2006 Update of ASCO Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer

Context

The 2006 Update Committee, composed of members from the original Tumor Markers Expert Panel, presents the ASCO 2006 Evidence-Based Clinical Practice Guideline on Tumor Markers in Gastrointestinal Cancer (*J Clin Oncol* doi:10.1200/JCO.2006.08.2644). The Panel performed an updated literature review and analysis of data published since 1999 through November 2005. The date range for the literature review conducted on new tumor markers (thymidine synthase [TS], dihydropyrimidine dehydrogenase [DPD], and thymidine phosphorylase [TP], microsatellite instability [MSI], 18q–loss of heterozygosity (LOH), and cancer antigen [CA] 19-9 testing for pancreatic cancer) included data published from 1966 to November 2005.

Updated 2006 Recommendations

See Table 1 for a complete summary of the updated 2006 recommendations.

Gastrointestinal Tumor Markers

Carcinoembryonic antigen (CEA) as a marker for colorectal cancer. Studies show that the specificity of CEA for identifying occult colorectal cancer is high, while its sensitivity is very low. CEA is not an adequate screening tool for colorectal cancer patients or the general public. However, the assessment of CEA levels for prognosis has been shown to be an important variable in predicting preoperative outcomes. Data from studies on postoperative colorectal cancer patients demonstrated that CEA measurement every 3 months for at least 3 years was a valuable and cost-effective component of follow-up, especially if aggressive resection of recurrent or metastatic disease could be performed. In addition, the recent ASCO guideline, "Colorectal Cancer Surveillance: 2005 Update" (J Clin Oncol 23:8512-8519, 2005), recommends that these patients receive an annual computed tomography scan of the chest and abdomen for 3 years. Except as an immediate or ephemeral consequence of chemotherapy, rising CEA levels should prompt re-evaluation and consideration of an alternative treatment strategy. Other exceptions include non–cancer-related causes such as gastritis, peptic ulcer disease, diverticulitis, liver diseases, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammatory state.

CA 19-9 as a marker for colon cancer. The 2006 Update Committee identified no literature supporting the role of CA 19-9 in colorectal cancer management. The test for this antigen is less sensitive than the CEA test for all stages of colorectal cancer. Additionally, CA 19-9 and CEA in combination do not improve the performance of the CEA test alone or add significant information to that provided by CEA, which is currently regarded as the marker of choice for patients with colorectal cancer.

DNA ploidy or flow cytometric proliferation analysis as a marker for colon cancer. In the last 10 years, the ASCO Tumor Markers Expert Panel has reviewed more than 70 series examining the prognostic value of DNA ploidy (DNA index) and proliferation analysis (% *S*-phase) in colorectal cancer. The 2006 Update Committee's review of evidence on DNA index and % *S*-phase revealed inconsistent results regarding utilization to determine operable colorectal cancer prognosis. As such, flow cytometric determination of DNA ploidy or proliferation should, at best, be considered an experimental tool.

p53 as a marker for colorectal cancer. For more than two decades, p53 abnormalities have been studied extensively, including translational research into their role in prognosis and response to therapy in colorectal cancer. Study results are often heterogeneous and conflicting, in part because p53 abnormalities are usually detected through various methodologies that do not address directly the functional status of the two alleles of the gene. Based on available evidence, p53 status is a poor guide to both prognosis, and response or resistance to therapy in patients with colorectal cancer.

ras *as a marker for colorectal cancer*. The results of studies investigating the possible role of *ras* mutation as a prognostic marker are diverse and contradictory. The majority of reported studies show *ras* mutation as an adverse prognostic indicator; however, the studies have wide variability in their specific results. Similar to the uncertain role of ras oncogene mutation in prognosis, its utility as a predictive marker is also unclear. Interpretation of the literature is complicated by the use of a variety of chemotherapeutic agents and regimens.

TS, DPD, and TP as markers in colorectal cancer. TS is the rate-limiting step in the biosynthesis of thymidine. TS is inhibited by fluorodeoxyuridylate, which is formed by TP, an enzyme that activates the fluoropyrimidine by converting fluorouracil (FU)—for which DPD is the major catabolizing enzyme—to fluorodeoxyuridine. Data from studies evaluating the roles of TS, DPD, and TP for prognosis of colorectal cancer and the prediction and monitoring of therapeutic response are heterogeneous and conflicting. Upon careful review of the evidence, the 2006 Update Committee found that many studies on these markers cannot be compared or interpreted for clinical use because of divergent study methodologies, faulty empirical evidence, or poorly designed research protocols.

Microsatellite instability (MSI) as a marker in colorectal cancer. MSI is a measure of the inability of the DNA nucleotide mismatch repair system to correct errors that commonly occur during the replication of DNA. The use of MSI testing for HNPCC is beyond the scope of the 2006 Update, which is limited to testing in nonfamilial/sporadic cases of colorectal cancer. Although there is suggestive evidence that MSI high early-stage colon cancers have a more favorable prognosis than MSI low/microsatellite-stable tumors, the data are insufficient to recommend using MSI profile as an independent prognostic test for use in the clinic. The data reviewed do not support the use of MSI status in the prediction of benefit from FU chemotherapy as an adjunct to surgery for early-stage colorectal cancer.

18q-LOH/DCC as markers for colorectal cancer. The long arm of chromosome 18 contains several genes with potential importance in colorectal cancer pathogenesis and progression. Deletion of portions of 18q has been implicated as an important step in the development of many colorectal cancers. Although there is suggestive evidence of an association of 18q loss with the natural history of colorectal cancer, the small number and retrospective nature of studies that found 18q status to be either an independent predictor of survival or of survival within stage II disease makes it premature to use this marker to determine prognosis.

