# PROGNOSTIC VALUE OF CEA SLOPE ANGLE CALCULATION IN PATIENTS WITH COLORECTAL CANCER*

Serša G., Rudolf Z., Plesničar S.

**Abstract** — In the present study 58 patients with colorectal adenocarcinoma were included. Carcinoembryonic antigen (CEA) levels were routinely performed, and slope angles calculated from serial CEA values in the follow-up. According to the clinical manifestation of the disease the patients were divided into three groups. In the group of 14 patients without recurrence of the disease the mean slope angle was $7^0 \pm 13^0$, in 15 patients with local recurrence $39^0 \pm 18^0$ and in the group of 29 disseminated patients $82^0 \pm 15^0$. Similar slope angle values were further calculated 4 months before clinical manifestation of the disease. Then, in patients with local recurrence the mean value of $25^0 \pm 19^0$ was found, and in disseminated patients $72^0 \pm 15^0$.
The results of the preliminary study indicate that the slope angle calculation may be helpful in predicting recurrence of the disease, as can be clearly seen from angles calculated 4 months before clinical confirmation of the recurrence. Slope angles in patients with distant metastases were steeper than in patients with local recurrence ($p = 0.001$).

**Introduction** — The most important use of the carcinoembryonic antigen (CEA) test is as an adjunct in clinical and pathological staging methods (2, 9, 11), and for monitoring the response to the treatment (4, 5, 6). Elevated CEA levels should return to normal following complete surgical removal of the colorectal cancer (1). In the contrast, persistent elevated levels suggest residual tumor mass in the body (3, 4, 8).

Elevated levels in the follow-up often precede the recurrence of the disease (3). Slowly rising levels are indicative for local recurrence. Rapidly increasing values (usually above 20 ng/ml) are often accompanied with hepatic and bone metastases (4, 10, 12). Some authors introduced the slope calculation from serial CEA levels (7, 10). The value of the slope in follow-up in patients after surgical removal of the colon carcinoma could help to discriminate between local recurrence and dissemination (3, 8, 10).

The purpose of the study was to evaluate prognostic value of slope angles, which were calculated from the serial CEA levels. Therefore, slope angles were calculated at the time of the clinical manifestation of the recurrence, and four months before that.

**Material and methods** — In the study 58 patients (26 male, 32 female) with histologically proven adenocarcinoma were included. In 55 patients (95 %) primary tumor was surgically removed, while in 3 cases (5 %) the tumor was unresectable.

After surgical removal of the tumor the patients were consecutively treated with radiotherapy (21 cases), chemotherapy (18 cases), combination of chemo- and radiotherapy (8 cases), with "second look" surgery (2 cases). In 9 patients no treatment was applied.

The patients were divided into three groups according to the clinical presentation of the disease. In the first group were 14 patients (median age 62 years) without recurrence, in the second group were 15 patients (59 years) with local recurrence,

and in the third group 29 patients (55 years) with distant metastases.

Carcinoembryonic antigen (CEA) serum levels were determined every 4 months by Abbott CEA-RIA kit. The slope was calculated from the formula of Koch (7):

$$S = \frac{\text{Follow-up CEA level (ng/ml)} - \text{Baseline CEA level (ng/ml)}}{\text{Interval in months}}$$

Each slope started with that value of CEA preceding its increase.

Angle, which is more illustrative, was calculated simply by trigonometric inversion ($\alpha = \text{arc tg } S$).

Slope angles were also calculated from the CEA levels 4 months before clinical manifestation of the disease for the possible prediction of recurrence before clinical demonstration of the disease.

**Results** — In the group of patients without recurrence CEA levels were in the range up to 20 ng/ml (mean value $5 \pm 4$ ng/ml), in patients with the local recurrence CEA levels were in the range up to 40 ng/ml (mean value $15 \pm 9$ ng/ml), and in the patients with distant metastases the CEA values were exceeding 5 ng/ml up to 6000 ng/ml in some cases (Table 1).

The values of the calculated slope angles were divided into five ranges from $-20^0$ to more than $80^0$ (Table 2). Patients without recurrence had angles from $-20^0$ to $40^0$, patients with local recurrence from $-20^0$ to $80^0$, concentrated in the range from $40^0$ to $60^0$. In the disseminated patients the angles were mostly over $80^0$, with one exception where the CEA angle was flat. The difference between mean slope angle values in patients without and with recurrence ($7^0 \pm 13^0$, $39^0 \pm 18^0$ respectively) was significant, $p = 0.001$, as well as the difference between patients with local recurrence and patients with distant metastases ($39^0 \pm 18^0$ and $82^0 \pm 15^0$ respectively), $p = 0.001$.

