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# Does Serum Carcinoembryonic Antigen Elevation in Patients With Postoperative Stage II Colorectal Cancer Indicate Recurrence? Comparison With Stage III

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**Background and Objectives:** The aim of this study was to determine the accuracy of postoperative monitoring of serum carcinoembryonic antigen (CEA) to detect or rule out recurrence in patients with stage II colorectal cancer (CRC) by comparing results with stage III.
**Methods:** A total of 303 patients with CRC who underwent curative surgery were enrolled. Serum CEA was assayed, and radiological examination was performed routinely for 5 years after surgery. Yearly recurrence rates, sensitivities, specificities, likelihood ratios, and posttest probabilities were calculated.
**Results:** Sensitivity and specificity of CEA monitoring in stage II patients are almost same as those in stage III. Whereas recurrences occurred early in stage III, they occurred almost as frequently in both early and late stage II. The obtained posttest probability of recurrence in stage II patients with CEA elevation was significantly lower (only 30% or less) than those in stage III (approximately 80%).
**Conclusion:** Elevation of CEA in patients with stage II CRC does not represent recurrence with high probability. One of the reasons for the unreliability of CEA monitoring was its high false-positive rate. Another tumor marker with a lower false-positive rate is necessary to follow-up stage II CRC patients.
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KEY WORDS: CEA; colorectal cancer; recurrence; follow-up; stage II

## INTRODUCTION

Relapse of colorectal cancer (CRC) occurs in 30–40% of patients who undergo curative resection. To provide adequate treatment, detection of recurrence as early as possible is necessary. Thus, follow-up testing should be performed postoperatively. However, the follow-up strategy is still under debate. Measuring serum tumor marker levels is commonly used to monitor recurrence of disease following potentially curative resection of CRC. Of the many tumor markers, carcinoembryonic antigen (CEA) is most commonly used clinically. Despite their widespread use, the utility of serial CEA assays in the detection of recurrent and metastatic CRC has been questioned. The surveillance strategies for postoperative patients are different in America and Europe [1–3]. In Japan, a serum CEA assay is recommended every 3–6 months for 5 years depending on the patient's stage. However, no study has assessed the accuracy of serum CEA measurement in stage II patients compared with stage III.

The recurrence rate of CRC is different between stages II and III. Thus, the accuracy of CEA measurements is difficult to evaluate with conventional sensitivity and specificity. Recently, new statistical technique of likelihood ratio and posttest probability has been reported to be superior to sensitivity and specificity because they are less influenced by morbidity rate. In this study, we used the likelihood ratio and posttest probability to evaluate the accuracy of monitoring serum CEA levels in stage II patients to detect and exclude recurrence of CRC.

## PATIENTS AND METHODS

Patients with CRC (N = 488) underwent curative resection in our hospital between 1990 and 2004. Patients with squamous cell carcinoma, more than one cancer, or insufficient follow-up were excluded. The remaining 303 patients were enrolled. Of these, 136 patients had lymphatic metastases (Table I).

All patients underwent routine serum CEA assays and radiological examination. CEA elevation was defined as >5 ng/ml. Moreover, we determined whether CEA was elevated and recurrence was present at each postoperative year (POY). We defined POY1 as within 1 year after surgery, POY2 as ≥1 to <2 years, POY3 as ≥2 to <3 years, and POY4 as ≥3 years. The recurrence rate in any given year was obtained by calculating the number of recurrences/the number of patients followed for that year. A marker elevation coincident with recurrence in the period was defined as a true positive, no marker elevation without recurrence as a true negative, no marker elevation with recurrence as a false negative, and marker elevation without recurrence as a false positive.

