Gastro Intestinal Tumors

Gastrointest Tumors
DOI: 10.1159/000488240
Received: January 11, 2018
Accepted: March 8, 2018
Published online: April 24, 2018

Mini Review

Carbohydrate Antigen 19-9, Carcinoembryonic Antigen, and Carbohydrate Antigen 72-4 in Gastric Cancer: Is the Old Band Still Playing?

Andrey Iskrenov Kotzev[a] Peter Vassilev Draganov[b]

[a]Clinic of Gastroenterology, University Hospital "Alexandrovska," Medical University Sofia, Sofia, Bulgaria; [b]Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

Keywords
Carbohydrate antigen 19-9 · Carbohydrate antigen 72-4 · Carcinoembryonic antigen · Diagnosis · Gastric cancer · Prognosis · Serum tumor markers

Abstract
Background: Gastric cancer (GC) is characterized by aggressive behavior and a high mortality rate. The diagnosis of GC is challenging because the GC is often diagnosed in an advanced stage. The use of tumor markers is a putative way to improve the detection and treatment in patients with GC. ***Summary:*** In this article, we review the significance of serum carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), and CA 72-4 in GC. The results from different studies regarding the diagnostic and prognostic role of CA 19-9, CEA, and CA 72-4 in GC are encouraging, but inadequate sensitivity and specificity obstruct their use as standardized and unconditionally reliable markers in GC. New prospective clinical trials are mandatory for clarifying their value in GC. ***Key Message:*** CA 19-9, CEA, and CA 72-4 should not be used for screening and early diagnosis in GC, whereas they are beneficial in the detection of late GC. CA 19-9, CEA, and CA 72-4 could be used as prognostic and monitoring tools in GC, and their combined measurement in shorter periods of time is the best method to increase sensitivity and specificity. ***Practical Implications:*** Serum CA 19-9, CEA, and CA 72-4 are useful diagnostic and prognostic tumor markers in GC.

Introduction

Gastric cancer (GC) is the fifth most common malignant disease worldwide with nearly one million new cases per year [1]. Substantial geographical differences exist, with GC occurring more often in Japan, China, Eastern Europe, and Central and South America, whereas

Andrey Iskrenov Kotzev
Clinic of Gastroenterology, University Hospital "Alexandrovska"
Medical University Sofia, 1, Sv. G. Sofiyski Blv.
BG–1431 Sofia (Bulgaria)
E-Mail dr_andrey_kotzev@abv.bg

the incidence of GC is much lower in North America, Western Europe, Australia, and parts of Africa [2]. The majority of cases with GC are seen in the developing countries and half of the cases are reported from Southeast Asia. A significant reduction in the incidence of GC has been observed in the last decades [1]. However, the prognosis of GC continues to be dismal. The disease develops insidiously and alarm symptoms tend to occur late when curative surgery is not possible. GC is the third most common cause of cancer death in males and females, and to no surprise the highest mortality rates are in the areas with the highest incidence, while the lowest mortality rates are recorded in North America [1]. Most cases with GC are diagnosed in late stages and the estimated 5-year survival rate is <30% [3]. New data show 5-year survival rates of 18.7% for Asian and 13.4% for Caucasian patients who were diagnosed with T4 GC and underwent gastrectomy [4].

A tumor marker is defined as a biochemical indicator that is usually found in abnormal concentration in the presence of a tumor [5]. As tumor markers can be different substances, which are produced by the tumor itself or by the normal tissue of the host in a response to tumor cells [5, 6], tumor markers may be found in tissues, blood, saliva, urine, and other body fluids [6, 7]. Serum tumor markers are helpful in clinical practice, although their relatively low sensitivity and specificity impede their independent use as a diagnostic and screening tool [8]. The ideal tumor marker must possess high sensitivity and specificity, high positive and negative predictive values, and be noninvasive and validated in large prospective trials [9]. Unfortunately, such a tumor marker is still not available.

We are still in search of the perfect tumor marker for GC, but carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), and CA 72-4 may be of value for the diagnosis and treatment monitoring of this fatal malignancy. Accumulated data show that these markers are convenient instruments for monitoring recurrence and distant metastasis as well as for evaluating the efficacy of chemotherapy and the prognosis in GC [10–13]. However, CA 19-9, CEA, and CA 72-4 are not adequate tools for screening and diagnosis of early GC [14]. Increased levels of these markers are also observed in other tumors and in some nonmalignant conditions [15, 16]. Moreover, the results of some studies question the benefit of CA 19-9, CEA, and CA 72-4 even as monitoring markers in GC [17, 18]. According to the Japanese Gastric Cancer Treatment Guidelines, due to the shortage of prospective studies concerning follow-up programs after gastrectomy, it is not possible to make any recommendation on how often the monitoring examinations should be performed. Uncertainty exists even on which examination to perform: medical examination, blood test including tumor markers, computed tomography and/or ultrasound, and endoscopy [19]. Nevertheless, the Japanese Gastric Cancer Treatment Guidelines mentioned that there are affirmative retrospective studies for the effectiveness of measurement of tumor markers (CEA and CA 19-9), along with computed tomography and endoscopy, in the detection of recurrence, gastric remnant cancer, and metachronous multiple cancer [19]. Ongoing debate exists about the applicability of CA 19-9, CEA, and CA 72-4 in GC. Therefore, in this review, we will discuss and evaluate the role of the serum CA 19-9, CEA, and CA 72-4 in the diagnosis and management of GC.

CA 19-9 in GC

CA 19-9 was initially discovered in 1979 as a tumor-associated antigen in colorectal cancer [20]. It is a mucin glycoprotein connected with the Lewis a blood group [21]. The exact biological role of CA 19-9 is still obscure, but it probably disrupts cell adhesion and promotes tumor invasion and metastasis through binding to the cell surface receptors E-selectin and P-selectin located on endothelial cells [22, 23]. CA 19-9 could also enforce carcinogenesis by triggering apoptosis of activated T cells [23]. CA 19-9 is available in normal epithelial tissues

of many organs, including the gallbladder, biliary ducts, pancreas, stomach, colon, prostate, endometrium, and salivary glands [16]. CA 19-9 is predominantly used for prognosis and follow-up in pancreatic adenocarcinoma, but this biomarker is not specific and is expressed in other malignancies, including GC [16, 24–26]. Increased serum levels of CA 19-9 are detected in 40–60% of patients with GC [26]. The cutoff value of serum CA 19-9 is 37 U/mL. CA 19-9 levels usually are highest in patients with pancreatic cancer or cholangiocarcinoma, but CA 19-9 is rarely extremely elevated in patients with GC [27]. The CA 19-9-positive rates depend on the TNM stage of GC. The data from a Japanese systematic review showed CA 19-9-positive rates of 9, 19.9, 32.2, and 44.7% for stage I, stage II, stage III, and stage IV, respectively [28].

