Neopterin
A Tumor Marker in Colorectal Carcinoma?

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Neopterin is compared with other tumor markers in colorectal carcinoma. Its sensitivity is clearly lower than that of CEA, TPA and CA 19/9 and is even lower than the sensitivity of the erythrocyte sedimentation rate. The ability of neopterin to discriminate between different tumor stages is also lower than that of the other markers. The discriminant analysis shows that measurement of neopterin in the serum of patients with colorectal carcinoma gives no essential additional information.

[Key words: Colorectal carcinoma; Tumor markers; Neopterin]

IN RECENT YEARS there has been an increase in the number of substances measured in body fluids that are regarded as potential tumor markers. Some tumor markers, such as carcinoembryonic antigen (CEA), have been the subject of numerous reports in connection with different kinds of malignancy. As a result it is possible to form at least a provisional view of the use and clinical performance of these markers.

In 1979, Wachter et al. were the first to point out that neopterin, a substance linked with the processes of cell-mediated immunity, is excreted in increased quantities in the urine of patients with malignancy. These authors proposed testing for neopterin in the diagnosis and follow-up of malignant growths. Since then other reports have been published dealing with neopterin as a potential tumor marker and comparing it for sensitivity with several other tumor markers. There is still a lack of investigations that compare neopterin with other markers under standardized conditions, however, and a meaningful comparison of the sensitivity of neopterin with that of other markers has so far been impossible. Such a comparison can be achieved by plotting receiver operated characteristic (ROC) curves.

It seems necessary to consider whether or not the addition of a further marker really enhances the information that can already be obtained from the determination of those already known; more specifically, does the additional measurement of neopterin increase the reliability with which a person is classified as tumor-free or not? The authors have attempted to answer this question with the aid of discriminant analysis.

This report compares the tumor markers CEA, tissue polypeptide antigen (TPA), and carbohydrate antigen 19/9 (CA 19/9) with neopterin in serum. It also evaluates the determination of the erythrocyte sedimentation rate (ESR) as being a simple and widely used procedure. For the sake of homogeneity, the study covers only patients with colorectal cancers.

Materials and Methods

CEA was determined by enzyme immunoassay (Roche, Basel, Switzerland); TPA by radioimmunoassay (AB
Sangtec, Bromma, Sweden), and CA 19/9 by radioimmunoassay (Centocor, Malvern, PA). The ESR was measured after 1 hour by the Westergren method.22

The control group consisted of 82 persons (47 women; 35 men) hospitalized for minor disorders such as inguinal hernias or varices. The age in the control group ranged from 17 to 89 years (median, 58 years). The tumor group consisted of 150 patients with colorectal cancer (90 women; 60 men), 27 to 85 years of age (median, 70 years). Twenty five patients had Dukes' A stage, 25 Dukes' B, and 79 Dukes' C; 21 patients were not further classified.

Results

Figure 1 shows the ROC curves of CEA, TPA, CA 19/9, neopterin, and ESR. CEA displays the highest degree of
sensitivity (the further the curve from the 45° line, the higher the sensitivity). The sensitivity of TPA is only slightly lower except for the sector of higher specificity, where the difference is more pronounced. Neopterin has the lowest sensitivity in every respect; even the sensitivity of the ESR is distinctly greater except for the sector of high specificity. The curve of CA 19/9 lies below that of CEA and TPA in every sector, indicating lower sensitivity. In the sector of low and medium specificity, the sensitivity of CA 19/9 is also below that of the ESR.

In order to examine the degree to which laboratory parameters are influenced by tumor stage, ROC curves contrasting the subgroups Dukes’ A and B with Dukes’ C were plotted. These curves are shown in Fig. 2. CEA turns
out to have the greatest ability to discriminate between tumor stages, followed by TPA. Neopterin shows the least reaction to the stage of the tumor.

Table 1 shows the results obtained from the discriminant analysis. The number of persons correctly reclassified based on the laboratory parameters only is listed in percent. Each result obtained from a single test is followed by the result for the combination of this test with neopterin. Table 2 shows the results of some favorable multiple combinations without and with neopterin.

