Validating Serum Markers for Monitoring of Cancer
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Most of the serum tumor markers available today were introduced decades ago and were applied to clinical use without rigorous evaluation of their clinical validity. Tumor markers are mainly used for monitoring the response to therapy and to facilitate earlier detection of a relapse. Many organizations have issued guidelines on the use of tumor markers, but most of the recommendations are not based on randomized prospective trials. In this issue of Clinical Chemistry, the European Group on Tumor Markers presents guidelines (MONITOR) for designing studies on the validity of tumor markers for the serial monitoring of cancer patients, with the aim of showing whether monitoring improves outcomes, compared with other routinely used methods (1). Guidelines are needed because the use of serum markers is variable and not necessarily based on evidence.

The need for validating the use of tumor markers was demonstrated in the recent evaluation of cancer antigen 125 (CA125) measurements for monitoring patients with ovarian cancer (2). The validity of this generally accepted practice was investigated in a study that fulfilled most of the criteria in the MONITOR guidelines. Enrolled in the study were 1442 patients with ovarian cancer who had achieved complete remission with normal CA125 concentrations after undergoing platinum-based chemotherapy. Patients were monitored every 3 months both by CA125 assay and by routine clinical and imaging methods. Patients with CA125 concentrations exceeding twice the upper reference limit were randomized into either a group receiving second-line chemotherapy or a second group that was treated only when other evidence of relapse was observed. There was no difference in survival between the groups, suggesting that earlier therapy for recurrence does not improve outcome (2); however, the study has been criticized for several reasons (i.e., the limit for a change in CA125 concentration was not optimal, and new therapies came into routine use during the study) (3). Whether these limitations affected the results is not clear. The study highlights a major problem in all studies of the validity of long-term monitoring with tumor markers. In most cancers, the effect of different therapeutic strategies can be evaluated only after many years, during which new therapeutic methods are likely to have been introduced.

This example also shows that a widely accepted practice may not be evidence based. It is therefore important to examine how other tumor markers used for monitoring cancer patients have been validated.

Quantifying prostate-specific antigen (PSA) to monitor patients with prostate cancer is standard practice. After primary therapy, disease recurrence is usually treated with androgen ablation, which may be initiated on the basis of increasing PSA concentrations or delayed until disease progression is detected on the basis of symptoms. Studies comparing these alternatives have shown that patients with a Gleason score ≥7 or a PSA-doubling time <12 months benefit from early therapy (4). The importance of monitoring for disease recurrence with PSA is obvious. Active surveillance is now increasingly used as an alternative to immediate radical therapy in patients with low-grade prostate cancers. Treatment is switched to curative therapy if the tumor shows signs of rapid progression (5). This strategy also relies heavily on the use of PSA for monitoring disease progression.

Monitoring patients through tumor marker quantification is also essential in the follow-up of testicular cancer. In 30%–40% of cases, a relapse after primary therapy is first detected on the basis of increasing marker concentrations, and second-line therapy is started without other evidence of disease (6). Monitoring of trophoblastic disease also relies heavily on measuring tumor markers, in this case human chorionic gonadotropin. A relapse is virtually always preceded by an increasing concentration of this hormone, and the initiation of treatment is based on this increase without other evidence of disease (7).

The use of marker measurements in the follow-up of patients with choriocarcinoma, testicular cancer, or prostate cancer is recommended in guidelines, although this practice has not been validated in prospective studies. Other evidence for the validity of this strategy is so strong, however, that randomized prospective studies are difficult to justify.
Patients with colorectal cancer are usually monitored by quantifying carcinoembryonic antigen (CEA) in serum in order to detect relapse earlier. The tumor often metastasizes to the liver, and some patients can be cured by liver resection. Various guidelines have recommended CEA monitoring, although it has not been prospectively validated. An increasing CEA concentration, often the first sign of recurrence, has to be confirmed by imaging before surgery. Whether the use of CEA improves outcomes could be prospectively evaluated.

Guidelines have also recommended that tumor markers be monitored for several other cancers, e.g., breast, lung, ventricular, hepatocellular, and pancreatic cancers. Monitoring these cancers with tumor markers is not very like to change outcomes, however, at least not until more effective therapy is available. The introduction of new, targeted therapies may change the situation, but that can be evaluated only when these therapies become available. Should we postpone evaluations of the validity of monitoring with markers for these diseases until we have therapies that make a difference in outcomes? And, should we not recommend monitoring with markers until the validity of this practice has been established?

The new MONITOR guidelines are welcome because they pinpoint the importance of validating the use of serum tumor markers. The protocol is demanding, and it will be interesting to see how it would be used to validate both presently available and future markers. The next best alternative is probably the use of archival samples to evaluate how well a marker or combination of biomarkers predicts disease recurrence and prognosis. Only markers that pass this test should be further validated according to MONITOR guidelines.

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