CA 19-9 has prognostic and predictive value in the late stages of GC, but the lack of sufficient sensitivity and specificity hampers its use as a test for early GC [29, 30]. In a recent study, Feng et al. [14] found a positive serum CA 19-9 in only 4.8% of >500 early GC patients who underwent radical gastrectomy. In a Finnish study exploring the preoperative serum concentrations of CEA and CA 19-9 in 100 patients with GC and in 77 patients with relevant benign diseases, a sensitivity of 30% and a specificity of 87% were reported for CA 19-9 (cutoff level 37 U/mL) [31]. The authors concluded that CA 19-9 might have an independent prognostic value in patients in late stages of GC, but that its diagnostic value is limited. A recent study from India showed a sensitivity of 42% and a negative predictive value of 63.29% for CA 19-9 in GC [32]. In a more recent study, Wang et al. [33] enrolled more than 1,600 patients with GC who underwent gastrectomy and were divided into training and validation cohorts. They discovered positive rates of 20.0, 42.3, and 19.2% for preoperative CA 19-9, CA 125, and CEA, respectively. The authors detected a significantly higher positive rate of CA 19-9 in female patients than in male patients and a higher positive rate of CA 19-9 in older patients than in younger patients. In the training cohort, the survival rate was 44% for CA 19-9-positive patients, compared to 63% for patients in the CA 19-9-negative group. Feng et al. [14] also discovered that an elevated CA 19-9 level was associated with female sex and presence of lymph node metastasis.

Sisik et al. [34] demonstrated a significant correlation between elevated CA 19-9 levels (>100 U/mL) and advanced TNM stages in patients with GC. Most investigators did not find any association between serum CA 19-9 expression and histology of GC [35, 36].

Data from a Chinese study revealed that the preoperative level of CA 19-9 was closely related to TNM grade, sex, distant metastasis, and ascites in patients with GC, and the authors inferred that CA 19-9 probably plays a significant role in predicting recurrence and metastasis [13]. Monitoring of serum CA 19-9 for recurrence after operation for GC could be beneficial in patients with elevated preoperative levels of CA 19-9, because in such cases CA 19-9 often turns positive a few months before any imaging abnormalities become apparent [28]. A nationwide Japanese prospective study, involving more than 300 participants, showed that CA 19-9 monitoring after operation was useful to predict the recurrence of GC, especially in patients with high preoperative levels of CA 19-9 [37]. In this study, the preoperative sensitivity of CA 19-9 increased from 29.2 to 55.0% for recurrence of GC, but the authors noted that a surge in CA 19-9 and CEA is observed much later compared to revealing of recurrence by imaging in some cases of GC. According to the findings of a Korean study, CA 19-9 was particularly trustworthy as a marker for peritoneal recurrence after radical gastrectomy for GC [38]. Data from a new Slovenian study showed that preoperative CA 19-9 serum levels are connected with a higher risk for hematogenous spread and micrometastases in node-negative patients, although the CA 19-9 serum levels were not sensitive enough [39].

The measurement of CA 19-9 could also be used for monitoring response and as a prognostic tool in patients with GC who underwent systemic chemotherapy [40]. Jo et al. [41] analyzed the expression of CA 19-9, CA 72-4, and CEA in 1,178 patients with metastatic or

recurrent GC before the start of first-line chemotherapy. Of the three markers, only elevated CA 19-9 concentration was significantly associated with shorter survival. However, some investigators challenge the role of CA 19-9 as a reliable tool for early detection of recurrence after curative surgery for GC or chemotherapy. Ohtsuka et al. [18] found that false-positive elevation of CA 19-9 and CEA was often observed after curative resection for GC, particularly in patients with an early stage of cancer and with chronic benign diseases such as bronchitis, liver dysfunction, diabetes mellitus, and renal dysfunction. The authors propose frequent evaluation of tumor markers paired with radiological testing for discrimination between false-positive and true-positive results. Moreover, in a Korean study, a transient surge in CA 19-9 and CEA was detected despite clinical benefits from chemotherapy in patients with metastatic or recurrent GC [42]. These findings prompted the investigators to declare that an initial rise in CA 19-9 or CEA levels after chemotherapy commencement is an unreliable marker for progression and that CA 19-9 or CEA levels should continuously increase 6 or 7 weeks for therapy evaluation.

In a recent Chinese study by Feng et al. [43] in which over 1,900 patients with GC were included, the prognostic value of normal levels of serum CA 19-9, CEA, alpha-fetoprotein (AFP), and CA 125 with cutoff values of 27 U/mL, 5 ng/mL, 8.1 ng/mL, and 35 U/mL, respectively, was estimated. The results reported by the authors showed that CA 19-9 and AFP levels were independent prognostic predictors. Interestingly, even relatively high levels of CA 19-9, AFP, and CA 125, still within the normal range, were associated with poor prognosis. Kim et al. [44] also confirmed the prognostic role of serum CA 19-9 in a study with more than 1,200 enlisted patients with gastric adenocarcinoma. They found that CA 19-9, along with CEA and CA 72-4, was prevalent in patients with lymphatic and venous invasion, serosal involvement, and lymph node metastasis. CA 19-9 was an independent prognostic factor, and patients with elevated CA 19-9 levels possessed a 3.35-fold higher risk of death than patients with low CA 19-9 levels. In a recent meta-analysis, Song et al. [45] corroborated the importance of CA 19-9 in GC. They reported substantial differences in the CA 19-9 levels between early- and advanced-stage groups, pT3/T4 and pT1/T2 groups, lymph node-positive and -negative groups, metastasis-positive and -negative groups, and vessel invasion-positive and -negative groups. A significant correlation was found between CA 19-9 and poor survival in patients with GC (Table 1). Xiao et al. [46], in another meta-analysis, also found that high serum CA 19-9 (>37 U/mL) was associated with poorer survival in patients with GC (Table 1).

Notably, elevated serum levels of CA 19-9 are also found in cancers of the pancreas, biliary tree, colon, esophagus, gallbladder, liver, lung, and ovary [16, 23]. Blood levels of CA 19-9 can also be increased in nonmalignant conditions such as pancreatitis, cholecystitis, bronchiectasis, bronchiolitis, emphysema, idiopathic interstitial pneumonia, collagen disease-associated pulmonary fibrosis, pleural effusion, tuberculosis, diabetes mellitus, cystic fibrosis, renal failure, autoimmune disorders, gastric ulcer, and benign ovarian cyst, although they are ordinarily much higher in malignancies [15, 16, 23, 47–50]. CA 19-9 levels can be very high in acute cholangitis, although after therapeutic intervention they fall and return to normal [51]. A considerable elevation in CA 19-9 is seen in patients with chronic hepatitis and liver cirrhosis, and therefore CA 19-9 is not indicative of GC in such cases [52, 53]. Heavy tea consumption could be a rare reason for vastly increased CA 19-9 levels [54]. CA 19-9 can be occasionally increased in apparently healthy individuals for unknown reasons [55, 56]. Approximately 5–7% of the population have the Lewis a–b– phenotype and do not produce CA 19-9. All these drawbacks question the application of CA 19-9 serum measurement under certain conditions in GC. Therefore, CA 19-9 cannot be utilized as a screening tool for GC.