### Statistics

The posttest probability was calculated from the pretest probability, sensitivity, specificity, and likelihood ratio each year. The relationship of pretest probability to recurrence rate each year was assessed. The sensitivity and specificity of CEA elevation to predict recurrence were calculated each year. Patients with prior recurrence and who had

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**TABLE I. Three Hundred Three Patients Characteristics According to Stage**

| Variable | Stage III (n = 136) | Stage II (n = 167) |
|---|---|---|
| Age, mean ± SD (range) | 63.4 ± 9.4 (44–88) | 68.3 ± 10.5 (38–92) |
| Gender (male/female) | 77:59 | 84:83 |
| Location | | |
| Colon | 89 | 112 |
| Rectum | 47 | 55 |
| Depth of tumor | | |
| T1 | 3 | 0 |
| T2 | 89 | 0 |
| T3 | 32 | 142 |
| T4 | 12 | 25 |
| Preoperative serum CEA (mean ± SD) | 28.6 ± 130.7 | 10.9 ± 25.3 |

persistent CEA elevation were excluded. Sensitivity was calculated using Formula 1.

$$\text{Sensitivity} = \text{true positive}/(\text{true positive} + \text{false negative}) \quad \text{(Formula 1)}$$

$$\text{Specificity} = \text{true negative}/(\text{true negative} + \text{false positive}) \quad \text{(Formula 2)}$$

$$\text{Likelihood ratio (test positive)} = \text{sensitivity}/(1 - \text{specificity}) \quad \text{(Formula 3)}$$

$$\text{Like lihoodratio (test negative)} = (1 - \text{sensitivity})/\text{specificity} \quad \text{(Formula 4)}$$

The likelihood ratios, pretest probabilities, and posttest probabilities of recurrence in each postoperative year were calculated using Formulas 5, 6, and 7.

$$\text{Pretest odds} = \text{pretest probability}/(1 - \text{pretest probability}) \quad \text{(Formula 5)}$$

$$\text{Posttest odds} = \text{likelihood ratio} \times \text{pretest odds} \quad \text{(Formula 6)}$$

$$\text{Posttest probability} = \text{posttest odds}/(1 + \text{posttest odds}) \quad \text{(Formula 7)}$$

# RESULTS

## Pretest Probability

In stage III patients, recurrence developed in 20, 18, 6, and 1 patient at 1, 2, 3, and 4 postoperative years, respectively. Thus, the yearly recurrence rates were 15.4% (21/136), 16.5% (19/115), 7.3% (7/96), and 4.5% (4/89). On the other hand, in stage II patients, recurrence developed in 5, 7, 5, and 6 patients at 1, 2, 3, and 4 postoperative years, respectively, and the corresponding yearly recurrence rates were 3.0% (5/167), 4.0% (7/162), 3.0% (5/155), and 4.0% (6/150) (Tables II and III). These rates were regarded as pretest probabilities in this study.

## Sensitivity and Specificity in Stages II and III

In stage III patients, recurrence developed in 21, 19, 7, and 4 patients from POY1 to POY4. CEA elevation was observed in 20, 8, 3, and 3 of these patients and in 6, 12, 8, and 5 patients without recurrence. The yearly sensitivity of elevated CEA (in %) to predict recurrence was 95.0, 44.4, 50.0, and 50.0. The yearly specificity of elevated CEA (in %) was 94.4, 87.5, 91.0, and 94.1.

On the other hand, in stage II patients, CEA elevation was observed in 9, 6, 1, and 0 patients with recurrence, and 11, 12, 5, and 2 patients without recurrence. Thus, the sensitivity and specificity in stage II patients each POY were 100.0, 71.0, 60.0, 70.0 and 90.0, 86.0, 85.0, 72.0, respectively. There was no significant difference in sensitivity and specificity between stages II and III (Table IV).

