SYSTEMATIC REVIEW

Article received on May 20, 2016 and accepted for publishing on June 19 2016.

Tumor markers in gastroenterology: useful or useless

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INTRODUCTION

Tumor markers are biomarkers that can be found in blood, urine or different body tissues, produced either by cancer cells or normal cells in response to cancer or in different noncancerous conditions (gastrointestinal stromal tumors). Their use varies from cancer screening on a population basis, to staging different tumors or to evaluate the efficiency of the treatment. Most frequently used in gastrointestinal malignancies are: carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and α-fetoprotein. However there are many markers that can be useful in dealing with gastrointestinal cancer such as: carbohydrate antigen 125, cyfra 21-1, chromogranin, tumor M2-PK, neuron-specific enolase, smooth muscle actin [1]. Future research show the utility of multiple tumor marker test, when by combining more tests in parallel the predictive value might be increased. For example: when talking about pancreatic or stomach cancer one might combine: CEA, CA19-9 and CA 72-4 [1,2].

ALPHA FETOPROTEIN

So far, alpha fetoprotein is the most studied serological marker in the surveillance of hepatocellular carcinoma, derived from the liver cells and yolk sac [3]. Its' use is debatable. Some studies show that a cut-off of 20 ng/mL carries a sensitivity of 41% to 65% and specificity between 80% and 94%, with a positive and negative predictive value of 25 and 98 percent. Even though The American Association for the Study of Liver Disease (AASLD) guidelines shows that cirrhosis is a possible cause of elevated AFP, its sensitivity (60%) is higher than that of ultrasound (58%). Therefore current data from the literature support the use of AFP combined with ultrasound as the surveillance tests of choice, taken every 6 months, leading to early detection of hepatocellular carcinoma (HCC) [4]. Despite the fact that more than 40% of the patients with HCC have normal AFP, serum levels higher than 500 mcg/L in a high-risk patient is diagnostic of HCC [3,5].

There is a demonstrated correlation between the tumor size and serologic AFP: higher levels with a sudden acceleration appear with HCC that measure more than 3 cm [6]. Moreover serum levels from 1,000 to 10,000 mcg/L are encountered in tumors past 5 cm in diameter. Date from the literature associate high levels of AFP with poorly-differentiated tumors, but further studies are required [7].

False positive values of AFP may be related to flares of activity in chronic viral hepatitis (B or C). Therefore the use of this serologic marker is very important in patients with hepatitis B or C during treatment with nucleotide analogues for hepatitis B or drug acting

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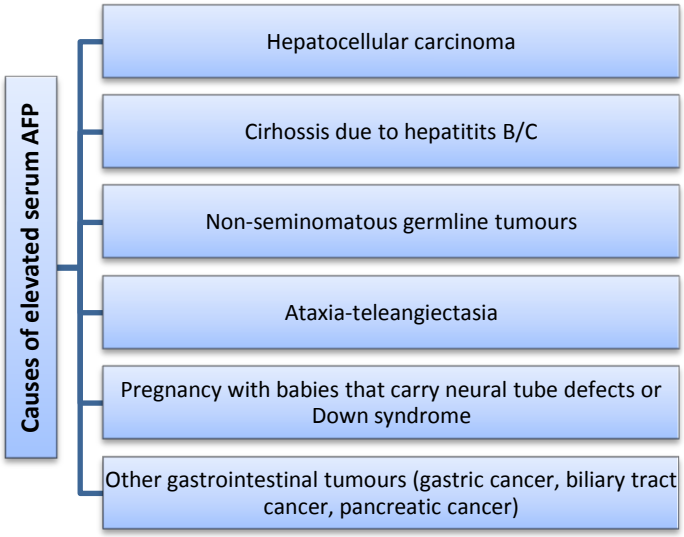
agents (interferon free) for hepatitis C, when we cannot encounter flares of transaminases [9].

