

National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Gastric Cancer

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Key words: Tumor marker, guidelines, CEA CA 72.4, CA 19.9, cytokeratins

Abbreviations: AFP, α -fetoprotein; TPA, tissue polypeptide antigen; TPS, tissue polypeptide specific antigen; hCG β , free β -subunit of human chorionic gonadotropin

INTRODUCTION

Gastric cancer is a major health problem worldwide, remaining the second most common digestive tract cancer, despite decreasing incidence. Gastric cancer is often not diagnosed until it is in the advanced stages. Even when surgical resection is possible, long-term survival is observed in only a minority of patients, with overall five-year survival of patients following gastrectomy less than 30% (1).

The most important prognostic factor influencing survival of patients with stomach cancer is the extent of disease as assessed by tumor stage (2). 80% of patients with Stage IA disease who undergo gastrectomy are alive at five years, but only 7% of patients with Stage IV disease reach five years survival. The ratio of involved and resected lymph nodes also has prognostic significance (3). Patients with a proximal location of the tumor generally have a worse prognosis than those with cancer in the distal or middle section (4).

Staging of gastric cancer often depends on the extent of resection of the tumor. In a D2 resection all tumor and N2 lymph nodes are resected, while in a D1 resection only N1 lymph nodes are removed and in a D0 resection only the tumor is removed without lymph nodes. Resections less complete than the D2 procedure will give a significant risk of under-staging (5-8).

The histological type of tumor is often regarded as an essential prognostic factor in gastric cancer. When diffuse lesions and the intestinal type with more nodular lesions are differentiated it is assumed that the latter carries a better prognosis (9,10).

With surgery alone only a minority of patients will be cured of gastric cancer, the development of symptomatic metastatic disease from unresected microscopical tumor remnants being the main cause of death. Prospective randomized trials have demonstrated that surgical resection of stomach, perigastric lymph nodes and omenta (D1) yields the same survival figures as more extensive (D2) surgical procedures including omental bursa and extensive lymph node resections (11). Conclusive evidence of any survival benefit of adjuvant chemotherapy is lacking (12).

As chemotherapy alone has not shown benefit, treatment with a combination of chemo- and radiotherapy is advocated. Since Moertel first reported prolonged survival in a group of patients treated with both 5-fluorouracil and radiation therapy as compared with a group of patients given 5-fluorouracil alone (13), several other studies have shown that concurrent chemo- and radiotherapy are superior to chemotherapy alone, although combination therapy has shown more morbidity (14, 15). In a large trial it was observed that postoperative adjuvant chemo- and chemo radiotherapy gave improved disease-free survival and survival rates (16). Trials assessing the efficacy of neo-adjuvant chemo radiation therapy are currently in progress (17, 18).

While there are some excellent guidelines relating to the clinical management of gastric cancer (19, 20), these generally do not include any mention of conventional tumor markers. However several studies have been conducted to assess the role of circulating tumor markers in the management of stomach cancer.

CURRENTLY AVAILABLE MARKERS FOR GASTRIC CANCER

Table 1 lists the most widely investigated tissue-based and serum-based tumor markers for gastric cancer. Also listed is the phase of development of each marker as well as the level of evidence for its clinical use.

TUMOR MARKERS IN GASTRIC CANCER: NACB RECOMMENDATIONS

The use of markers for diagnosis of gastric cancer cannot be recommended. Serum CEA and CA19.9 measurements have been shown to be useful aids in the detection of recurrence in patients following surgery, but it is not possible to indicate which marker is superior for this application.

CLINICAL APPLICATION OF TUMOR MARKERS IN GASTRIC CANCER

Screening

In the Western hemisphere the low and decreasing incidence of gastric cancer together with the invasiveness of diagnostic gastroscopy and the lack of a suitable alternative test has precluded the investigation of screening for gastric cancer. While there is considerable debate in the Far East about screening for gastric cancer, with some trials in the process of implementation, none have included candidate tumor markers (21). Members of families with a strong history of diffuse gastric cancer who are carriers of germ line truncating E-Cadherin mutations might be helped by genetic counseling, with prophylactic gastrectomy a possibility (22). The relation of the presence of *Helicobacter pylori* to an increased risk (relative risk 2-5) for gastric cancer has been attributed to the resulting chronic gastritis (23). In a large Swedish study a negative result almost excluded precancerous conditions in a screening situation. A major problem is the low detection of early gastric cancer by endoscopic means (24).

Diagnosis

The diagnostic procedure is to obtain a biopsy by gastroscopy, which can be used for definitive histological diagnosis. None of the tumor markers that may be used in the management of gastric cancer is specific and sensitive enough to be included in a diagnostic procedure (25-27).

Prognosis

The most important prognostic factor influencing survival of patients with stomach cancer is, as described above, the extent of disease. If a D2 resection is not performed there is a significant risk of under-staging (6, 28, 29).