**TABLE III. Positive Rate of CEA According to Recurrence Site and Stage**

| | Stage III (n = 51) | Stage II (n = 23) |
|---|---|---|
| Recurrence site | Positive (%) | Positive (%) |
| Liver | 14/20 (70.0) | 9/12 (75.5) |
| Lung | 8/18 (44.4) | 2/4 (50.0) |
| Lymph node | 4/6 (66.7) | |
| Peritoneum | 3/4 (75.0) | 4/6 (50.0) |
| Local | 2/2 (100) | 1/1 (100.0) |
| Others | | 1/1 (100.0) |

## Likelihood Ratio and Posttest Probability

In stage III patients, from sensitivities and specificities, positive and negative likelihood ratios were calculated as described in Table IV. The positive likelihood ratio each year was 18.3, 3.6, 5.6, and 12.7, and the negative likelihood ratio was 0.05, 0.6, 0.5, and 0.3. The corresponding posttest probabilities were 75.6, 39.5, 31.8, and 24.1 (with postoperative CEA elevation), and 0.6, 9.2, 3.0 and 1.0 (without postoperative CEA elevation) (Fig. 1). When postoperative CEA was elevated, the probability of recurrence was approximately 80% in POY1, with values decreasing in successive years (3 years, 30%). When the postoperative CEA was normal, this probability was low in POY1 (0.5%), with values increasing in POY2 and POY3 (9.3% and 3.0%, respectively).

In contrast, in stage II patients, the positive and negative likelihood ratios were 10.0, 6.2, 4.0, 2.4 (positive, POY1–4) and 0, 0.33, 0.47, 0.46 (negative, POY1–4). Obtained posttest probabilities when CEA was elevated were 27%, 20%, 12%, and 10%, and those when CEA was normal were 0%, 1.0%, 1.5%, and 1.8%. These results showed that in stage II patients, whereas normal CEA is useful to rule out recurrence, CEA elevation indicates recurrence only with one-third probability.

# DISCUSSION

The optimum follow-up strategy for patients with CRC remains controversial. The guidelines for follow-up in Europe, the US, and Japan differ from each other. In these guidelines, monitoring of serum tumor markers is regarded as an important follow-up strategy. The American Society of Clinical Oncology (ASCO) recommends that postoperative serum CEA testing should be performed every 1–3 months in patients not only stage III but also stage II disease for at least 3 years after diagnosis [2]. The European Group on Tumour Markers (EGTM) also recommends CEA testing every 2–3 months for patients with Dukes' B and C [4]. Although regarded as one of the most important methods for surveillance of CRC recurrence, little is known

**TABLE II. Recurrence Rate in Every Year After Surgery According to Stage**

| POY | 1 | 2 | 3 | 4 | Total |
|---|---|---|---|---|---|
| Stage III | 21/136 (15.4%) | 19/115 (16.5%) | 7/96 (7.3%) | 4/89 (4.5%) | 51/136 (37.5%) |
| Stage II | 5/167 (3.0%) | 7/162 (4.3%) | 5/155 (3.2%) | 6/150 (4.0%) | 23/167 (13.8%) |

**TABLE IV. Sensitivities, Specificities, and Likelihood Ratios According to Stage**

| | Stage III | | | | Stage II | | | |
|---|---|---|---|---|---|---|---|---|
| POY | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Sensitivity[a] | 95.0 (20/21) | 44.4 (8/19) | 50.0 (3/7) | 75.0 (3/4) | 100.0 (5/5) | 71.1 (5/7) | 60.0 (3/5) | 66.7 (4/6) |
| Specificity[b] | 94.8 (109/115) | 87.5 (84/96) | 91.0 (81/89) | 94.1 (80/85) | 90.0 (145/162) | 86.0 (130/155) | 85.0 (127/120) | 72.2 (103/144) |
| LR (CEA elevation) | 18.3 | 3.6 | 5.6 | 12.7 | 10.0 | 6.2 | 4.0 | 2.4 |
| LR (normal CEA) | 0.05 | 0.6 | 0.5 | 0.3 | 0 | 0.33 | 0.47 | 0.46 |

LR, likelihood ratio.
Numbers in parentheses were numbers of patients.
[a]Sensitivity is calculated by (recurrence with tumor marker elevation/recurrence).
[b]Specificity is calculated by (without recurrence with normal tumor marker/without recurrence).

about the accuracy and efficacy of CEA monitoring [3–12]. One unsolved issue is whether CEA monitoring is accurate in stage II same as stage III. CEA can be elevated by some benign diseases [13], leading to false-positive results. Some studies using conventional statistical techniques have reported the usefulness of CEA monitoring in stage II patients [14,15], but those reports were based on sensitivity and specificity which are not including the information of false positive.

