MAURIE MARKMAN, MD
Dr. Markman is chairman of the Department of Hematology/Medical Oncology at the Cleveland Clinic, and an associate editor of the *Cleveland Clinic Journal of Medicine*.

When and how to use serum tumor markers in clinical practice

We measure tumor markers mostly in following up patients who have cancer

Clinicians have long wished for a simple blood or urine test that would be sensitive enough to detect cancer in its early stages when the tumor volume is small, yet specific enough to avoid large numbers of false-positive results. Such a test would measure tumor markers—substances that, in abnormal concentrations, suggest the patient has cancer.

Unfortunately, no such ideal test exists, or is likely to. The problem is that the structural and biochemical differences between normal and malignant cells are remarkably limited, and the differences in the proteins and other substances that normal and malignant cells secrete are far more quantitative than qualitative.

ROLE OF TUMOR MARKERS IN CLINICAL PRACTICE

Nevertheless, we do measure certain tumor markers in certain situations, mostly in following up patients who have cancer, in whom we want to monitor the course of the disease, assess the effect of treatment, and check for recurrence (**TABLE**).

Increases or decreases in the serum levels of some tumor markers can influence therapeutic strategies. For example, a rising human chorionic gonadotropin (HCG) level in a patient with testicular cancer would indicate that the treatment needs to be changed.

Other tumor markers provide prognostic information, although we may not know yet whether changing the therapy on the basis of these data can either improve quality of life or prolong survival. An example would be a rising carcinoembryonic antigen (CEA) level after definitive surgery for colon cancer.

Some tumor markers also find use as diagnostic tests, but because most are not specific for cancer, they do not by themselves prove that cancer is present, and are therefore used only in conjunction with other tests.

Dangers of overinterpreting tumor marker levels

It is important to not overinterpret changes in tumor marker levels, for several reasons.

The value may be incorrect, due to tests being run on the wrong patient's serum, problems with laboratory technique, or transcription errors.

The test may not be specific. Abnormal laboratory values can indicate a benign rather than malignant condition. For example, the prostate-specific antigen (PSA) level can be elevated in benign prostatic hyperplasia; the carbohydrate antigen 125 (CA-125) level can be elevated in endometriosis or pregnancy.

Because the diagnosis of cancer or the documentation of disease recurrence or progression has great therapeutic, prognostic, and emotional significance, the burden of proof must be extremely high. Thus, in general, histologic analysis remains the "gold standard" for decision-making in oncology, while tumor markers play a supportive role.

TABLE

TUMOR MARKERS AND THEIR CLINICAL USES

Marker	Abbreviation	Normal limit	Use
Prostate-specific antigen	PSA	≤ 4.0 ng/mL	Prostate cancer screening and follow-up
Human chorionic gonadotropin	HCG	Undetectable	Testicular cancer follow-up
Alpha fetoprotein	AFP	< 10 ng/mL	Testicular cancer follow-up
Carcinoembryonic antigen	CEA	< 2.3 ng/mL	Colorectal cancer follow-up
Carbohydrate antigen 15-3	CA-15-3	< 29 U/mL	Breast cancer follow-up
Carbohydrate antigen 125	CA-125	< 35 U/mL	Ovarian cancer follow-up
5-Hydroxyindole acetic acid	5-HIAA	< 10 µg/mg creatinine*	Carcinoid tumor diagnosis and follow-up

*Measured in urine

CLINICALLY USEFUL TUMOR MARKERS

The combination of a PSA test and a rectal examination appears to be an effective way to screen for prostate cancer

Prostate-specific antigen (PSA)

As mentioned above, an elevated PSA level is not specific for prostate cancer. However, the combination of a PSA test and a rectal examination appears to be an effective way to screen for prostate cancer. In one study, PSA testing by itself had a positive predictive value of 31.5%, vs 21% for digital rectal examination and 48% for the combination of the two. Several authorities propose a PSA level of 4.0 ng/mL as a normal limit in prostate screening studies.

PSA is also of value in detecting the early recurrence of prostate cancer after surgery or radiation therapy. In this setting the PSA level is elevated in 90% or more of cases, frequently more than a year before symptoms of disease progression appear. Unfortunately, the therapeutic options in this situation are limited and generally palliative in intent.

