Prognostic criteria in colorectal carcinoma constructed by the combination of tumor-related and host-related factors

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KEYWORDS: Colorectal carcinoma; Tumor-related factor; Host-related factor; C-reactive protein; Lymph node metastasis; Prognostic indicator

Abstract

BACKGROUND: The significance of prognostic criteria based on a combination of tumor-related and host-related factors for patients with colorectal carcinoma has not been appreciated fully.

METHODS: Correlation of tumor-related and host-related score (TRHRS), which are constructed by the combination of serum elevation of C-reactive protein and pathologic lymph node metastasis (scores ranging 0 to 2), with clinicopathologic features including prognosis was studied in 271 patients with colorectal carcinoma who had been treated with curative resection.

RESULTS: Significant difference regarding survival was observed both between TRHRS 0 and 1 ($P = .028$) and between TRHRS 1 and 2 ($P < .0001$). Multivariate analysis showed that histologic types ($P = .040$) and TRHRS ($P < .0001$) were independent prognostic indicators.

CONCLUSION: Criteria for the prediction of prognosis in colorectal carcinoma treated with curative resection based on both tumor-related and host-related factors could provide a strict stratification.

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Patient progression and invasion of human malignant tumors might be mediated by both tumor-related and host-related factors. Therefore, the criterion to determine the aggressiveness of the tumors and/or prognosis of the patients with malignant tumors should be formed based on these elements.

Lymph node metastasis can undoubtedly account for one of the tumor-related factors to measure the biological potential of the tumors and prognosis of the patients with malignant tumors.1,2

An inflammatory response to the tumors has been known as the most important factor concerning the progression and invasion of the tumors,3 and the serum elevation of the acute phase protein, C-reactive protein (CRP), can be the representative phenomenon in the host inflammatory response. Indeed, series of investigations have demonstrated the significance of serum elevation of CRP as a definitive prognostic indicator in some human tumors.4–8

In this study, we attempted to create an appropriate cumulative score, formed by both tumor-related and host-related factors, to determine the prognosis of patients with advanced colorectal carcinoma who had been treated with curative resection.

Patients and Methods

Patients, collection of blood samples, and measurement of C-reactive protein

Two hundred seventy-one patients with colorectal carcinoma, which had been treated by curative resection in our...
institute from 2003 to 2011, were enrolled in this study. Patients who have had malignant tumors in other organs or had other chronic inflammatory diseases influencing the value serum elevation of CRP were excluded from this study.

The patients were aged from 24 to 91 years with a mean of 70.7 and were composed of 166 men and 105 women. No neoadjuvant therapy had been given for the patients who had been enrolled in this study.

All blood samples to measure serum value of CRP were collected just before the operation and patients who had the serum concentration of >1.0 mg/dL were included in CRP positive group.

Pathologic investigation

Pathologic factors including depth and differentiation of the tumors, lymphatic invasion, and venous invasion were examined by 2 pathologists in our institute and the grade of the factors were determined according to TNM classification of malignant tumors prescribed by the International Union Against Cancer.9

Definition of tumor-related and host-related score

Among patients with colorectal carcinoma without lymph node metastasis (n = 153), the survival of patients who had serum elevation of CRP (n = 37) was significantly worse than that of patients who did not (n = 116, P = .0004; Fig. 1A). Similarly, among patients with lymph node metastasis (n = 118), the survival of patients who had serum elevation of CRP (n = 35) was significantly worse than that of patients who did not (n = 83, P < .0001; Fig. 1B). Therefore, combination of these factors was speculated to possibly form an appropriate criterion to determine prognosis of patients with colorectal carcinoma with a favorable prognostic stratification.

Then, patients who had both serum elevation of CRP and pathologic lymph node metastasis were allocated a tumor-related and host-related score (TRHRS) of 2. Patients who had only one and neither were allocated a TRHRS of 1 and 0, respectively.

Follow-up of the patients

The follow-up for patients was continued until their death and only patients who died of colorectal carcinoma were included in the tumor-related deaths. The period from the operation to the date of death was defined to be the survival time. The interval of the follow-up after operation ranged from 2 months to 8 years and 3 months.

Statistical analysis

All statistical analyses were performed using StatView (SAS Institute Inc, Cary, NC). Chi-square test and t test were used to compare the difference regarding values in each TRHRS. Survival curves were made by the Kaplan–Meier method, and the Mantel–Cox test was used to analyze the equality of the survival curves. Cox proportional hazards model in a forward stepwise manner was used in the multivariate analysis to determine the independent prognostic indicators. A P value of <.05 was considered significant.

Results

Correlation of the cumulative score (TRHRS) with clinicopathologic characteristics was shown in Table 1. Significant differences were observed regarding depth of tumors (P < .0001), histological types (P = .003), lymphatic invasions (P < .0001).

The prognosis of TRHRS 1 patients with a 5-year survival rate of 84.0% was significantly worse than that
of TRHRS 0 patients with a 5-year survival rate of 94.6% \((P = .028)\). And the prognosis of TRHRS 2 patients with a 5-year survival rate of 42.3% was significantly worse than that of TRHRS 1 patients \((P < .0001, \text{Fig. 2})\).

Depth of the tumors, lymphatic invasion, venous invasion, histologic type, as well as TRHRS proved to be factors correlated with the survival of the patients in the univariate analysis. Then, multivariate analysis with the entry of these factors demonstrated that histologic type \((P = .040)\) and TRHRS \((P < .0001)\) were factors that are independently associated with worse prognosis of the patients with colorectal carcinoma (Table 2).