A reasonable approach to increase the effectiveness of serum CA 19-9 measurement in GC patients is to use a CA 19-9 cutoff value >37 U/mL. Qiu et al. [57] studied more than 180

Gastrointest Tumors
DOI: 10.1159/000488240

Table 1. Summary of recent meta-analyses evaluating the role of the serum tumor markers CA 19-9, CEA, and CA 72-4 in gastric cancer

Marker; reference	Included studies (range)	Number of patients	Main findings	Conclusions	Limitations
CEA; Deng et al. [75], 2015	41 (1982–2014)	14,651	pretreatment serum CEA may be an independent prognostic factor in GC (OS: HR = 1.681, 95% CI 1.425–1.982; DSS: HR = 1.900, 95% CI 1.441–2.505; DFS: HR = 2.579, 95% CI 1.935–3.436)	CEA-positive patients with GC have a worse prognosis and intensive neoadjuvant therapy would be more beneficial compared with CEA-negative patients	significant heterogeneity among the studies
CA 19-9; Song et al. [45], 2015	38 (1995–2014)	11,408	serum CA 19-9 was significantly associated with poor OS (HR = 1.83, 95% CI 1.56–2.15), DFS (HR = 1.85, 95% CI 1.16–2.95), and DSS (HR = 1.33, 95% CI 1.10–1.60) in GC	CA 19-9 shows clinicopathologic characteristics of GC and is connected with poor prognosis	missing detailed individual information, significant heterogeneity, and lack of conclusive result for the optimal CA 19-9 cutoff value
CA 19-9; Xiao et al. [46], 2014	12 (2000–2013)	5,072	elevated serum CA 19-9 (>37 U/mL) was associated with poorer OS in patients with GC (fixed-effects HR = 1.36, 95% CI 1.24–1.48, $p < 0.001$)	CA 19-9 plays an important prognostic role in patients with GC	subgroup analysis by treatment method was not done and many retrospective cohort studies were included
CA 72-4; Chen et al. [93], 2012	33 (1999–2007)	5,283	positive serum CA 72-4 in GC patients had the highest OR (32.86, 95% CI 16.34–6.09) compared to controls; the sensitivity of CA 72-4 is limited, but CA 72-4 + CEA + CA 19-9 could improve sensitivity without affecting specificity	CA 72-4 or CA 72-4 + CEA + CA 19-9 could help in the diagnosis of GC	only a Chinese population was studied

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; GC, gastric cancer; HR, hazard ratio; OR, odds ratio; OS, overall survival.

patients with resectable gastric adenocarcinoma and reported that the specificity to monitor recurrence increased to 93.3 from 60% for CA 19-9-positive patients when the CA 19-9 elevation level was set at 100 U/mL.

CEA in GC

CEA, initially discovered by Gold and Freedman in human colon carcinoma in 1965 [58], is a glycosylphosphatidylinositol cell surface glycoprotein. CEA, a member of immunoglobulin super family, is an E- and L-selectin ligand that serves as an intercellular adhesion molecule [59, 60]. These data could clarify the connection between enhanced CEA expression and the development and promotion of the metastatic process.

CEA was originally considered a specific tumor marker for colon cancer, but later it was proved that serum CEA could be detected in all endodermal-derived digestive system cancers [61, 62]. The term "carcinoembryonic antigen" was coined because CEA was available in embryonic and fetal digestive tissues [62].

CEA is routinely used in clinical practice. This is based on the fact that CEA is considerably expressed in tumors and shed in the blood circulation, whereas it is scarcely found in the normal tissues and secreted in low amounts in the serum of adult healthy individuals. CEA is predominantly used as a serum tumor marker in preoperative staging and postoperative follow-up of patients with colon cancer, but increased levels of CEA are also demonstrated in different gastrointestinal, ovarian, urinary tract, breast, lung, and medullary thyroid cancers [8, 9, 63–66]. Occasionally, elevated serum levels of CEA could be detected in other type of cancers [67]. Elevation of serum CEA could be ascertained in various benign gastrointestinal and hepatic conditions such as pancreatitis, cholecystitis, peptic ulcer disease, liver cirrhosis, hepatitis, inflammatory bowel disease, and benign extrahepatic biliary obstruction [68, 69]. It must be underlined that the levels of CEA in these cases are commonly <10 ng/mL [69]. We must keep in mind that the liver is the basic site for CEA metabolism and that liver damage could cause higher serum CEA concentrations in patients with concomitant malignancies, including GC.

The elevation of serum CEA in patients with GC depends on the stage of the disease. A normal CEA value is <2.5 ng/mL for nonsmokers and <5 ng/mL for smokers. Shimizu et al. [70] found that in patients with resectable GC, the preoperative CEA values and CEA positivity rates were 2.4 ± 1.5 ng/mL and 7.7% for stage I, 24.9 ± 72.0 ng/mL and 10.0% for stage II, 21.6 ± 84.1 ng/mL and 17.9% for stage III, and 6.3 ± 8.4 ng/mL and 27.1% for stage IV cancers, while in patients with nonresectable cancers, the CEA value was 83.0 ± 235.5 ng/mL and the CEA positivity rate was 47.8%. Of all 252 studied patients with primary GC, 47(18.7%) were positive for CEA.