| | Follow-up CEA level (ng/ml) | | | | | |
|---|---|---|---|---|---|---|
| | Range | | | | | |
| Clinical status | 0—5 ng/ml | 5—10 ng/ml | 10—30 ng/ml | 30—400 ng/ml | > 400 ng/ml | A. M. $\pm$ 1. S. D. ng/ml |
| Without recurrence N° of patients | 10 | 3 | 1 | — | — | $5 \pm 4$ |
| Local recurrence N° of patients | 1 | 4 | 9 | 1 | — | $15 \pm 9$ |
| Distant metastases N° of patients | — | 1 | 2 | 16 | 10 | $1172 \pm 2091$ |

Table 1 — Follow-up CEA levels of patients divided into three groups according to the clinical manifestation of the disease

Tabela 1 — CEA koncentracije pacijenata podeljenih u tri grupe s obzirom na kliničku manifestaciju bolesti

| | CEA slope angle ($\alpha$) — range | | | | | |
|---|---|---|---|---|---|---|
| Clinical status | (—20)°—20° | 20°—40° | 40°—60° | 60°—80° | > 80° | A. M. $\pm$ 1. S. D. |
| Without recurrence N° of patients | 12 | 2 | — | — | — | $7° \pm 13°$ |
| Local recurrence N° of patients | 2 | 4 | 8 | 1 | — | $39° \pm 18°$ |
| Distant metastases N° of patients | 1 | — | 1 | 4 | 23 | $82° \pm 15°$ |

Table 2 — Comparison of CEA slope angles and activity of the disease in patients with colorectal adenocarcinoma

Tabela 2 — Usporedba uglova nagiba CEA i kliničke manifestacije bolesti

Beside the calculation of slope angles at the time of the clinical manifestation of the disease, we calculated angles 4 months before that. The patients who subsequently developed local recurrence had moderate angles, mostly in the range up to 40°. In the contrary, the patients with dissemination (mostly in the liver and bones) had similar angles even 4 months before clinical manifestation of the disease. Majority of the patients had slope angles from 60° to more than 80° (Table 3).

When mean values of the slope angles 4 months before, and at the time of clinical confirmation were compared, a distinct prognostic value was found, especially in disseminated patients ($25^0 \pm 19^0$ versus $39^0 \pm 18^0$ in patients with local recurrence, and $72^0 \pm 25^0$ versus $82^0 \pm 15^0$ in patients with distant metastases), (Table 4).

| Clinical status 4 months before | CEA slope angle ($\alpha$) — range | | | | | |
|---|---|---|---|---|---|---|
| | $(-20)°—20°$ | $20°—40°$ | $40°—60°$ | $60°—80°$ | $> 80°$ | A. M. $\pm$ 1. S. D. |
| Without recurrence N° of patients | 14 | — | — | — | — | $3° \pm 8°$ |
| Local recurrence N° of patients | 6 | 3 | 3 | — | — | $25° \pm 19°$ |
| Distant metastases N° of patients | 2 | 3 | 1 | 5 | 18 | $72° \pm 25°$ |

Table 3 — Comparison of CEA slope angles 4 months before manifestation of the disease
Tabela 3 — Usporedba uglova nagiba CEA 4 meseca prije kliničke manifestacije bolesti

| Clinical manifestation of the disease | | CEA slope angle ($\alpha$) 4 months before | Confirmed |
|---|---|---|---|
| | N° of patients | A. M. $\pm$ 1. S. D. | A. M. $\pm$ 1. S. D. |
| Local recurrence | 15 | $25° \pm 19°$ | $39° \pm 18°$ |
| Distant metastases | 29 | $72° \pm 25°$ | $82° \pm 15°$ |

Table 4 — Mean values of CEA slope angles related to clinical status
Tabela 4 — Usporedba prosećnih uglova nagiba CEA i kliničkog statusa

**Discussion** — Serial CEA determinations are useful as an adjunct to the clinical management of patients with CEA producing tumors, particularly in early detection of recurrence or metastases (3, 8, 10, 12). In order to normalize intervals in which CEA plasma samples are obtained, CEA slopes rather than single plasma levels are compared (10), or as in our study slope angles.

Because of little practical value of the single CEA determination the slope angle determinations were introduced. From our and other results (10), calculation of CEA slope angles represents a prognostic tool for the prediction of subsequent course of the disease. The predictive value was confirmed by the calculations of slope angles 4 months before clinical presentation of the disease.

In patients with metastases we often observed a steady rising levels regardless of the therapy used. The CEA levels may be in these patients an indicator of the progressing disease and failure of the treatment.