AFP remains an important prognostic marker in patients after resection or in those who are taken into consideration for transplant. High values over 1,000 mcg/L (believed a surrogate of vascular invasion) associates extremely high risks of recurrent disease after transplantation. Moreover some studies assign this value as an exclusion criterion for liver transplantation in patients with HCC that meet the Milan criteria, in order to improve posttransplant outcome [10]. An assay of serum AFT post-transplant is in order every 3 months for 2 years if initially elevated, then every 6 months. This serologic marker remains an independent prognostic predictor of outcome after ortotopic liver transplant for HCC [11].

Table 1: Causes of elevated serum alpha-fetoprotein [8]



CARCINOEMBRYONIC ANTIGEN

Discovered in 1965, CEA is a glycoprotein associated with colorectal cancer with a rather low sensitivity and specificity. Even though CEA is not used as a diagnostic test, levels over 5.0 ng/mL can predict a unfavorable prognosis, regardless the tumor stage [12].

A Cochrane review showed that a cut-off value of 2.5mcg/L for CEA carries a pooled sensitivity of 82 percent and specificity of 80 percent. For a cut-off of 10 mcg/L the sensitivity lowered to 68%, but the specificity reached 97 percent, due to fewer false positive values. CEA testing should be done once every 3 to 6 months. One must bear in mind the possible false positive values of CEA (most encountered between 5 and 10 ng/mL).

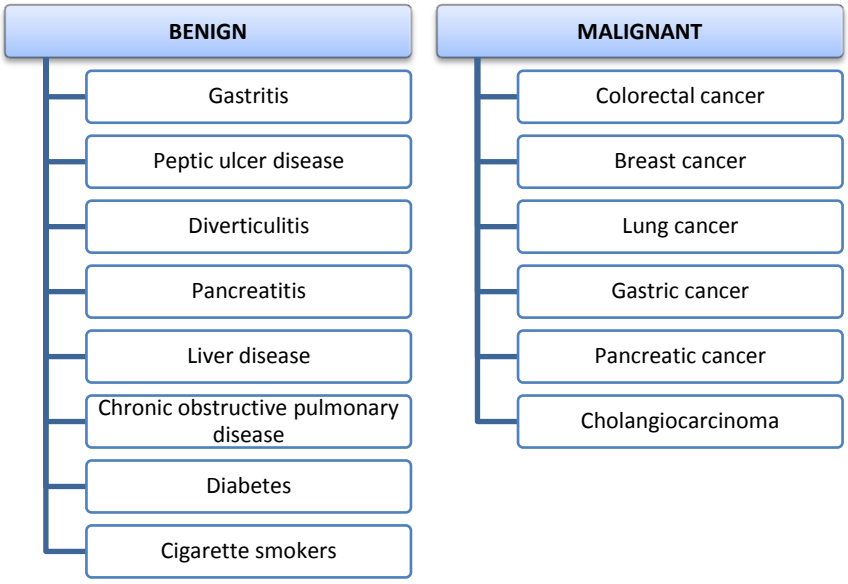
One possible cause is due to the adjuvant therapy with fluorouracyl (therefore some recommend the end of adjuvant treatment before measuring CEA).

There are many arguments against using CEA as a screening test such as: almost half of the recurrences of CRC present normal values of CEA; is has no impact on improving survival and the quality of life and it is not cost-effective. One strong argument in favor of testing CEA is the detection of recurrences [13].

Even though CEA is prohibited in the mass screening and diagnostic pathway of colorectal carcinoma (CRC), it has value in the follow-up of patients with diagnosed CRS according to the American Society of Clinical Oncology guidelines: from surgical treatment planning to post-treatment follow-up and prognosis [14,15]. High serum levels of CEA after 4 weeks of the surgery (this being twice the plasma half-life of CEA) indicate the persistence of the disease, occult metastasis and the need to reevaluate the prognosis

[8]. In conclusion, CEA levels can be associated to the TNM classification of CRC, due not only to its prognostic value, but also the decision of adjuvant chemotherapy.

Table 2: Benign and malignant causes of high levels of seric CEA[8,13]



Studies showed that high CEA even in node negative patients show a worse prognosis, a higher rate of recurrence, therefore adjuvant chemotherapy could be considered [16].

CEA can be used to monitor the response to treatment in metastatic disease. Whilst the decrease of seric levels of CEA shows the favorable response to the treatment, the rising level of CEA is incompatible with tumor regression [8].

