Postoperative Lymphocyte Percentage Influences the Long-term Disease-free Survival Following a Resection for Colorectal Carcinoma

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Objective: The aim of this study is to examine the relationship between postoperative laboratory parameters of inflammation and the disease-free survival in patients undergoing resection for colorectal cancer.

Methods: Six hundred seventy-five consecutive patients who underwent an elective resection for primary colorectal cancer from October 1999 to March 2004 were included in this study. We examined the associations between cancer recurrence and white blood cell count, lymphocyte percentage, neutrophil percentage and C-reactive protein.

Results: Lymphocyte percentage on postoperative days 3 and 7 was significantly higher in patients without recurrence than in those with recurrence. Lymphocyte percentage on postoperative day 7 differed the most between the two groups. On postoperative day 7, Stage II patients with lymphocyte percentage \( \geq 15\% \) had significantly longer survival compared with the patients with lymphocyte percentage \( \leq 15\% \). A multivariate analysis showed lymphocyte percentage \( \geq 15\% \) on postoperative day 7 to be an independent prognostic factor, along with lymph node metastases and serosal invasion. Logistic regression analysis showed that blood loss (>250 ml) and postoperative complications were significant independent predictors of lymphocyte percentage \( \leq 15\% \) on postoperative day 7.

Conclusions: Lymphocyte percentage \( \leq 15\% \) on postoperative day 7 is an independent prognostic factor for the patients undergoing a resection for colorectal cancer.

Key words: colorectal carcinoma – lymphocyte percentage – less invasive surgery

INTRODUCTION

Surgery remains the definitive treatment for advanced colorectal cancer. However, major surgery causes significant alterations in metabolic, immune and endocrine functions. It has been well documented that major surgery alters multiple immune parameters and accelerates tumor growth (1–4). Links between cancer and inflammation have not been elucidated. In some types of cancer, inflammatory conditions are present before a malignant change occurs. The mediators and cellular effectors of inflammation are important constituents of the local environment of tumors (5). Some studies show that the presence of inflammation is correlated with poor prognosis in the patients with malignancies (6,7). However, the impact of the postoperative inflammatory response on the recurrence of cancer has not been elucidated.

Laparoscopic surgery has led to great progress in the treatment of colorectal cancer. Recently, published randomized trials comparing laparoscopic and open surgery do not show inferior oncologic results in patients who undergo laparoscopic surgery (8,9). Lacy et al. (10) report significant improvement in 3-year survival in patients with advanced stage cancer who undergo laparoscopic surgery. The better survival might be attributed to the favorable immunologic response and lower stress response in patients who have undergone laparoscopic surgery.

The prognostic value of biological markers in patients with advanced cancer has been investigated in palliative care. There is some evidence that abnormalities in certain laboratory parameters [e.g. leukocytosis, lymphocytopenia and an elevated C-reactive protein (CRP) level] have prognostic values (11). However, the prognostic values of these
parameters in the perioperative period have not yet been examined in patients undergoing potentially curative surgery.

We examined the preoperative and postoperative white blood cells (WBCs), neutrophil percentage (NEUTRO%), lymphocyte percentage (LYMPH%) and level of CRP. The aim of this study is to clarify the impact of these parameters on the recurrence of cancer.

PATIENTS AND METHODS

Patients

Patients with histologically proven colorectal cancer who had undergone a potentially curative resection and had routine laboratory findings were included in this study. We retrospectively reviewed a database of 675 patients between August 1999 and March 2004 at the National Cancer Center East. Demographic and clinical data (age, sex, tumor location, tumor stage, differentiation, carcinoembryonic antigen (CEA) level, surgical approach, operating time, blood loss and postoperative complication) were collected. Patients with an emergency operation, non-curative resection, no laboratory data or preoperative chemoradiotherapy were excluded. The surgical approach was decided with the consent of the patients after thorough discussion on the advantages and disadvantages of the approaches. Patients with large, fixed tumors with invasion to other organs were advised against laparoscopic resection.

Data Collection

Routine laboratory measurements were taken before the operation and on postoperative days (PODs) 1, 3 and 7. In all blood samples, WBC, LYMPH%, NEUTRO% and CRP were measured.

Statistical Analysis

The statistical analysis was performed using the SPSS 11.0.1 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Comparisons of categorical ordinal variables were performed using the Pearson χ² test. The Mann–Whitney U-test was used to compare laboratory data at each time point between two groups. Survival rates were calculated with the Kaplan–Meier method, and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model. Logistic regression analysis was used to estimate the odds ratio with 95% confidence intervals for LYMPH% ≤ 15%. A P value of <0.05 was considered to be statistically significant.

RESULTS

The median follow-up duration was 46.3 months. Within the observation period, 124 patients developed recurrence. We compared laboratory data (WBC, LYMPH%, NEUTRO% and CRP) from patients with recurrence and those without recurrence. WBC and NEUTRO% on PODs 3 and 7 in patients without recurrence were significantly lower than in those with recurrence (Fig. 1a and c). LYMPH% on PODs 3 and 7 in the patients without recurrence was significantly higher than in patients with recurrence (Fig. 1b). The difference in LYMPH% on POD 7 (LYMPH%7POD) was most evident between the two groups. We compared clinicopathological factors and disease-free survival according to LYMPH%7POD. The patients with ≤15% LYMPH%7POD were classified in the low group and those with more than 15% LYMPH%7POD were classified in the high group. The median of LYMPH%7POD was 15.8%.