CA 19-9 as a marker for pancreatic cancer. Cancer antigen, serum CA19-9, is a tumor-associated antigen, which was originally defined by a monoclonal antibody that has been produced by a hybridoma prepared from murine spleen cells immunized with a human colorectal cancer cell line. Reports are mixed regarding this antigen and pre- and postoperative determinations, as well as CA 19-9 measurements to monitor patients receiving chemotherapy or radiotherapy. The specificity and sensitivity of CA 19-9 is inadequate for reliable diagnosis in pancreatic cancer if used alone. However, CA 19-9 monitoring in conjunction with other studies has been shown to be useful for locally advanced or metastatic pancreatic cancer.

Additional Resources

The 2006 Update is available in the November 20, 2006, print edition of the *JCO* and also at www.jco.org (*J Clin Oncol* doi:10.1200/JCO.2006.08.2644). In addition to the full text of the guideline recommendations available online (http://www.asco.org/guidelines), further resources from ASCO include a patient guide, a PowerPoint slide set, and tables for CEA testing and recommendation updates. Other useful tools from ASCO include colon and rectal cancer follow-up sheets for the patient record. These flow sheets are provided to assist oncologists in colorectal cancer surveillance, including the tracking of CEA values.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

The ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer were developed and written by Gershon Y. Locker, Stanley Hamilton, Jules Harris, John M. Jessup, Nancy Kemeny, John MacDonald, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr, for the American Society of Clinical Oncology Tumor Markers Expert Panel.

Table 1: Summary of Recommendations

CEA (colorectal cancer)
Screening CEA is not recommended to be used as a screening test for colorectal cancer.
Staging/treatment planning CEA may be ordered preoperatively in patients with colorectal carcinoma if it would assist in staging and surgical treatment planning. Although elevated preoperative CEA (>5 mg/mL) may correlate with poorer prognosis, data are insufficient to support the use of CEA to determine whether to treat a patient with adjuvant therapy.
Postoperative Postoperative serum CEA testing should be performed every 3 months in patients with stage II or III disease for at least 3 years after diagnosis, if the patient is a candidate for surgery or systemic therapy. An elevated CEA, if confirmed by retesting, warrants further evaluation for metastatic disease, but does not alone justify systemic therapy for presumed metastatic disease. Since chemotherapy may falsely elevate CEA levels, waiting until chemotherapy is finished to initiate surveillance is advised.
Monitoring response to therapy CEA is the marker of choice for monitoring metastatic colorectal cancer during systemic therapy. CEA should be measured at the start of treatment for metastatic disease and every 1 to 3 months during active treatment. Persistently rising values above baseline should prompt restaging, but suggest progressive disease even in the absence of corroborating radiographs. Caution should be used when interpreting a rising CEA level during the first 4 to 6 weeks of a new therapy since spurious early rises may occur, especially after oxaliplatin.
CA19-9 (colon cancer)
Present data are insufficient to recommend CA19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.
DNA ploidy or flow cytometric proliferation analysis (colon cancer)
Neither flow cytometrically derived DNA index nor %S phase should be used to determine prognosis of early-stage colorectal cancer.
p53 (colorectal cancer)
Present data are insufficient to recommend the use of p53 expression or mutation for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.
***ras* (colorectal cancer)**
Present data are insufficient to recommend the use of the *ras* oncogene for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.

Table 1: Summary of Recommendations (continued)

TS, DPD, TP (colorectal cancer)
Screening TS, DPD, and TP are tissue markers that have been used to predict response to treatment of established carcinomas and thus are not useful for screening.
Prognosis None of the three markers—TS, DPD, or TP—are recommended for use in determining the prognosis of colorectal carcinoma.
Predicting response to therapy There is insufficient evidence to recommend use of TS, DPD, or TP as predictors of response to therapy.
Monitoring response to therapy There is insufficient evidence to recommend use of TS, DPD, or TP for monitoring response to therapy.
MSI (colorectal cancer)
MSI ascertained by PCR is not recommended at this time to determine the prognosis of operable colorectal cancer nor to predict the effectiveness of FU adjuvant chemotherapy.
18q-LOH/DCC (colorectal cancer)
Assaying for LOH on the long arm of chromosome 18 (18q) or DCC protein determination by immunohistochemistry should not be used to determine the prognosis of operable colorectal cancer, nor to predict response to therapy.
CA19-9 (pancreatic cancer)
Screening CA19-9 is not recommended for use as a screening test for pancreatic cancer.
Operability The use of CA19-9 testing alone is not recommended for use in determining operability or the results of operability in pancreatic cancer.
Evidence of recurrence CA19-9 determinations by themselves cannot provide definitive evidence of disease recurrence without seeking confirmation with imaging studies for clinical findings and/or biopsy.
Monitoring response to therapy Present data are insufficient to recommend the routine use of serum CA19-9 levels alone for monitoring response to treatment. However, CA19-9 can be measured at the start of treatment for locally advanced metastatic disease and every one to three months during active treatment. If there is an elevation in serial CA19-9 determinations, this may be an indication of progressive disease and confirmation with other studies should be sought.

Abbreviations: CEA, carcinoembryonic antigen; TS, thymidine synthase; DPD, dihydropyrimidine dehydrogenase; TP, thymidine phosphorylase; MSI, microsatellite instability; PCR, polymerase chain reaction; LOH, loss of heterozygosity; DCC, deleted in colon cancer.