Some studies show that bile CEA levels are elevated in cholangiocarcinoma, but not in benign diseases. Used as a single tumor marker, CEA is neither sensitive enough, nor specific enough to diagnose cholangiocarcinoma [8]. Different combinations of CEA and CA 19-9 are used to diagnose cholangiocarcinoma in patients with primary sclerosing cholangitis.

When using cut-off values of 5.2ng/mL for CEA and 180 U/mL for CA 19-9 the sensitivity was 100% and the specificity reached 78%. Despite this, other data from the literature show a sensitivity of 63% for detecting cholangiocarcinoma in patients with PSC, whilst the specificity when using a combined CA 19-9 and CEA only reaches 33%, albeit with higher specificity [13,17].

CARBOHYDRATE ANTIGEN 19-9

Most frequently used serological marker for cholangiocarcinoma, CA 19-9 has a wide variation in sensitivity and specificity. However, values over 1000 IU/mL are encountered in advanced disease with peritoneal dissemination [18].

CA 19-9 levels can be elevated in 45% of patients with non-malignant affliction since the tumor marker is produced by abnormal cyst epithelium. Benign diseases that can be associated with high values of CA 19-9 are: cholestasis, cirrhosis and cholestatic diseases [18,19].

In patients with primary biliary cholangitis CA 19-9 levels can be increased due to cholangitis or biliary obstruction. Literature states that a cut-off value of 100 IU has a 86% sensitivity and a 89% specificity for cholangiocarcinoma [4]. However CA 19-9 remains the most commonly used serological marker in cholangiocarcinoma with a sensitivity of 89% and a specificity of 86% for a cut-off over 100 IU/mL.

Moreover values over 1,000 IU/mL are associated with unresecability [17].

CA 19-9 has a higher specificity in the diagnosis of cholangiocarcinoma in patients with PBS. Therefore CA 19-9 combined with ultrasound or magnetic resonance cholangiopancreatography (MRCP) are recommended in the annual screening of PBS patients for cholangiocarcinoma [17,20].

Studies shows that the median preoperative CA 19-9 levels in pancreatic adenocarcinoma were 379 IU/mL in patients who would not benefit a curative resection, whilst in patients where it was resected it was 130 IU/mL.

Moreover, values over 130 U/mL postoperative demonstrate unresectability, the likelihood of R0 resection and long-term outcomes [4]. CA 19-9 has a low specificity; therefore studies show that it should not be used as a screening test for pancreatic cancer. However serial testing once every one to three months of this tumor serological marker in the follow-up of patients after curative surgery or in patients with advanced disease that receive chemotherapy was proven useful. Moreover, elevated values of CA 19-9 could precede the radiological images of recurrent disease (must be confirmed with imaging studies or biopsy) [21].

Table 3: Malignant causes of high values of CA 19-9 [18]