Measurement of preoperative serum CEA could help in the determination of tumor stage, risk of peritoneal metastases, and prognosis in patients with GC. Wang et al. [12] reported that CEA, along with CA 125, was an independent prognostic factors for overall survival in patients with metastatic or recurrent GC, and CEA was more often found in patients with liver metastases, while CA 125 was more abundant in peritoneal involvement. In a recent study, Nan et al. [71] analyzed the prognostic value of pretreatment serum CEA levels in predicting the outcomes of multiple tumors subjected to treatment, including 77 patients with GC. In the group with GC, they reported that the 3-year survival rate was 70.45% for patients with a serum CEA <2.885 ng/mL and 33.33% for patients with a serum CEA ≥2.885 ng/mL. A Finnish study by Victorzon et al. [31] explored the prognostic value of CEA and CA 19-9 in patients with GC. The sensitivity of both CEA (cutoff level 3 ng/mL) and CA 19-9 (cutoff level 37 U/mL) for GC was 30%, and the specificities were 73 and 87%, respectively. A significant difference in prognosis for CEA and CA 19-9 between patients with high versus low preoperative serum levels was observed. The authors also found a significant difference in 5-year

survival in stages II, III, and IV between GC patients with high versus low preoperative serum levels only for CA 19-9 and concluded that high preoperative CEA serum levels could predict higher disease stage, but that both CEA and CA 19-9 play a restricted role in the diagnosis of GC. Tachibana et al. [72] studied the correlation between serum CEA levels and clinicopathologic features as well as prognostic information in 196 patients with resectable GC. They found that CEA-positive patients were characterized by more macroscopically infiltrative tumors, more prominent serosal invasion, more frequent lymph node involvement, and a more advanced stage than CEA-negative patients. CEA-positive patients had 3- and 5-year cumulative disease-specific survival rates of 39.6 and 31.7%, respectively, while CEA-negative patients had much more favorable 3- and 5-year cumulative disease-specific survival rates of 83.0 and 77.3%, respectively. Similar results were obtained in a Korean study, in which the GC patients with preoperative serum CEA levels >10.0 ng/mL had a more noteworthy serosal and lymphatic invasion, more advanced stage, and more poorly differentiated GC than the patients with preoperative serum CEA levels <5.0 ng/mL [73]. The survival rate of patients with serum CEA levels >10.0 ng/mL was poorer than that of patients with serum CEA levels between 5.0 and 10.0 ng/mL and that of patients with serum CEA levels <5.0 ng/mL. Horie et al. [74] discovered that plasma CEA could reach extreme values of >1,000 ng/mL in patients with signet ring or poorly differentiated GC and without liver metastasis. They also found that enhanced plasma CEA concentration could discriminate patients with lymph node and peritoneal metastasis. Conversely, Mattar et al. [35] did not detect any correlation between CEA and CA 19-9 levels and the stage of GC. They also reported that serum levels of CA 72-4, CEA, CA 19-9, and AFP were not associated with the histological types of GC.

Choi et al. [38] claimed that positive serum CEA could be used as a marker for recurrence to the liver in GC patients who were treated with radical gastrectomy. In the study of Shimizu et al. [70], the patients with GC recurrence had a CEA value averaging 41.8 ± 101.8 ng/mL, with a positivity rate of 63%, and the highest rate was reported in patients with liver metastasis. They found increased CEA levels about 4.8 months before the clinical detection of cancer recurrence in 4 of 13 patients with GC recurrence. A recent meta-analysis by Deng et al. [75] confirmed the association of elevated pretreatment serum CEA levels with a poor prognosis for GC and a nearly doubled risk of mortality in GC patients (Table 1). The authors concluded that serum CEA may serve as an independent prognostic factor for patients with GC and that CEA could facilitate therapeutic decisions in CEA-positive patients. Sun and Zhang [76] reported a positive predictive value for clinical disease progression after neoadjuvant chemotherapy in GC patients with a CEA >50 ng/mL and a significant reduction in CEA, CA 72-4, and CA 125 after neoadjuvant chemotherapy.

The impediments of CEA use as a tumor marker for GC are associated with its insufficient sensitivity and low specificity due to the observed elevated CEA levels in different cancers and versatile benign conditions. Smoking must also be considered when interpreting serum CEA levels, because smokers tend to have higher levels of serum CEA than nonsmokers [77–79]. Age also influences the results of serum CEA measurement, and otherwise healthy elderly individuals could display higher levels of CEA than young people [79, 80]. In accordance with the data for CA 19-9, an initial CEA surge could also be recognized after the beginning of chemotherapy in patients with metastatic or recurrent GC [41].

CA 72-4 in GC

CA 72-4, initially described by Colcher in 1981 [81], is a mucin-like, high-molecular-weight protein which was designated as a tumor-associated glycoprotein-72 (TAG-72) antigen [81, 82]. TAG-72 antigen was defined as an oncofetal pancarcinoma antigen because

TAG-72 was found in different epithelial-derived cancers and in fetal colon, stomach, and esophagus, whereas expression of TAG-72 was not observed in normal adult tissues [83]. Increased serum levels of CA 72-4 are detected predominantly in patients with gastrointestinal and gynecological cancers, but CA 72-4 can present in the serum of patients with pancreatitis, liver cirrhosis, pneumonia, rheumatic illness, and ovarian cysts, too. The normal result for serum CA 72-4 varies for different laboratories with a range from <2.5 to <7 U/mL.

The results from different studies during the last decades support the idea for the diagnostic and prognostic role of CA 72-4 in GC. Guadagni et al. [84] demonstrated that serum TAG-72 as measured by the CA 72-4 assay could play a role in the diagnosis of late GC and in the prediction of disease recurrence. In a Japanese study by Hamazoe et al. [85], CA 72-4 and CEA serum levels were measured in 86 patients with GC. The results showed that CA 72-4 levels were increased with significantly higher frequency compared to CEA in patients in late stages, in patients with Borrmann type 4, and in patients with peritoneal metastasis. CA 72-4 levels were decreased 1 month after gastrectomy in 25 of 39 patients with resected cancers, and in each of 4 patients with recurrence, postoperative lower serum CA 72-4 levels were followed by elevation of CA 72-4. Based on these data, the investigators concluded that CA 72-4 was highly specific to GC and could be a better tumor marker than CEA for GC patients. Goral et al. [86] reported significant high levels of serum CA 72-4 in GC patients, and the CA 72-4 elevation was more pronounced in patients with liver metastases. Guadagni et al. [87] reported a sensitivity of approximately 40% for CA 72-4 in GC and colorectal cancer and of 50% in ovarian cancer, with an overall specificity of >95%. Safi et al. [88] reported a sensitivity of 61% for serum CA 72-4, whereas CEA and CA 19-9 were positive in 37% of patients with GC. CA 72-4 serum levels were correlated with GC stage as CA 72-4 was positive in 31, 48, 68, and 88% of patients with stage I, II, III, and IV disease, respectively. Moreover, CA 72-4 appeared to be more sensitive than CEA and CA 19-9 in detecting recurrences of GC. Spila et al. [89] reported that serum CA 72-4 showed higher sensitivity compared with either CA 19-9 or CEA in a study with 242 patients with primary or recurrent GC. They found that positive serum CA 72-4 levels were correlated with lymph node involvement, poor prognosis, and advanced stage of GC, while postoperative disappearance of CA 72-4 was associated with curative surgery and longer disease-free interval. In the systematic review of Shimada et al. [28], the highest positive rates of 30% was reported for CA 72-4 in patients with GC compared to 21.1 and 27.8% for CEA and CA 19-9, respectively. In agreement with previous data, a Brazilian study by Mattar et al. [35] showed a higher CA 72-4 positivity rate for GC of 47.7% compared to CEA (25%), CA 19-9 (25%), and AFP (0%). The CA 72-4 level was connected with the stage of GC, because serum CA 72-4 was positive in 9% of patients at stages I and II and in 60.6% of patients at stages III and IV. Conversely, data from the study by Joypaul et al. [10] showed that CA 72-4 had a slightly lower sensitivity of 42% compared to 46% for CA 19-9 in the preoperative diagnosis of GC, although the specificity of CA 72-4 was 100 and 72% for CA 19-9. Postoperative serum CA 72-4 rose to diagnostic values from near-normal levels almost 6 months before clinical diagnosis of recurrence, and the authors presumed that postoperative serial measurements of CA 72-4 could reveal early recurrences in GC patients. Marrelli et al. [90] also reported a higher preoperative positivity for serum CA 19-9 (35%) than for CA 72-4 (20%) in patients with GC, while the preoperative positivity for serum CEA was 16%.