**Conclusion** — On the basis of our results it can be concluded that calculation of CEA slope angles should be introduced in the follow-up procedures since it could be useful for early detection of tumor recurrence and/or dissemination. Of course, steep angle is not by itself verification of the recurrence, but represents an early warning for more careful follow-up examinations.

## Sažetak

### PROGNOSTIČKA VREDNOST IZRAČUNAVANJA UGLA NAGIBA CEA KONCENTRACIJA U SERUMU BOLESNIKA SA KOLOREKTALNIM KARCINOMOM

Serša G., Rudolf Z., Plesničar S.

Analizirali smo 58 slučajeva pacijenata sa kolorektalnim adenokarcinomom kojima su bile periodično određivane koncentracije karcinoembrionalnog antigena (CEA). Za vreme praćenja bolesnika (follow-up) određivali smo ugao nagiba iz periodičnih koncentracija CEA. S obzirom na kliničku manifestaciju bolesti, pacijente smo podelili na tri grupe. U prvoj grupi od 14 pacijenata bez recidiva prosećna vrednost nagiba bila je $7^0 \pm 13^0$, u grupi 15 pacijenata sa lokalnim recidivima $39^0 \pm 18^0$ i u trećoj grupi 29 pacijenata sa diseminacijom $82^0 \pm 15^0$. Slične nagibe izračunali smo i četiri meseca pre manifestacije bolesti. Pacijenti sa lokalnim recidivima imali su prosećnu vrednost uglova $25^0 \pm 19^0$, dok pacijenti sa diseminacijom $72^0 \pm 15^0$.

Rezultati ove preliminarne studije pokazuju, da može izračunavanje uglova nagiba poslužiti za predviđanje recidiva i diseminacije bolesti, kao što se može videti uz uglova izračunatih 4 meseca prije klinički ustanovljenog recidiva ili metastaza. Uglovi nagiba kod pacijenata sa metastazama bili su veći od uglova kod pacijenata sa lokalnim recidivima ($p = 0,001$).

## References

1. Alsabti E.: Carcinoembryonic antigen (CEA) as prognostic marker in colonic cancer. J. Surg. Oncol. 12: 127—129, 1979.

2. Arnaud J. P., Koehl C., Adloff M.: Carcinoembryonic antigen (CEA) in diagnosis and prognosis of colorectal carcinoma. Dis. Colon Rectum 23 (3): 141—144, 1980.

3. Attiyeh F. F., and Stearns M. W.: Second-look laparotomy based on CEA elevations in colorectal cancer. Cancer 47: 2119—2125, 1981.

4. Conference Statement: Carcinoembryonic antigen: its role as a marker in the management of cancer- National Institutes of Health Consensus Development. Cancer Res. 41 (5): 2017—2018, 1981.

5. Goldenberg D. M.: Carcinoembryonic antigen in the management of colorectal cancer. Acta Hepato-Gastroenterol. 26: 1—3, 1979.

6. Ichiki A. T., Krauss S., Israelsen K. L., Sonoda T., and Collmann I. R.: Sequential carcinoembryonic antigen levels. Oncology 38: 27—30, 1981.

7. Koch M., Paterson A. H. G., and McPherson T. A.: Slope analysis of plasma carcinoembryonic antigen levels in monitoring response to treatment in patients with metastatic carcinoma of the breast. Clinical Oncology 6: 323—327, 1980.

8. Lavin P. T., Day J., Holyoke E. D., Mittelman A., and Chu T. M.: A statistical evaluation of baseline and follow-up carcinoembryonic antigen in patients with resectable colorectal carcinoma. Cancer 47: 823—826, 1981.

9. Plesničar S., Rudolf Z., Berčič I.: Klinična vrednost določanja karcinoembroničnega antigena (CEA) v serumu bolnikov z gastrointestinalnimi malignomi. Zdrav. Vestn. 46: 677—680, 1977.

10. Staab H. J., Anderer F. A., Stumpf E., Fischer R.: Slope analysis of the postoperative CEA time courses and its possible application as an aid in diagnosis of disease progression in gastrointestinal cancer. Am. J. Surg. 136 (3): 322—327, 1978.

11. Staab H. J., Anderer F. A., Brümmendorf T., Stumpf E., and Fischer R.: Prognostic value of preoperative serum CEA level compared to clinical staging. Br. J. Cancer 44: 652—662, 1981.

12. Staab H. J., Anderer F. A., Hornung A., Stumpf E., and Fischer R.: Doubling time of circulating CEA and its relation to survival of patients with recurrent colorectal cancer. Br. J. Cancer 46: 773—781, 1982.

Author's address: Serša G., The Institute of Oncology, Zaloška 2, 61000 Ljubljana.