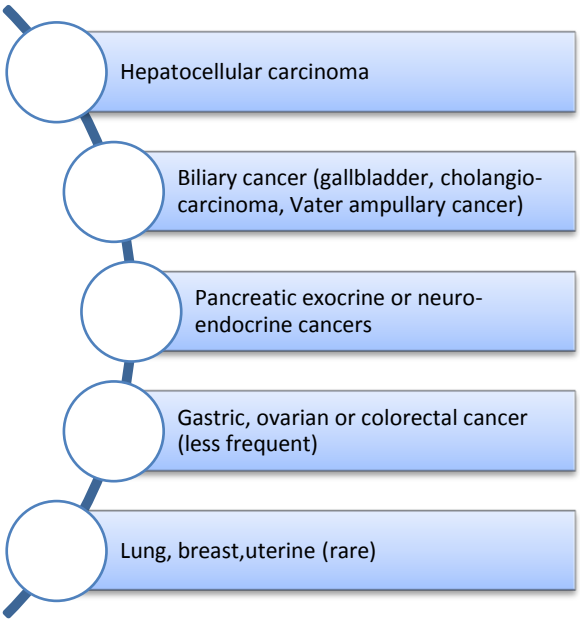
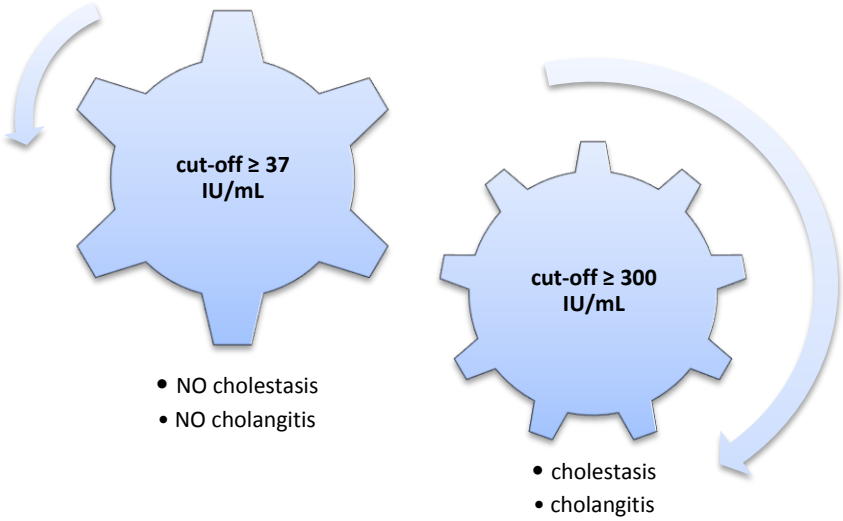


Table 4: Cut-off values for CA 19-9 related to the presence of cholangitis (may associate fever, right upper quadrant pain and leukocytosis) or cholestasis (serum bilirubin larger than 3mg/dL) [18]



In patients that underwent curative surgery, the normalization of the values of CA 19-9 within 6 months is associated with twice the mean of survival than in patients that kept elevated CA 19-9 [17].

In individuals with negative Lewis phenotype (7% of the population), CA19-9 is unreliable since the tumor marker needs the expression of Lewis blood group antigen, leading to a false negative response [21].

Tumor markers could be used to differentiate chronic pancreatitis and pancreatic cancer. CA 19-9 was once used for this purpose, however due to its' low specificity and sensitivity this purpose was forgotten. Despite the fact that CA 19-9 is not used for surveillance in chronic pancreatitis, it can be helpful in families with hereditary pancreatitis [22].

OTHER TUMOR MARKERS

Cancer Antigen 125 (CA 125) is a glycoprotein most frequently used in the diagnosis, screening and prognosis of ovarian cancer, but with a very low sensitivity and specificity especially in early disease. It can have elevated values in non-gynecologic cancers such as: colon, liver, gallbladder cancer [4,8].

Carbohydrate Antigen 72.4 (CA 72.4) is a serological tumor marker used as a specific predictor for clinical recurrence in patients with gastric and colorectal cancer that undergo surgery and to follow up the treatment [23,24]. CA 72.4 with values higher than 7 IU/mL postoperative are associated with a worse prognosis, higher risk of recurrence and higher death risk. Studies show that in stage II colorectal cancer this tumor marker discriminates better than CEA the patients that will relapse or die from those with a favorable prognosis [25,26].

Chromogranin A is a protein contained by the neuroendocrine tumor cells. Elevated values can be encountered in a number of benign and malignant diseases. When referring to gastrointestinal disease we can find high values of chromogranin A in: carcinoid tumors of the gastrointestinal tract, pancreatic neuroendocrine tumors, colon cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, liver cirrhosis, chronic atrophic gastritis, inflammatory bowel disease, and others. Chromogranin A has been associated with treatment response and might have prognostic value in neuroendocrine tumors [4,27].

CONCLUSION

Tumor markers remain a helpful tool in different afflictions. *AFP* is now considered the surveillance test of choice along with ultrasound in hepatocellular carcinoma. *CEA* is not used in the diagnosis of colorectal cancer, but in the prognosis and follow-up after curative surgery. *CA 19-9* is especially useful in the diagnosis pathway of cholangiocarcinoma in patients with PBS. Moreover, values over 1000 IU/ml are highly suggestive for cancer.

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