The important role of serum CA 72-4 for the follow-up of GC was identified in an Italian longitudinal study with more than 160 included patients [91]. Approximately half of the patients with recurrent GC had positive presurgical CA 72-4 levels compared to approximately 24% of the patients who remained free of disease. Moreover, the median preoperative serum CA 72-4 levels were significantly increased in relapsing patients and the CA 72-4 level was an independent prognostic factor in predicting recurrence. The data from a French study revealed that pretherapeutic positive CA 72-4 levels were associated with a worse prognosis

in males with metastatic GC and normal values of CA 19-9 and CEA, but CA 72-4 showed lack of significance as an independent prognostic factor when adjusted for CA 19-9 and sex [92]. The results from a retrospective study with 184 GC patients who underwent a 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) neoadjuvant chemotherapy regimen followed by surgical treatment showed that a decrease (>70%) in CA 72-4 may predict pathologic response to neoadjuvant chemotherapy [76].

In a recent study, Yu et al. [36] studied the serum levels of CEA, CA 19-9, and CA 72-4 in 216 patients with gastric adenocarcinoma. They found that the serum levels of CA 72-4, along with those of CEA and CA 19-9, did not show a significant difference according to sex, age, or histological classification.

The data about comparatively good CA 72-4 sensitivity and sizable specificity label CA 72-4 as the optimal serum tumor marker for patients with GC. The results from a Chinese meta-analysis showed that CA 72-4 was the most correlative serum tumor marker for GC in the Chinese population among CA 72-4, CA 242, CA 19-9, CEA, CA 125, and CA 15-3, and significantly superior to others (Table 1) [93]. Nevertheless, the measurement of serum CA 72-4, like the measurement of CA 19-9 and CEA, is not the preferred test for screening of GC. CA 72-4 could be successfully used in the staging and monitoring for recurrence of patients with GC.

Combined Usage of CA 19-9, CEA, and CA 72-4 in GC

Findings from studies in GC patients support the hypothesis that combined use of serum tumor markers could increase their utility in clinical practice. Joypaul et al. [10] detected that CA 72-4 and CA 19-9 had sensitivities of 42 and 46% for the preoperative detection of GC, but the combined sensitivity for the two was 63%. Marrelli et al. [90] detected that the sensitivity in 75 recurrent cases from 133 GC patients who underwent potentially curative surgery was 44% for CEA, 56% for CA 19-9, and 51% for CA 72-4, while the combined use of the CEA, CA 19-9, and CA 72-4 increased the sensitivity to 87%, which reached 100% in patients with positive preoperative levels. Mattar et al. [35] also found that the combination of preoperative serum CA 72-4, CEA, and CA 19-9 increased the sensitivity to 61.4% in patients with GC. Recent concordant data presented by Yu et al. [36] showed that the combined positive rate of serum CEA, CA 19-9, and CA 72-4 was significantly elevated (44.91%) compared to the individual CEA (22.69%), CA 19-9 (18.98%), and CA 72-4 (22.69%) positivity rates in patients with GC. They supposed that the reason for the higher sensitivity of CEA, CA 19-9, and CA 72-4 combination compared to isolated biomarkers is less co-presentation of CEA, CA 19-9, and CA 72-4 in patients with GC. The results from the systematic review by Shimada et al. [28] showed that combinations of CEA, CA 19-9, and CA 72-4 are the most effective ways for staging before surgery or chemotherapy in patients with GC. Jing et al. [94] reported that the combined detection of serum CEA, CA 19-9, CA 24-2, and CA 72-4 showed greater sensitivity and specificity in GC and cardiac cancer patients. In a recent study, Liang et al. [29] investigated the serum CEA, CA 19-9, and CA 72-4 levels in more than 2,200 patients with GC and more than 1,800 healthy volunteers or patients with benign gastric diseases. They found that the serum levels of CEA, CA 19-9, and CA 72-4 were higher in the GC patients than in the control group and that the sensitivity of CEA, CA 19-9, and CA 72-4 in the diagnosis of GC was 20.1–27.6% individually and increased to 48.2% when the three biomarkers were combined. Interestingly, they created an equation which demonstrated better accuracy and diagnostic efficiency compared to the combination of CEA, CA 19-9, and CA 72-4.

Table 2. Application of the serum tumor markers CA 19-9, CEA, and CA 72-4 in patients with gastric cancer

Serum markers	Screening and early diagnostic tool	Prognostic and predictive tool	Monitoring tool
CA 19-9	no	yes	yes
CEA	no	yes	yes
CA 72-4	no	yes	yes

CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

Conclusion

The serum tumor markers CA 19-9, CEA, and CA 72-4 are not suitable for screening and early diagnosis in GC. However, they could contribute to the diagnosis of advanced GC, serve as prognostic tools, predict recurrent or metastatic disease, and help in posttherapeutic follow-up (Table 2). Combined measurement of CA 19-9, CEA, and CA 72-4 in GC patients could elevate their sensitivity. The interpretation of the data for serum levels of CEA, CA 19-9, and CA 72-4 in GC patients must be done cautiously, especially in cases where the concentrations of these tumor markers are borderline or not very high. Regular measurement of the serum CEA, CA 19-9, and CA 72-4 levels in proper intervals probably will raise specificity. Large prospective studies are needed to validate the clinical significance of serum CA 19-9, CEA, and CA 72-4 in GC.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–E386.
2 Kamangar F, Dores GM, Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137–2150.
3 Maconi G, Manes G, Porro GB: Role of symptoms in diagnosis and outcome of gastric cancer. World J Gastroenterol 2008;14:1149–1155.
4 Wang J, Sun Y, Bertagnolli MM: Comparison of gastric cancer survival between Caucasian and Asian patients treated in the United States: results from the Surveillance Epidemiology and End Results (SEER) database. Ann Surg Oncol 2015;22:2965–2971.
5 Virji MA, Mercer DW, Herberman RB: Tumor markers in cancer diagnosis and prognosis. CA Cancer J Clin 1988;38:104–126.
6 Schrohl AS, Holten-Andersen M, Sweep F, Schmitt M, Harbeck N, Foekens J, Brünner N; European Organisation for Research and Treatment of Cancer (EORTC) Receptor and Biomarker Group: Tumor markers: from laboratory to clinical utility. Mol Cell Proteomics 2003;2:378–387.
7 Bates SE, Longo DL: Use of serum tumor markers in cancer diagnosis and management. Semin Oncol 1987;14:102–138.
8 Perkins GL, Slater ED, Sanders GK, Prichard JG: Serum tumor markers. Am Fam Physician 2003;68:1075–1082.
9 Duffy MJ: Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract 2013;22:4–11.