## Comments

The number of patients with colorectal cancer has been increasing all around the world. Colorectal carcinoma is the second leading cause of cancer deaths in Europe and United States\(^\text{10}\) and moreover it accounts for the largest number of cancer deaths in woman and the third largest in men in our country.\(^\text{11}\) Therefore simple and convenient criteria to definitively predict patients’ outcome of this popular disease are required for both physicians and patients.

Moreover, it holds natural that prognosis of patients with less invasive colorectal carcinomas containing neither lymph node metastasis, lymphatic invasion, nor venous

### Table 1: Relationship between TRHRS and clinicopathologic factors

<table>
<thead>
<tr>
<th>TRHRS 0 ((n = 116))</th>
<th>TRHRS 1 ((n = 120))</th>
<th>TRHRS 2 ((n = 35))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (63.8)</td>
<td>69 (57.5)</td>
<td>23 (65.7)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (36.2)</td>
<td>51 (42.5)</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>Age</td>
<td>69.9 ± 11.2</td>
<td>70.6 ± 11.0</td>
<td>73.3 ± 10.5</td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>76 (65.5)</td>
<td>84 (70.0)</td>
<td>28 (80.0)</td>
</tr>
<tr>
<td>Rectum</td>
<td>40 (34.5)</td>
<td>36 (30.0)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Depth of tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>39 (33.6)</td>
<td>14 (11.7)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>T3</td>
<td>76 (65.5)</td>
<td>102 (85.0)</td>
<td>30 (85.7)</td>
</tr>
<tr>
<td>T4</td>
<td>1 (.9)</td>
<td>4 (3.3)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Histology*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>38 (32.8)</td>
<td>27 (22.5)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Moderately</td>
<td>73 (62.9)</td>
<td>83 (69.2)</td>
<td>22 (62.9)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>5 (4.3)</td>
<td>10 (8.3)</td>
<td>8 (22.8)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>90 (77.6)</td>
<td>51 (42.5)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (22.4)</td>
<td>69 (57.5)</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>Venous invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>89 (76.7)</td>
<td>85 (70.8)</td>
<td>26 (74.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (23.3)</td>
<td>35 (29.2)</td>
<td>9 (25.7)</td>
</tr>
</tbody>
</table>

Values in parenthesis are percentages.
TRHRS = tumor-related and host-related factor.
*Well = well differentiated adenocarcinoma; Moderately = moderately differentiated adenocarcinoma; Undifferentiated = poorly differentiated adenocarcinoma or mucinous carcinoma.

### Table 2: Factors independently determining prognosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic type (differentiated vs undifferentiated)</td>
<td>2.43 (2.60–11.5)</td>
<td>.040</td>
</tr>
<tr>
<td>TRHRS (0, 1 vs 2)</td>
<td>5.43 (1.04–5.68)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

TRHRS = tumor-related and host-related factor.

![Figure 2: TRHRS and survival curves.](image-url)
invasion is quite favorable and that prognosis of patients with far advanced tumor associated with metastatic tumors in the distant organs is extremely worse. Therefore an appropriate criterion to predict the outcomes should be mandatory, especially for patients with advanced tumors that could be treated with curative surgical resection.

Among many factors concerning tumor progression and invasion, clinical approach to predict the malignant potential of the tumors and outcome of the patients have been performed based on the 2 most important tumor-related and host-related factors.

Although Dukes’ stage criteria\textsuperscript{12} and the criteria of TNM classification of malignant tumors have been used as the most popular criteria to determine prognosis in colorectal carcinoma, incidence of lymph node metastasis included in these criteria accounts for one of the most prominent tumor-related factors reflecting the prognosis of patients with colorectal carcinoma that had been treated with curative resection.\textsuperscript{1} Although number of lymph nodes metastasized by cancer cells and ratio of the metastasized lymph nodes in the retrieved lymph nodes have been reported to be prognostic factors in colorectal carcinoma,\textsuperscript{13,14} in this study, to create an appropriate and simple criterion, the presence of lymph node metastasis was applied as a representative to evaluate the tumor-related factors in patients with colorectal carcinoma.

The dynamics of acute phase protein might account for the representative phenomenon in host-related factors concerning tumorigenesis and progression in human malignant tumors. Above all, serum elevation of CRP has been known as a chief host-responder to the tumors and has been reported as an indicator of malignant potential of the tumors and worse prognosis of patients with colorectal carcinoma that had been treated with curative resection.\textsuperscript{1} Although number of lymph nodes metastasized by cancer cells and ratio of the metastasized lymph nodes in the retrieved lymph nodes have been reported to be prognostic factors in colorectal carcinoma,\textsuperscript{13,14} in this study, to create an appropriate and simple criterion, the presence of lymph node metastasis was applied as a representative of tumor-related factors, can also be a convenient system to predict prognosis of colorectal carcinoma that had been treated with curative resection.

To predict the outcome of the patients with colorectal carcinoma, it could be quite important to consider the point of view in both aspects of tumor-related and host-related factors. TRHRS system that could be determined by the serum levels of CRP, a representative of host-related factors, and existence of lymph node metastasis, a representative of tumor-related factors, can also be a convenient and useful system to determine prognosis of colorectal carcinoma that had been treated with curative resection with a strict prognostic stratification.

\textbf{References}