The correlation between clinicopathological factors and LYMPH%7POD are shown in Table 1. LYMPH%7POD was significantly correlated with gender (P = 0.01), tumor location (P < 0.01) and tumor stage (P < 0.01). Disease-free survival was significantly higher (P < 0.01) in the LYMPH%7POD > 15% group than in the LYMPH%7POD ≤ 15% group (Fig. 2). Three-year survival rates in patients with LYMPH%7POD ≤ 15% and in those with LYMPH%7POD > 15% were 70.7 and 85.1%, respectively. More patients with advanced stage cancer had LYMPH%7POD ≤ 15%; therefore, disease-free survival was compared according to TMN tumor stage. As shown in Fig. 3, patients with LYMPH%7POD > 15% had longer survival compared with those with LYMPH%7POD ≤ 15% in Stage II. Only three patients with Stage I tumors had recurrence, and there was no significant difference between the two groups in Stage I. Disease-free survival in the patients with Stage III and VI tumors was longer in the LYMPH%7POD > 15% group, but the difference was not statistically significant. To determine the importance of the LYMPH%7POD as a predictor of disease recurrence, a multivariate analysis using the Cox proportional hazards model was performed. The analysis identified LYMPH%7POD ≤ 15% as an independent prognostic factor, along with lymph node metastases and serosal invasion (Table 2).

DISCUSSION

To date, laboratory parameters, such as CRP (6,7), lymphocytopenia and leukocytosis (12,13), have been described as significant prognostic factors in patients with advanced
cancer. However, little information is available regarding the prognostic role of postoperative laboratory parameters in patients undergoing resection for colorectal carcinoma. In this study, we evaluated whether postoperative laboratory data, such as WBC, LYMPH%, NEUTRO% and CRP, are associated with recurrence of colorectal carcinoma. This study demonstrated LYMPH%7POD ≤ 15% to significantly correlate with the recurrence of carcinoma as well as lymph node metastases and serosal invasion.

Figure 1. White blood cell (WBC), lymphocyte percentage (LYMPH%), neutrophil percentage (NEUTRO%) and C-reactive protein (CRP) in patients undergoing resection for colorectal carcinoma. Sample points were taken preoperative (PRE) and on postoperative days 1 (1POD), 3 (3POD) and 7 (7POD) (P \( < 0.05 \)).

Table 1. The correlation between clinicopathological factors and LYMPH%7POD

<table>
<thead>
<tr>
<th>Clinicopathological Factors</th>
<th>LYMPH%7POD &gt; 15% (n = 248)</th>
<th>LYMPH%7POD ≤ 15% (n = 258)</th>
<th>P value</th>
</tr>
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<tr>
<td>Median age</td>
<td>63.6</td>
<td>62.6</td>
<td>0.31</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>143/105</td>
<td>178/80</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumor location</td>
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<td></td>
</tr>
<tr>
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<td>52</td>
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</tr>
<tr>
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<td>23</td>
<td>17</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>41</td>
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<tr>
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<td>152</td>
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</tr>
<tr>
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<td>68</td>
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<td>88</td>
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</tr>
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<tr>
<td>Poorly and others</td>
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LYMPH%7POD, lymphocyte percentage on postoperative day 7.

Figure 2. The disease-free survival rates of the patients with LYMPH%7POD > 15% and those with LYMPH%7POD ≤ 15%.

disease this study, we evaluated whether postoperative laboratory data, such as WBC, LYMPH%, NEUTRO% and CRP, are associated with recurrence of colorectal carcinoma. This study demonstrated LYMPH%7POD ≤ 15% to significantly correlate with the recurrence of carcinoma as well as lymph node metastases and serosal invasion.

The LYMPH% is an important parameter in patients with advanced cancer (11,14,15). Some reports demonstrated that the neutrophil–lymphocyte ratio predicts survival in patients with colorectal cancer (16–18). Our results suggest that decreased LYMPH% may indicate an impaired host immune response to the tumor or inflammatory conditions that are
associated with recurrence of the tumor. It is well known that lymphocytes are the most important factor in the antitumor immune system. Patients with decreased LYMPH% may exhibit a poorer lymphocyte-mediated immune response to malignancy, thereby increasing the risk of tumor recurrence. There is no correlation between LYMPH% and mode of recurrence. This study showed the difference in LYMPH% between the recurrent group and the non-recurrent group was evident on POD 7. During postoperative course, the condition of patients on POD 7 may be the most symbolic state of the recovery after surgery.

The LYMPH% shows a relative decrease in cases with inflammation. The connection between inflammation and cancer is now generally accepted. In some types of cancer, inflammatory conditions are present before a malignant change occurs.

However, it is not clear whether postoperative inflammation increases the recurrence of cancer. The relationship between surgical stress and host resistance to cancer was demonstrated in a murine model. Eggermont et al. (19) showed that a surgical procedure with entry into the abdominal cavity resulted in augmented tumor growth; conversely, a surgical incision on the animal’s back did not promote tumor growth. Some authors show that anastomotic leak is associated with poor survival or local recurrence (20,21). These results suggest that acute inflammatory response may promote tumor spread and metastases. The LYMPH% may be a good indicator of systemic inflammatory response.

We demonstrated that LYMPH%7POD was significantly correlated with gender, tumor location and tumor stage. The reason for the association is speculative at present. The surgery for the patients with these variables may be more invasive and postoperative inflammatory response for these patients may be increased. We also demonstrated that blood loss (>250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD ≤ 15%. Surgical techniques that minimize blood loss and postoperative complications may be associated with improved postoperative immune and nutritional status that promote long-term disease-free survival. In this study, laparoscopic surgery tended to show a decreasing LYMPH%7POD, but the decline was not significant. The LYMPH% may also be a good indicator of the immune and nutritional status in the postoperative period.

In conclusion, our data demonstrated an association between LYMPH% on POD 7 and cancer recurrence. The postoperative
LYMPH% may be a good anti-inflammatory marker and a sensitive predictor of cancer recurrence in colorectal cancer.

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**Conflict of interest statement**

None declared.

**References**