10 Joypaul B, Browning M, Newman E, Byrne D, Cuschieri A: Comparison of serum CA 72-4 and CA 19-9 levels in gastric cancer patients and correlation with recurrence. Am J Surg 1995;169:595–599.
11 Emoto S, Ishigami H, Yamashita H, Yamaguchi H, Kaisaki S, Kitayama J: Clinical significance of CA125 and CA72-4 in gastric cancer with peritoneal dissemination. Gastric Cancer 2012;15:154–161.
12 Wang Q, Yang Y, Zhang YP, Zou Z, Qian X, Liu B, Wei J: Prognostic value of carbohydrate tumor markers and inflammation-based markers in metastatic or recurrent gastric cancer. Med Oncol 2014;31:289.
13 Jing J, Xu X, Du L, Tian B, Sun T, Zhao X, Han C: Clinical assessment and prognostic evaluation of tumor markers in patients with gastric cancer. Int J Biol Markers 2013;28:192–200.
14 Feng F, Tian Y, Xu G, Liu Z, Liu S, Zheng G, Guo M, Lian X, Fan D, Zhang H: Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. BMC Cancer 2017;17:737.
15 McLaughlin R, O'Hanlon D, Kerin M, Kenny P, Grimes H, Given HF: Are elevated levels of the tumour marker CA19-9 of any clinical significance? – An evaluation. Ir J Med Sci 1999;168:124–126.
16 Pavai S, Yap SF: The clinical significance of elevated levels of serum CA 19-9. Med J Malaysia 2003;58:667–672.
17 Polat E, Duman U, Duman M, Derya Peker K, Akyuz C, Fatih Yasar N, Uzun O, Akbulut S, Birol Bostanci E, Yol S: Preoperative serum tumor marker levels in gastric cancer. Pak J Med Sci 2014;30:145–149.
18 Ohtsuka T, Sato S, Kitajima Y, Tanaka M, Nakafusa Y, Miyazaki K: False-positive findings for tumor markers after curative gastrectomy for gastric cancer. Dig Dis Sci 2008;53:73–79.
19 Japanese Gastric Cancer Association: Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4): Gastric Cancer 2017;20:1–19.
20 Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P: Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genet 1979;5:957–971.
21 Magnani JL, Steplewski Z, Koprowski H, Ginsburg V: Identification of the gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. Cancer Res 1983;43:5489–5492.
22 McEver RP, Cummings RD: Perspectives series: cell adhesion in vascular biology. Role of PSGL-1 binding to selectins in leukocyte recruitment. J Clin Invest 1997;100:485–491.
23 Duffy MJ: CA 19-9 as a marker for gastrointestinal cancers: a review. Ann Clin Biochem 1998;35:364–370.
24 Del Villano BC, Brennan S, Brock P, Bucher C, Liu V, McClure M, Rake B, Space S, Westrick B, Schoemaker H, Zurawski VR Jr: Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA 19-9. Clin Chem 1983;29:549–552.
25 Ballehaninna UK, Chamberlain RS: The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol 2012;3:105–119.
26 Steinberg W: The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol 1990;85:350–355.
27 Kato K, Taniguchi M, Kawakami T, Nagase A, Matsuda M, Onodea K, Yamaguchi H, Higuchi M, Furukawa H: Gastric cancer with a very high serum CA 19-9 level. Case Rep Gastroenterol 2011;5:258–261.
28 Shimada H, Noie T, Ohashi M, Oba K, Takahashi Y: Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer 2014;17:26–33.
29 Liang Y, Wang W, Fang C, Raj SS, Hu WM, Li QW, Zhou ZW: Clinical significance and diagnostic value of serum CEA, CA19-9 and CA72-4 in patients with gastric cancer. Oncotarget 2016;7:49565–49573.
30 Zheng TH, Zhao JL, Guleng B: Advances in molecular biomarkers for gastric cancer. Crit Rev Eukaryot Gene Expr 2015;25:299–305.
31 Victorzon M, Haglund C, Lundin J, Roberts PJ: A prognostic value of CA 19-9 but not of CEA in patients with gastric cancer. Eur J Surg Oncol 1995;21:379–384.
32 Bagaria B, Sood S, Sharma R, Lalwani S: Comparative study of CEA and CA19-9 in esophageal, gastric and colon cancers individually and in combination (ROC curve analysis). Cancer Biol Med 2013;10:148–157.
33 Wang W, Chen XL, Zhao SY, Xu YH, Zhang WH, Liu K, Chen XZ, Yang K, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK: Prognostic significance of preoperative serum CA125, CA19-9 and CEA in gastric carcinoma. Oncotarget 2016;7:35423–35436.
34 Sisik A, Kaya M, Bas G, Basak F, Alimoglu O: CEA and CA 19-9 are still valuable markers for the prognosis of colorectal and gastric cancer patients. Asian Pac J Cancer Prev 2013;14:4289–4294.
35 Mattar R, Alves de Andrade CR, DiFavero GM, Gama-Rodrigues JJ, Laudanna AA: Preoperative serum levels of CA 72-4, CEA, CA 19-9, and alpha-fetoprotein in patients with gastric cancer. Rev Hosp Clin Fac Med Sao Paulo 2002;57:89–92.
36 Yu J, Zhang S, Zhao B: Differences and correlation of serum CEA, CA19-9 and CA72-4 in gastric cancer. Mol Clin Oncol 2016;4:441–449.
37 Takahashi Y, Takeuchi T, Sakamoto J, Touge T, Mai M, Ohkura H, Kodaira S, Okajima K, Nakazato H; Tumor Marker Committee: The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study. Gastric Cancer 2003;6:142–145.
38 Choi SR, Jang JS, Lee JH, Roh MH, Kim MC, Lee WS, Qureshi W: Role of serum tumor markers in monitoring for recurrence of gastric cancer following radical gastrectomy. Dig Dis Sci 2006;51:2081–2086.
39 Jagric T, Potrc S, Mis K, Plankl M, Mars T: CA19-9 serum levels predict micrometastases in patients with gastric cancer. Radiol Oncol 2016;50:204–211.

