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Relations of Serum CEA Levels to Clinicopathologic Variables and Proliferating Cell Nuclear Antigen (PCNA) Labeling Indices in Colorectal Cancer

Yoshiki Tabuchi¹, Takeshi Nakamura² and Shiro Nakae²

Relations of serum CEA levels to 13 clinicopathologic variables of cancer lesions and proliferating cell nuclear antigen (PCNA) labeling indices (LIs) of cancer cells were examined in 57 colorectal center patients. Six variables including deep invasion into the colorectal wall, lymphatic and venous invasion, node metastasis, liver metastasis and advanced stages were more in 28 patients with positive CEA levels (≥ 5.0 ng/ml) than in 29 patients with negative CEA levels (< 5.0 ng/ml). The mean (54.5%) of PCNA LIs in the former was significantly higher than that (44.1%) in the latter. A significant relationship representing by a formula, \( Y (\log \text{CEA, ng/ml}) = 0.026X (\text{PCNA LI, %}) - 0.478 \), was found between CEA levels and PCNA LIs. The results suggest that CEA produced by the cancer cells in the invaded vessels of the primary lesions and by the node and liver metastatic cancer cells enters the draining veins and/or lymphatics in the whole blood. Serum CEA levels is also suggested to increase semilogarithmically in parallel with the proliferative activity of cancer cells representing by PCNA LIs in the colorectal cancer lesions.

Key Words
serum CEA,
Clinicopathologic variables,
Proliferating cell nuclear antigen (PCNA),
Colorectal cancer,
Proliferative activity.

INTRODUCTION

Recently, the analysis of proliferating cell nuclear antigen (PCNA), which is DNA polymerase delta auxiliary protein¹ and accumulates in late G1 and early S-phases², has been available for the evaluation of cellular proliferative activity, using immunohistochemical staining of paraffin-embedded specimens. Thereafter, the relationships between PCNA labeling indices (LIs) and cancer progression and/or prognosis are vigorously examined in various cancers³⁻⁷. Meanwhile, carcinoembryonic antigen (CEA)⁸ is widely used as one of the most useful tumor markers⁹ for various cancers, especially for colorectal cancer, although several tumor markers have been recently developed. The main mechanism of serum CEA elevation has been clarified up to the last 30 years⁹,¹⁰,¹²⁻²⁶. However, the relationship between serum CEA levels and proliferative activity of primary cancer cells has not yet been examined.
In the present study, preoperative serum CEA levels, 13 clinicopathologic variables of cancer lesions and PCNA LIs in the primary cancer lesions were examined in 57 colorectal cancer patients, and their relationships were analyzed.

MATERIALS AND METHODS

1. Patients and serum CEA determination

Fifty-seven patients (median age: 64.7 years; range: 32-83 years), who underwent operative resection of colorectal cancer lesions during 3 years from 1991 to 1994, were included in this study. None of them had received anti-cancer therapy prior to the resection and showed any hepatobiliary dysfunction. Preoperative serum CEA levels just before the resection were determined by EIA method, using a CEA Dinapack Diagnostic kit (Dainabot Co., Tokyo, Japan). The cut-off levels were 5.0 ng/ml by this kit. Thus, the CEA levels greater and less than 5.0 ng/ml were treated as "CEA positive" and "CEA negative" respectively.

2. Clinicopathologic examination

Surgically removed specimens were immediately fixed in 10% neutral buffered formaldehyde solution and embedded in paraffin. The fixation time did not exceed 48 hours, to avoid the reduction of immunohistochemical activity of PCNA

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parts of an identical cancer tissue. PCNA LIs were expressed as the ratio (%) of PCNA positive cancer nuclei to all of the examined nuclei.

4. Statistic analysis

The data were analyzed by the Student's t test and the chi-square test or Fisher's exact probability calculation method. P values less than 0.05 were estimated to be significant.

RESULTS

1. Relations of CEA positive and negative patients to clinicopathologic variables

Table 1 shows the clinicopathologic variables in the CEA positive and negative patients. Significant differences in 6 clinicopathologic variables including depth of cancer invasion into the colorectal wall, lymphatic and venous invasion, node metastasis, liver metastasis and stage classification were found between both CEA positive and negative patients: the lesions with sm (a2) ~ sei (a3), lymphatic and venous invasion, node metastasis, liver metastasis and with stages III ~ IV were more in the CEA positive patients than in the CEA negative patients, Reversely, the lesions with ss ~ ss (a1), without lymphatic and venous invasion, without node and liver metastases and with stages I ~ II were more in the latter than in the former (Table 1). It a word, the
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Table 2. PCNA LI s in the patients with CEA negative and positive patients.