Recently, a new statistical technique for assessing test accuracy, the likelihood ratio, has appeared [16,17]. It is thought to be superior to sensitivity and specificity in comparing the accuracy of tests for differences in morbidity, and to be useful as a measure of the probability of obtaining a positive or negative test result [17–19]. In CRC follow-up, yearly rates of recurrence after surgery vary between stages II and III [20,21], thus, the likelihood ratio and posttest probability are more suitable than sensitivity and specificity as an accurate measure of yearly tumor marker monitoring.

Same as other report, our result of sensitivity and specificity of CEA were almost the same in both stages II and III. Thus, it seems that measuring CEA in stage II is as accurate as in stage III patients. On the other hand, likelihood ratio and posttest probability revealed that in patients with stage III CRC and postoperative CEA elevation in the first year, the probability of recurrence is approximately 80%, and in those with normal CEA, it is 0.5%, suggesting that this probability statistic is a very reliable indicator of recurrence. Our results show the high accuracy of postoperative CEA monitoring in stage III patients to detect or exclude recurrence within 1 postoperative year. However, in stage II patients, CEA elevation indicated recurrence with almost 30% probability, which was not reliable at all. These are quite different from the result based on sensitivity and specificity. One possible reason for this paradox is the low morbidity in stage II patient and high false-positive rate of CEA. CEA is elevated not only with recurrence but also as a false positive. The false-positive rate was not different between stages II and III. However, the recurrence rate decreased significantly in stage II. Thus, false-positive rate increases relatively in stage II patients. As a result, CEA elevation indicates recurrence in stage II patients only with 30% of probability. From our result, for stage II patients, use of a novel tumor marker with a lower false-positive rate alone or in combination with CEA measuring is necessary to rule out recurrence.

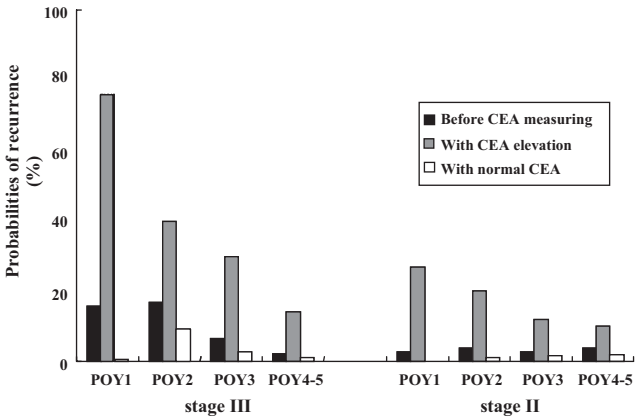


Fig. 1. Probabilities of CRC recurrence in stage II and III patients according to postoperative serum CEA status (before test: black square, probability when CEA elevated: gray square, and those when CEA is normal: white square). Whereas postoperative CEA elevation indicated recurrence of approximately 80% in stage III patients, that indicated only 30% or less in stage II patients. POY: postoperative year.

## CONCLUSIONS

Sensitivity and specificity cannot point out any difference between stages II and III. Although this seems like CEA measurement in stage II patients is as accurate as in stage III, the likelihood ratio and posttest probability revealed that CEA elevation in stage II patients has less power to indicate recurrence than in stage III. To detect and exclude metastasis in postoperative stage II patients, the serum CEA level is not very reliable, in contrast to stage III. This result is due to the presence of a certain frequency of false-positive cases. A novel tumor marker with lower false-positive rates is necessary to follow-up stage II CRC patients who rarely develop recurrence.

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