40 Yamao T, Kai S, Kazami A, Koizumi K, Handa T, Takemoto N, Maruyama M: Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. Jpn J Clin Oncol 1999;29:550–555.
41 Jo JC, Ryu MH, Koo DH, Ryoo BY, Kim HJ, Kim TW, Choi KD, Lee GH, Jung HY, Yook JH, Oh ST, Kim BS, Kim JH, Kang YK: Serum CA 19-9 as a prognostic factor in patients with metastatic gastric cancer. Asia Pac J Clin Oncol 2013;9:324–330.
42 Kim HJ, Lee KW, Kim YJ, Oh DY, Kim JH, Im SA, Lee JS: Chemotherapy-induced transient CEA and CA19-9 surges in patients with metastatic or recurrent gastric cancer. Acta Oncol 2009;48:385–390.
43 Feng F, Sun L, Liu Z, Liu S, Zheng G, Xu G, Guo M, Lian X, Fan D, Zhang H: Prognostic values of normal preoperative serum cancer markers for gastric cancer. Oncotarget 2016;7:58459–58469.
44 Kim JH, Jun KH, Jung H, Park IS, Chin HM: Prognostic value of preoperative serum levels of five tumor markers (carcinoembryonic antigen, CA19-9, alpha-fetoprotein, CA72-4, and CA125) in gastric cancer. Hepatogastroenterology 2014;61:863–869.
45 Song YX, Huang XZ, Gao P, Sun JX, Chen XW, Yang YC, Zhang C, Liu HP, Wang HC, Wang ZN: Clinicopathologic and prognostic value of serum carbohydrate antigen 19-9 in gastric cancer: a meta-analysis. Dis Markers 2015;2015:549843.
46 Xiao J, He X, Wang Z, Hu J, Sun F, Qi F, Yang S, Xiao Z: Serum carbohydrate antigen 19-9 and prognosis of patients with gastric cancer. Tumour Biol 2014;35:1331–1334.
47 Marcouizos G, Ignatiadou E, Papanikolaou GE, Ziogas D, Fatouros M: Highly elevated serum levels of CA 19-9 in choledocholithiasis: a case report. Cases J 2009;2:6662.
48 Pyeon SY, Park JY, Ki KD, Lee JM: Abnormally high level of CA-19-9 in a benign ovarian cyst. Obstet Gynecol Sci 2015;58:530–532.
49 Kim HR, Lee CH, Kim YW, Han SK, Shim YS, Yim JJ: Increased CA 19-9 level in patients without malignant disease. Clin Chem Lab Med 2009;47:750–754.
50 Kodama T, Satoh H, Ishikawa H, Ohtsuka M: Serum levels of CA19-9 in patients with nonmalignant respiratory diseases. J Clin Lab Anal 2007;21:103–106.
51 Sheen-Chen SM, Sun CK, Liu YW, Eng HL, Ko SF, Kuo CH: Extremely elevated CA19-9 in acute cholangitis. Dig Dis Sci 2007;52:3140–3142.
52 Mathurin P, Cadranel JF, Bouraya D, Bronstein JA, Collot G, Devergie B, Poynard T, Opolon P: Marked increase in serum CA 19-9 level in patients with alcoholic cirrhosis: report of four cases. Eur J Gastroenterol Hepatol 1996;8:1129–1131.
53 Bertino G, Ardiri AM, Boemi P, Bruno CM, Valenti M, Mazzarino MC, Consolo M, Calvagno GS, Pulvirenti D, Neri S: Meaning of elevated CA 19-9 serum levels in chronic hepatitis and HCV-related cirrhosis. Minerva Gastroenterol Dietol 2007;53:305–309.
54 Howaizi M, Abboura M, Krespine C, Sbai-Idrissi MS, Marty O, Djabbari-Sobhani M: A new cause for CA19.9 elevation: heavy tea consumption. Gut 2003;52:913–914.
55 Yaman E, Coskun U, Buyukberber S, Ozturk B, Osman Kaya A, Yildiz R, Uner A, Yamac D, Benekli M: Persistent elevation of CA 19-9 in an apparently-healthy 56-year-old woman. Lab Med 2007;38:485–486.
56 Kaneko Y, Shibata Y, Nakamura H, Kuroda M, Nakazima T, Kasakura S: Extraordinary high elevation of serum CA19-9 levels in an apparently healthy subject (in Japanese). Rinsho Byori 1999;47:943–948.
57 Qiu MZ, Lin JZ, Wang ZQ, Wang FH, Pan ZZ, Luo HY, Li YH, Zhou ZW, He YJ, Xu RH: Cutoff value of carcinoembryonic antigen and carbohydrate antigen 19-9 elevation levels for monitoring recurrence in patients with resectable gastric adenocarcinoma. Int J Biol Markers 2009;24:258–264.
58 Gold P, Freedman SO: Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121:439–462.
59 Benchimol S, Fuks A, Jothy S, Beauchemin N, Shirota K, Stanners CP: Carcinoembryonic antigen, a human tumor marker, functions as an intercellular adhesion molecule. Cell 1989;57:327–334.
60 Thomas SN, Zhu F, Schnaar RL, Alves CS, Konstantopoulos K: Carcinoembryonic antigen and CD44 variant isoforms cooperate to mediate colon carcinoma cell adhesion to E- and L-selectin in shear flow. J Biol Chem 2008;283:15647–15655.
61 Gold P, Freedman SO: Specific carcinoembryonic antigens of the human digestive system. J Exp Med 1965;122:467–481.
62 Diamandis EP, Bast RC Jr, Gold P, Chu TM, Magnani JL: Reflection on the discovery of carcinoembryonic antigen, prostate-specific antigen, and cancer antigens CA125 and CA19-9. Clin Chem 2013;59:22–31.
63 Grunnet M, Sorensen JB: Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 2012;76:138–143.
64 Hegele A, Mecklenburg V, Varga Z, Olbert P, Hofmann R, Barth P: CA19.9 and CEA in transitional cell carcinoma of the bladder: serological and immunohistochemical findings. Anticancer Res 2010;30:5195–5200.
65 Machens A, Ukkat J, Hauptmann S, Dralle H: Abnormal carcinoembryonic antigen levels and medullary thyroid cancer progression: a multivariate analysis. Arch Surg 2007;142:289–293.
66 Kurebayashi J, Nishimura R, Tanaka K, Kohno N, Kurosumi M, Moriya T, Ogawa Y, Taguchi T: Significance of serum tumor markers in monitoring advanced breast cancer patients treated with systemic therapy: a prospective study. Breast Cancer 2004;11:389–395.
67 Momma T, Kimura S, Saito S, Onoda N: Prostate cancer with high serum level of CEA and CA19-9: a case report (in Japanese). Hinyokika Kiyo 1998;44:187–191.

▶68 Khoo SK, Mackay IR: Carcinoembryonic antigen in serum in diseases of the liver and pancreas. J Clin Pathol 1973;26:470–475.
▶69 Loewenstein MS, Zamcheck N: Carcinoembryonic antigen (CEA) levels in benign gastrointestinal disease states. Cancer 1978;42:1412–1418.
▶70 Shimizu N, Wakatsuki T, Murakami A, Yoshioka H, Hamazoe R, Kanayama H, Maeta M, Koga S: Carcinoembryonic antigen in gastric cancer patients. Oncology 1987;44:240–244.
▶71 Nan J, Li J, Li X, Guo G, Wen X, Tian Y: Preoperative serum carcinoembryonic antigen as a marker for predicting the outcome of three cancers. Biomark Cancer 2017;9:1–7.
▶72 Tachibana M, Takemoto Y, Nakashima Y, Kinugasa S, Kotoh T, Dhar DK, Kohno H, Nagasue N: Serum carcinoembryonic antigen as a prognostic factor in resectable gastric cancer. J Am Coll Surg 1998;187:64–68.
▶73 Kim DY, Kim HR, Shim JH, Park CS, Kim SK, Kim YJ: Significance of serum and tissue carcinoembryonic antigen for the prognosis of gastric carcinoma patients. J Surg Oncol 2000;74:185–192.
▶74 Horie Y, Miura K, Matsui K, Yukimasa A, Ohi S, Hamamoto T, Kawasaki H: Marked elevation of plasma carcinoembryonic antigen and stomach carcinoma. Cancer 1996;77:1991–1997.
▶75 Deng K, Yang L, Hu B, Wu H, Zhu H, Tang C: The prognostic significance of pretreatment serum CEA levels in gastric cancer: a meta-analysis including 14,651 patients. PLoS One 2015;10:e0124151.
▶76 Sun Z, Zhang N: Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. World J Surg Oncol 2014;12:397.
▶77 Fukuda I, Yamakado M, Kiyose H: Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. J Med Syst 1998;22:89–93.
▶78 Cullen KJ, Stevens DP, Frost MA, Mackay IR: Carcinoembryonic antigen (CEA), smoking, and cancer in a longitudinal population study. Aust NZ J Med 1976;6:279–283.
▶79 Alexander JC, Silverman NA, Chretien PB: Effect of age and cigarette smoking on carcinoembryonic antigen levels. JAMA 1976;235:1975–1979.
▶80 Touitou Y, Proust J, Klinger E, Nakache JP, Huard D, Sachet A: Cumulative effects of age and pathology on plasma carcinoembryonic antigen in an unselected elderly population. Eur J Cancer Clin Oncol 1984;20:369–374.
▶81 Colcher D, Hand PH, Nuti M, Schlom J: A spectrum of monoclonal antibodies reactive with human mammary tumor cells. Proc Natl Acad Sci USA 1981;78:3199–3203.
▶82 Johnson VG, Schlom J, Paterson AJ, Bennett J, Magnani JL, Colcher D: Analysis of a human tumor-associated glycoprotein (TAG-72) identified by monoclonal antibody B72.3. Cancer Res 1986;46:850–857.
▶83 Thor A, Ohuchi N, Szpak CA, Johnston WW, Schlom J: Distribution of oncofetal antigen tumor-associated glycoprotein-72 defined by monoclonal antibody B72.3. Cancer Res 1986;46:3118–3124.
▶84 Guadagni F, Roselli M, Amato T, Cosimelli M, Perri P, Casale V, Carlini M, Santoro E, Cavaliere R, Greiner JW, et al: CA 72-4 measurement of tumor-associated glycoprotein 72 (TAG-72) as a serum marker in the management of gastric carcinoma. Cancer Res 1992;52:1222–1227.
▶85 Hamazoe R, Maeta M, Matsui T, Shibata S, Shiota S, Kaibara N: CA72-4 compared with carcinoembryonic antigen as a tumour marker for gastric cancer. Eur J Cancer 1992;28A:1351–1354.
▶86 Goral V, Yesilbagdan H, Kaplan A, Sit D: Evaluation of CA 72-4 as a new tumor marker in patients with gastric cancer. Hepatogastroenterology 2007;54:1272–1275.
▶87 Guadagni F, Roselli M, Cosimelli M, Ferroni P, Spila A, Cavaliere F, Casaldi V, Wappner G, Abbolito MR, Greiner JW, et al: CA 72-4 serum marker – a new tool in the management of carcinoma patients. Cancer Invest 1995;13:227–238.
▶88 Safi F, Kuhns V, Beger HG: Comparison of CA 72-4, CA 19-9 and CEA in the diagnosis and monitoring of gastric cancer. Int J Biol Markers 1995;10:100–106.
▶89 Spila A, Roselli M, Cosimelli M, Ferroni P, Cavaliere F, Arcuri R, Tedesco M, Carlini S, D'Alessandro R, Perri P, Casciani CU, Greiner JW, Schlom J, Guadagni F: Clinical utility of CA 72-4 serum marker in the staging and immediate post-surgical management of gastric cancer patients. Anticancer Res 1996;16:2241–2247.
▶90 Marrelli D, Pinto E, De Stefano A, Farnetani M, Garosi L, Roviello F: Clinical utility of CEA, CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer. Am J Surg 2001;181:16–19.
▶91 Aloe S, D'Alessandro R, Spila A, Ferroni P, Basili S, Palmirotta R, Carlini M, Graziano F, Mancini R, Mariotti S, Cosimelli M, Roselli M, Guadagni F: Prognostic value of serum and tumor tissue CA 72-4 content in gastric cancer. Int J Biol Markers 2003;18:21–27.
▶92 Ychou M, Duffour J, Kramar A, Gourgou S, Grenier J: Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. Dis Markers 2000;16:105–110.
▶93 Chen XZ, Zhang WK, Yang K, Wang LL, Liu J, Wang L, Hu JK, Zhang B, Chen ZX, Chen JP, Zhou ZG, Mo XM: Correlation between serum CA724 and gastric cancer: multiple analyses based on Chinese population. Mol Biol Rep 2012;39:9031–9039.
▶94 Jing JX, Wang Y, Xu XQ, Sun T, Tian BG, Du LL, Zhao XW, Han CZ: Tumor markers for diagnosis, monitoring of recurrence and prognosis in patients with upper gastrointestinal tract cancer. Asian Pac J Cancer Prev 2014;15:10267–10272.