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<tr>
<th>CEA levels (ng/ml)</th>
<th>No.</th>
<th>PCNA LI (Mean±S.D.)</th>
<th>P value</th>
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<tr>
<td>CEA (&lt;5.0)</td>
<td>29</td>
<td>44.1±12.9</td>
<td></td>
</tr>
<tr>
<td>CEA (≥5.0)</td>
<td>28</td>
<td>54.5±11.5</td>
<td>P&lt;0.01</td>
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advanced cancer lesions were significantly more in the CEA positive patients than in the CEA negative patients.

2. Relationship between CEA levels and PCNA LI s

The mean of PCNA LI s in the CEA positive and negative patients were 54.5% and 44.1% respectively, and the mean in the former was significantly higher than that in the latter (Table 2). A significant relationship representing by a formula, \( Y = 0.026X - 0.478 \) (\( r = 0.598, P<0.001 \)), was found between the CEA levels and PCNA LI s (Fig. 2).

DISCUSSION

Several tumor markers have been developed, since CEA was identified by Gold and Freedman\(^9\). However, CEA is still widely used as one of the most available tumor markers in colorectal cancer. Recently, serum CEA levels are thought to be controlled by many pathophysiologic process\(^{10-26}\) including production of CEA by cancer cells\(^{9,10,15-17,23}\), release of CEA into the surrounding tissues and entrance into the blood-stream and/or lymphatics\(^{15,17,24-26}\), metabolic degradation and excretion by the liver\(^{11,20,26}\) and reabsorption from the intestinal wall\(^{16}\). However, the relationship between the proliferative activity of cancer cells and serum CEA levels has not yet been examined. Meanwhile, PCNA has been recently available for the evaluation of cellular proliferative activity\(^{1,2}\). Thereafter, the relationships between PCNA LI and cancer progression and/or prognosis are vigorously examined in various cancers, and the determination of PCNA LI is generally accepted as a simple method of cellular proliferative activity\(^3-7\). Thus, in this study, the relations of serum CEA levels to clinicopathologic variables of the cancer lesions and proliferative activity of cancer cells representing by PCNA LI s were examined in colorectal cancer.

The advanced cancer lesions with s (a1) sei (a3), lymphatic and venous invasion, node and liver metastases and stages III ~ IV were confirmed to be significantly more in the CEA positive patients than in the CEA negative
patients in the present study. In a word, advanced cancer lesions were confirmed to be significantly more in the former than in the latter, as already reported by many investigators. From the result, CEA produced by the cancer cells in the invaded vessels of the primary lesions and by the node and liver metastatic cancer cells is thought to enter the draining veins and/or lymphatics and circulate in the whole blood, as previously reported by us.

Regarding the relationship between PCNA LI and CEA levels, the mean of PCNA LI in the CEA positive patients was significantly higher than that in the CEA negative patients. Furthermore, a semilogarithmic linear correlation representing by a formula, \( Y \) (log CEA, ng/ml) = 0.026X (PCNA LI) - 0.478 (r = 0.598), was found between serum CEA levels (Y) and PCNA LI (X). These results clearly indicate that the CEA productive rate reflects the proliferative activity of the cancer cells. In other words, CEA, being a type of glycoprotein, seems to be produced by the proliferative cancer cells, because many kinds of proteins are understood to be actively produced in the proliferative cancer cells. This view may be supported by the recent reports that the actual tumor doubling time of metastatic cancer lesions accords with CEA doubling time.

In conclusion, the relations of serum CEA levels to 13 clinicopathologic variables of colorectal cancer lesions and proliferative activity of cancer cells representing by PCNA LI in the colorectal cancer lesions were examined in 57 patients, and their relationships were analyzed. From the results, CEA produced by the cancer cells of the invaded in the cancer lesions and by the node and liver metastatic cancer seems to enter the draining veins and/or lymphatics and circulate in the whole blood. Therefore, serum CEA levels is thought to elevate in the patients with these variables. Furthermore, the CEA levels are suggested to increase semilogarithmically in parallel with the proliferative activity representing by PCNA LI in the cancer lesions.

REFERENCES


Vol. 12, 1996
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liferating cell nuclear antigen antibody in gastric tissue specimens obtained by endoscopic biopsy. Cancer 71: 2448-2453, 1993
29. Wasseem NH, Lane DP. Monoclonal antibody analysis of the proliferating cell nuclear antigen (PCNA): structural conservation and the detection of a nucleolar form. J Cell Sci 96:
