

CLASSIC TUMOR MARKERS IN GASTRIC CANCER. CURRENT STANDARDS AND LIMITATIONS

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Abstract

The progress made in the last few years made available a large amount of information that needs to be integrated and ordered by oncologists. Tumor markers are one of the pieces that physicians need to fit into the bigger puzzle. This article will detail the most frequent etiologies for the surges in the carcinoembryonic antigen (CEA), cancer-related antigen 72-4 (CA 72-4), cancer-related antigen 19-9 (CA 19-9) serum levels and their indications.

Although tumor markers are an invaluable asset to medical practice, their role in screening, diagnosis and oncologic treatment remains poorly standardized. Ongoing or future clinical trials will shed light on pending problems.

Keywords: tumor markers, CEA, CA 72-4, CA 19-9, gastric cancer.

Cancer represents a big public health issue, its incidence and mortality rate being on the rise. Globocan 2012 estimates that 14.1 million new cases are diagnosed every year, with a mortality of 8.2 million [1]. Gastric cancer is the fifth most common form of cancer, with approximately one million new cases diagnosed every year. It is the sole form of cancer for which a drop in incidence was recorded [1]. 50% of these cases are encountered in developing countries. The drop in the number of cases of gastric cancer is not coupled with a decrease in the mortality rate. Gastric cancer ranks third in terms of mortality rates, which proves that it remains one of the tumor sites with an extremely severe prognosis [1]. In Romania, its incidence and mortality rate are both over the European average, being 5.2 and 7.1/100000 habitants respectively by comparison

with 3.5 and 4.9 respectively [2]. In Romania, gastric cancer is a neoplasia with a marked increase in incidence. The number of deaths caused by gastric cancer is higher than the European average.

Less than 20% of the newly diagnosed cases are stage I or II, the rest of them already being regional or distant metastases, in which case the chances of recovery are close to zero and the average survival rate is of 6 months to 1 year [3].

Gastric cancer represents a difficult tumor site due to late diagnosis. In the light of current available data, international oncology clinical practice guidelines do not recommend population screening but an active monitoring of the subjects at high risk [4].

The amount of information on this neoplastic disease is overwhelming for readers interested in the latest news in the field. Daily, thousands of articles bring an element

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of novelty which contributes to a better understanding of this neoplastic disease. Tumor markers represent such an element, whose role in cancer management was long overrated. The modern medical approach in oncological diseases is an integrative one: information from all fields must be put together as in a puzzle. Tumor markers are nothing more than a piece of this puzzle.

The ideal tumor marker is a biochemical indicator selectively secreted by cancer cells alone, in the blood or in other body fluids, which should theoretically allow an accurate and relatively simple diagnosis of neoplasia. Still, in reality, these markers are neither specific (high levels being encountered in pathologies other than neoplasia as well) nor sensitive (metastatic cases may involve non-secreting tumors). Besides, normal levels were set using the Gaussian function. The cut-off value that can differentiate between cancer and a benign condition is undoubtedly different. Thus, studies which included cancer patients, patients suffering from benign gastric conditions and a group of healthy subjects revealed the fact that setting a higher reference level for cancer-related antigen 72-4 (CA 72-4) through regression curves increases the discrimination sensitivity of the diagnosis of malignant pathologies by comparison with other pathologies [5,6]. International guidelines do not accept tumor markers in the process of diagnosis of gastric cancer [4]. Their usefulness in gastric cancer can be acknowledged in:

- monitoring the effectiveness of cytostatics – radiological assessment remains the gold standard [4].
- the follow-up period – their role is controversial because an early detection of relapse does not improve survival rates [4].

The ideal tumor marker meets the following criteria:
- is determined by a simple and inexpensive method; - has a specificity of at least 70% and a sensitivity of 90% [7]. In practice, the main limitations of their use are: limited organ specificity as well as low sensitivity, which prevent early cancer diagnosis or determine increases even in benign conditions, which entail false positive results.

In gastric cancer, the most used tumor markers are: CA 72-4, carcinoembryonic antigen (CEA) and cancer-related antigen 19-9 (CA 19-9).

Cancer-related antigen 72-4

CA 72-4 is a glycoprotein found on the surface of tumor cells, with a weight of 200-420 kDA [8]. The tumor spectrum in which it is grown includes, besides gastric cancer, pancreatic, ovarian, breast and colorectal tumors [9,10].

Normal value (depending on the laboratory technique): <6.9 U/mL [11]. Detection limit: 0.2 u/mL [11].

The overall sensitivity of this test is estimated to be of 40% in gastric cancer (as in colorectal cancer; it is of 50% in ovarian cancer), with an overall specificity of 95% [12].