Reports on the sensitivity of tumor markers are inevitably influenced by the accuracy of staging procedures, while use of different cut off levels makes it difficult to compare results from different studies. The reported sensitivities of several markers of early and advanced disease are listed in Table 2. Most studies include CEA, CA 19.9 and CA 72.4 (30, 31, 32), all of which have prognostic value for postoperative survival, but in multivariate analysis they are not always independent of stage (33-38).

However, the prognosis of patients with identical clinical stages of disease has been reported to be significantly different, depending on the extent of elevation of tumor markers (35, 39). In general it may be concluded from the literature that increasing levels of tumor markers are inversely related to post-operative survival (35, 37). Additional markers that have been studied in relation to prognosis include α -fetoprotein (α FP) (40), cytokeratins [Tissue Polypeptide Antigen (TPA), Cyfra 21-1 and Tissue Polypeptide Specific Antigen (TPS)] (34, 38, 41-43), and the free β -subunit of chorionic gonadotropin (hCG β) (44, 45), which appears to be a "pan marker" for tumor activity (46) although no correlation with its presence in tumor tissue has been found (47).

When preoperative serum levels of circulating tumor markers are related to the occurrence of recurrence none of the above mentioned appears to have independent prognostic value (34, 48).

Peritoneal dissemination is an important cause of recurrence and death in patients with gastric cancer. Conventional cytological examination of intra-operative peritoneal lavage fluid is useful in detecting free cancer cells in peritoneal cavity, which in turn contribute to peritoneal dissemination, but the sensitivity is low. Elevated CEA levels in the peritoneal lavage fluid have been shown to correlate with peritoneal recurrence and poor survival (49, 50). Also, CEA mRNA measured by RT-PCR in blood and peritoneal washings has been shown to be related to tumor burden and to predict recurrence (51, 52). Intraperitoneal CEA is not in clinical use yet, but might have important clinical application in the future with the development of adjuvant therapy regimens.

Monitoring of patients post-operatively

In principle, post-operative follow up of patients may be helpful for early detection of recurrence. Most studies on the use of CEA, CA 19.9 or CA 72.4 for early detection of relapse indicate a high sensitivity and a lead-time between 0-10 months, especially for recurrence in the liver. Most studies have been retrospective and clinical detection methods

varied (53-57), making it difficult to compare results from different studies. In a nationwide prospective study CEA and CA 19.9 detected recurrence earlier than diagnostic imaging, with an average lead-time of 3 months and in some cases a lead-time of more than one year (58). Monitoring response to therapy is an important tool to which can spare non-responding patients potentially serious side effects from chemo (radiation) therapy. While the number of investigations is limited, results suggest that tumor markers correlate with responses as measured by conventional imaging techniques (59, 60).

CONCLUSIONS

Most studies concerning the use of tumor markers have been directed towards the prognostic power of preoperative serum levels. The retrospective nature of the studies and the inadequacy of the statistics frequently applied means that it is difficult to draw any firm conclusions about the relative merits of different markers in identifying patient groups at high risk of either short disease-free survival or survival alone. Differences in surgical and diagnostic procedures also make it difficult to compare tumor marker sensitivity and specificity in relation to stage. However no currently available marker can be recommended for use in diagnosis of gastric cancer, as specificity and sensitivity are clearly not sufficient. The few reports on the use of CEA or CA19.9 in follow up of patients with this disease suggest that their measurement may be of benefit in the detection of recurrence.

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Table 1. Currently available serum markers for gastric cancer

Marker	Proposed use	Phase of development	Level of evidence	References
CEA	Prognosis Post-operative monitoring	Conflicting data Needs further trials	III, IV	33-37, 53, 54, 56, 58-60
CA 19.9	Prognosis Post-operative monitoring	Conflicting data Needs further evaluation	III, IV	33, 34, 36, 37, 53, 54, 56, 58-60
CA 72.4	Prognosis Post-operative monitoring	Needs further evaluation	III, IV	33, 34, 53-57, 59
Cytokeratins (Cyfra 21.1, TPA, TPS)	Prognosis	Needs further evaluation	IV	38, 42, 43
HCG β	Prognosis	Needs further evaluation	IV	44, 45

Table 2. Reported pretreatment sensitivity (percentage elevated level) of serum markers

	Cut off level	Early stage	Advanced disease	References
CEA	5 μ g/L	<20%	40-50	33-37, 39, 53, 56, 57
CA 19.9	37 kU/L	<20%	20-50	33-37, 39, 53, 56, 57
CA 72.4	6 kU/L	<20%	30-40	33, 34, 38, 39, 53, 56, 57
Cytokeratins (Cyfra 21.1, TPA, TPS)	Variable	15-25	30-50	34, 38, 41, 42
HCG β	4 μ g/L	20-35	30-50	44, 47

Data from cited references