### Discussion

In 1979, Wachter et al.\(^9\) were the first to report that neopterin is excreted in increased quantities in the urine of patients with malignant disease.\(^9\) The same investigators suggested that neopterin might possibly be of use in the diagnosis and monitoring of malignancy. Other studies during the following years confirmed increased neopterin excretion in leukemia and malignant lymphatic disorders, gynecologic carcinomas, bronchial carcinoma, neuroblastoma, carcinoma of the prostate, and other cancers.\(^10-16\) At the same time it became clear that a number of nonmalignant disorders also lead to increased urinary neopterin excretion, e.g., viral infections, tuberculosis, dermatitis, polyarthritis, allograft rejections, and also fractures, wounds, and burns.\(^14,15\)

Experiments showed that the mechanism of neopterin elevation consists of stimulation of the T-lymphocytes, resulting in the secretion of gamma-interferon by the T-cells. The gamma-interferon induces the production of neopterin by macrophages. Thus, the release of neopterin accompanies the processes of cell-mediated immunity.\(^15\)

A radioimmunoassay was developed that is suitable for the rapid determination of the level of neopterin in a routine laboratory and is easier to perform than the previously used HPLC method. It is now possible to determine the level of neopterin in serum in large numbers of samples.\(^12,23\)

In addition to the investigations outlined above, it appeared necessary to investigate the degree of sensitivity of neopterin in comparison with other more or less tumor-specific laboratory parameters. To be valid, a method of comparison must make it possible to compare degrees of sensitivity on the basis of identical specificities. This can be done by plotting ROC curves.\(^17,18\) While the sensitivity of neopterin and that of other markers have been correlated before,\(^12,15,16\) either the relevant specificities were not indicated at all or the specificities also varied, so that valid comparisons were impossible.

The tumor group in this study consisted of patients with colorectal cancers only. The control group was composed of persons hospitalized for minor disorders that, as far as was known, involved neither malignancy nor an infectious or inflammatory disease. The authors deliberately did not take blood donors as a control group, as is often done, because this section of the population is usually in an above-average state of health. The purpose of tumor marker tests is not to distinguish between blood donors and persons with disorders, but to identify patients with malignancy from people seeking medical treatment. Using blood donors as a control group would have resulted in unwarranted optimism about the test since the incidence of nonspecific elevations would have been kept particularly low.\(^24\)

The results, as presented by ROC curves, show that the sensitivity of neopterin is clearly lower than that of CEA, TPA, or CA 19/9. The sensitivity of neopterin is even lower than that of the ESR, which was included in the investigation as a simple, nonspecific method of long standing.

The other question considered was that of the degree to which parameters are influenced by tumor stage and consequently can be regarded as indicators of that stage. In the ROC curves derived from the stages, Dukes' A and B contrasted with Dukes' C, the greatest effect of tumor stage was found with CEA, the slightest with neopterin. Even the ESR discriminates better between Dukes' A and B and Dukes' C than neopterin.

The discriminant analysis was intended to show whether or not the measurement of neopterin yields information relating to discrimination between tumor patients and tumor-free persons exceeding what was known already. The proportion of patients reclassified

### Table 1. Discriminant Analysis (Discriminants: Control Group, Dukes' A, B, Dukes' C)*

| Parameter       | Percent with Neopterin (Percent) |
|-----------------|---------------------------------|
| CEA             | 56.7 57.6                        |
| TPA             | 53.9 57.6                        |
| ESR             | 51.5 52.1                        |
| CA 19/9         | 48.5 47.4                        |
| Neopterin       | 44.2                             |

*Total number of persons correctly reclassified, given in percent for each of the individual parameters and for the combination of this parameter with neopterin.

### Table 2. Discriminant Analysis (Discriminants: Control Group, Dukes' A, B, Dukes' C)*

| Parameter       | Percent with Neopterin (Percent) |
|-----------------|---------------------------------|
| CEA/CA 19/9/ESR | 60.7 60.4                        |
| CEA/TPA/ESR     | 62.2 60.0                        |
| CEA/TPA/CA 19/9/ESR | 63.4 63.8            |

*Total number of persons correctly reclassified, given in percent for combinations of various parameters and for each combination with the addition of neopterin.
correctly is enhanced only slightly, if at all, by the additional determination of neopterin.

It is concluded that the measurement of neopterin in the serum of patients with colorectal carcinoma is a method with a very low degree of sensitivity. Other tests such as CEA and TPA are clearly superior. The same applies also to the ability to discriminate between different tumor stages. Discriminant analysis confirms that neopterin gives no essential additional information in colorectal carcinoma.

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