This marker is assayed in peripheral blood, but there are studies that compared serum levels to peritoneal lavage fluid levels [13]. It appears that the surge in serum levels best correlates with the stage of lymph node involvement (N category), whereas peritoneal fluid levels correlate with the N stage and T stage as well (serum involvement), characterizing more accurately the advanced locoregional stage of the gastric tumor, as well as prognosis [14,15].

Other studies outlined the role of CA 72-4 in the selection of operable patients, the correlation between serum levels and tumor resectability being statistically significant [16].

Chen's meta-analysis [17], which included 33 published studies, found an overall accuracy of 77% for CA 72-4, much higher than the accuracy of the other markers under scrutiny.

Carcinoembryonic antigen

CEA is a glycoprotein attached to the surface of enterocytes, with a weight of 200 kDA and a role in programmed cell death and cell adhesion [18].

Normal values are of <3 ng/mL in nonsmokers or of <5 ng/mL in smokers [11]. Its half-life is, on average, 3 days, which makes it possible to repeat the marker every 7 days.

High pre-therapeutic levels of CEA are correlated with the stage of the disease, especially in patients with peritoneal serous carcinoma [19].

Like for CA 72-4, the sensitivity of CEA was studied both in peripheral blood and in peritoneal fluid. In Mandorwski's study [20], CA 72-4 is the most sensitive marker in the serum, whereas in the peritoneal fluid the marker that correlates best with the stage of the disease (especially in the case of peritoneal serous carcinoma) is CEA. In some studies [21], the cut-off value for CEA in the peritoneal lavage fluid was of 100 ng/mL. Xiao's meta-analysis proved that high CEA levels in the peritoneal fluid statistically correlate significantly better with the diagnosis of peritoneal recurrence of gastric cancer than standard cytology [22].

Some of the studies proved that the correlation between CEA and locoregional relapse is statistically significant [23,24], being a predictive factor in gastric cancer. In the case of liver metastasis relapse, the CEA level may increase approximately 3 months prior to the radiological confirmation of the disease.

Normal pre-therapeutic levels can be a positive predictive factor correlated with better survival, in particular in patients receiving perioperative chemotherapy [25]. Normal postoperative levels for a period that does not exceed 2 months also correlate with a better overall survival [26,27]. An increase in its level generally indicates relapse, at least at peritoneal level. It is less sensitive for other sites of cancer metastasis [28,29].

An interesting clinical particularity consists in the

occurrence of gastric cancer in young patients aged between 18 and 30 years old, for whom the secretion of CEA by the tumor is statistically significant far more often, serum levels are much higher – this being a predictive factor for overall survival – the tumors larger and the lymph-vascular involvement more frequent [30].

Cancer-related antigen 19-9

CA 19-9 is a protein which plays a role in cell adhesion. Its normal value is of <37 UI/L. Its half-life is of 1 to 3 days [11].

It is assayed in peripheral blood. Measuring the level of CA 19-9 in peritoneal fluid appears to have higher accuracy in terms of preoperative predictability of the stage of the disease [22].

At the end of the surgical treatment, CA 19-9 must return to normal values in maximum 2 months. Past 2 months, elevated values entail a guarded prognosis [27,31]. The preoperative level can be tied to the early stage of the disease [14,16].

CA 19-9 was studied as preoperative assessment in patients with gastric cancer. It statistically correlated with lymph node involvement [32], but did not contribute as much as CEA in the identification of operable patients [33].

In the monitoring of patients with gastric cancer, the regular assessment of CA 19-9 serum levels confirms relapse approximately 2 months earlier than the radiological method [24].

CA 19-9 appears to be an independent predictive factor in the case of metastatic or recurrent patients and possibly for those undergoing curative surgery as well [34].

Comparisons Between the Tumor Markers Used in Gastric Cancer

CEA versus CA 19-9

The sensitivity and specificity of tumor markers was compared in various studies. Bagaria assessed these markers in different tumor sites: esophagus, stomach, and colon. In gastric cancer, the sensitivity of CEA is of approximately 30%, with a negative predictive value (NPV) of 58.82%, by comparison with colorectal cancer, in which its sensitivity is of 74% and the NPV of 79.36%. The sensitivity of CA 19-9 in gastric cancer is higher than that of CEA, being of 42%, with a NPV of 63.29%. By contrast, in colorectal cancer, CA 19-9 is less effective, its sensitivity being of only 26%, with an NPV of 57.47%. If cases are assessed by associating the two markers, sensitivity increases to 58%, with an NPV value of 70.42% [35]. CEA appears to be the marker to be preferred in colorectal cancer, whereas CA 19-9 seems to be more sensitive in gastric cancer.

