidines is that oncologists can prescribe these agents on an outpatient basis for longer periods without much fear of a severe adverse drug reaction (30). Several reports demonstrated that adjuvant chemotherapy with intravenous administration provided only a small or no benefit for disease-free and overall survival in patients with stage II colon cancer (5-7, 31, 32).

On the other hand, the meta-analysis by Sakamoto et al. (33) showed that the oral fluoropyrimidines improve disease-free survival and survival of patients after resection of early-stage, including stage II, colorectal cancer. Since depth of invasion was the only tumor-related and most significant factor for cancer-related survival, we chose those patients with tumor exposed at the serosa or with invasion of other organs as a high-risk group to investigate the efficacy of adjuvant chemotherapy with oral fluoropyrimidines. Our retrospective analysis showed the efficacy of the oral fluoropyrimidines on cancer-related survival and hematogenic metastasis in a high-risk group of Dukes’ B patients. To clarify these clinical benefits, a randomized control study is needed. These chemotherapeutic agents could prove very attractive in terms of patient quality of life and also in terms of the cost-effectiveness of the chemotherapy.

References