Another use of PSA testing is to monitor the effects of therapy in patients with metastatic prostate cancer.

Human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP)

These two tumor markers are not sensitive enough to serve as screening tests for testicular cancer, but in a man known to have germ cell cancer, a confirmed elevation (ie, abnormal value on repeated tests) in either marker warrants starting therapy. Similarly, failure of these marker levels to normalize after surgery or chemotherapy (depending on the status of the cancer) indicates the need to change the therapeutic strategy.

The sensitivity of these tests for small volumes of testicular cancer makes it possible for carefully selected patients to be treated conservatively (ie, with more limited surgery or without chemotherapy). Such patients undergo frequent blood tests for several years and begin chemotherapy if these markers become elevated, even without other signs or symptoms.

The serum levels of HCG and AFP at the start of therapy, and their rate of decline during therapy, correlate well with tumor volume and the number of tumor cells killed, respectively. For this reason, these markers have been used to evaluate different treatments in testicular cancer.

Carcinoembryonic antigen (CEA)

The serum CEA level is commonly elevated in a number of malignant (eg, colorectal cancer) and nonmalignant conditions (eg, cigarette smoking). The CEA level is used most frequently to follow up patients with known colorectal cancer, whom a confirmed rise in the CEA level after definitive local therapy

(usually surgery with or without local radiotherapy) generally indicates recurrence.

Unfortunately, for now, the therapeutic implications of a rising CEA level are limited, as chemotherapy in this setting is only palliative in intent. Some investigators suggest that monitoring the CEA level after definitive surgery may allow for more successful surgical removal of metastases (eg, in the liver). However, the clinical utility of such a strategy needs to be defined in well-designed clinical trials.

Carbohydrate antigen 15-3 (CA-15-3)

The serum level of this glycoprotein antigen has been demonstrated to correlate reasonably well with the total body burden of breast cancer. Thus, CA-15-3 measurements have been used to monitor patients with breast cancer and to determine their response to chemotherapy. This antigen can also be used to demonstrate progression of disease after definitive local therapy.

Carbohydrate antigen 125 (CA-125)

CA-125 is a cell-surface antigen secreted by both malignant and normal tissue. Although not specific for any malignant disease, it is most commonly elevated in cancer of the ovary. Like CA-15-3 testing, CA-125 testing is most frequently used to follow the progress of the disease, and especially the response to chemotherapy.

Unfortunately, while an abnormal CA-125 level in a woman treated for ovarian cancer strongly indicates the cancer is still present (even in the absence of signs or symptoms), a normal value does not mean the cancer is gone. In fact, several studies demonstrated that 50% of women with advanced ovarian cancer whose CA-125 levels returned to normal by the end of chemotherapy still had microscopic or small-volume residual macroscopic disease within the abdominal cavity.

5-Hydroxyindole acetic acid (5-HIAA)

The urinary 5-HIAA level, used to detect carcinoid tumors, is perhaps the closest a tumor marker can come to being "diagnostic" for a particular cancer. Serotonin, which is secreted by carcinoid tumors, is degraded into 5-HIAA which is secreted into the urine.

5-HIAA levels can be monitored to follow the natural history of carcinoid tumor or its response to treatment. In addition, in a patient with histologically documented cancer in which the primary site is undetermined and in which carcinoid tumor is included in the differential diagnosis, an elevated 5-HIAA level can confirm the diagnosis. ■

SUGGESTED READING

American Society of Clinical Oncology. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. J Clin Oncol 1996; 14:2843–2877.

Bates S. Clinical applications of serum tumor markers. Ann Intern Med 1991; 115:623–638.

Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer (published erratum appears in N Engl J Med 1991; 325:1324). N Engl J Med 1991; 324:1156–1161.

Moertel CG, Fleming TR, Macdonal JS, Haller DG, Laurie JA, Tangen C. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA 1993; 270:943–947.

Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. JAMA 1993; 269:57–60.

Wolf AMD, Nasser JF, Wolf AM, Schorling JB. The impact of informed consent on patient interest in prostate-specific antigen screening. Arch Intern Med 1996; 156:1333–1336.

ADDRESS REPRINT REQUESTS to Maurie Markman, MD, Department of Hematology/Medical Oncology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

Unfortunately, a normal CA-125 level does not mean that ovarian cancer is gone