Ishigami's study compared CEA to CA 19-9 in preoperative assessment. By considering the cut-off value of the statistical analysis to be twice the normal value (10 ng/mL for CEA and 74 U/mL for CA 19-9), CEA was found to be more valuable in making a prognosis concerning the

success of the surgical curative resection, lymph node involvement and the T stage in these patients. In these patients, surges in both markers contribute to a much better assessment of the positivity of their metastatic status [36]. A more recent study identified a predictive role of the pre-therapeutic values of CEA and CA 19-9, which were correlated with the TNM stage, lymph node invasion and the T category [37]. Neoadjuvant chemotherapy reduces the amount of CEA and CA 19-9 secreted by the primitive tumor, quantified by immunohistochemical staining with unclear significance.

CEA versus CA 19-9 versus CA 72-4

As far as perioperative assessment is concerned, a Korean study on patients who underwent curative surgery showed that CEA appears to be the marker with the highest sensitivity both in early gastric cancer and in more advanced stages of the disease: 40% and 100% respectively, by comparison with CA 19-9 (5.6% and 68.2%) and CA 72-4 (2.8% and 51.3%) [38]. The postoperative level of CEA is a predictive factor for recurrence [38].

In other studies, CA 72-4 is credited with an accuracy of 77%, higher than for other tumor markers [17]. The use of tests for all the enumerated markers increases sensitivity to 74% without however increasing specificity [17].

A Japanese meta-analysis has studied the role of tumor markers in gastric cancer. Over 4900 articles were selected from the available publications. Out of these articles, only 187 had references to CEA and CA 19-9 and only 19 to all three markers. The overall true positive rate was of 21% for CEA, of 27.8% for CA 19-9 and of 30% for CA 72-4 [24]. Available data suggest a statistically significant correlation between serum level on the one hand and tumor stage and survival on the other hand. Monitoring patients using tumor markers allows the early diagnosis of metastases or of relapse, despite the fact that the ESMO guidelines underline that early diagnosis does not improve survival [4,24].

The data concerning 1500 patients with gastric cancer who underwent radical surgical procedures revealed the fact that a significant statistical correlation existed between CEA and the risk of lymph node involvement, whereas CA 19-9 and CA 72-4 were negative predictive factors for the overall survival in the N1-N2 stages (up to 6 invaded lymph nodes) [14].

In metastatic patients with lesions that are undetectable through CT, the assessment of the effectiveness of oncologic treatment and, implicitly, the therapeutic decision, can be made based on the evolution of the tumor markers, with a positive statistically significant effect on overall survival [39]. The dynamic assessment of tumor markers allows the selection of patients with favorable prognosis [40].

The detection of high levels in the peritoneal fluid can mean that the case is inoperable or that there is

a risk of tumor residue after resection (R1). This is very useful in primary assessment or at the end of neoadjuvant chemotherapy, the risk of an early relapse at peritoneal level being high in this category of patients [41].

The usefulness of the markers in treatment monitoring is disputed. An increase of the marker after one cycle or during inter-treatment cannot be automatically labeled as tumor progression – the increase may also be triggered by tumor destruction, as proven in Kim's study [42], this "surge phenomena" being coupled with a radiological response to chemotherapy. The length of this "surge phenomena" depends on the pharmacokinetics of the markers. For CEA, it may take 2.8 weeks to reach the peak and it may last 9.1 weeks in total. For CA 19-9, these values are of 2.3 weeks and 7.1 weeks respectively. High CEA and CA 19-9 values at the end of adjuvant chemotherapy may suggest a high risk of early relapse [43].

There are studies which compared the sensitivity and specificity of the markers used in gastric cancer in the follow-up period. Among them, CA 72-4 appears to have the highest sensitivity and specificity (Se= 50%, Sp=100%), by comparison with CEA (Se= 16%, Sp=100%) and CA 19-9 (Se= 33,3%, Sp= 93,3%) [44,45]. Some authors consider CEA to be of greater interest, to the detriment of CA 72-4 [45]. The cut-off values for CEA and CA 19-9 during follow-up seem to be 5 ng/mL and 100 UI/mL respectively.

Conclusion

The usefulness of tumor markers, as well as their indications, is currently under debate. They may play a role in the selection of the patients who benefit the most from their use during follow-up or in the assessment of treatment in case of relapse or metastasis. Current data are mostly provided by retrospective studies which included a small number of patients and which do not allow us to draw clear-cut conclusions, for now. This is the reason why international guidelines are not very precise.

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