THERAPEUTIC, PROGNOSTIC AND DIAGNOSTIC IMPORTANCE OF THE TUMOUR MARKERS IN COLORECTAL CARCINOMA

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Keywords: *colorectal carcinoma, tumor markers*

Abstract: *Colorectal carcinoma represents a frequent neoplasia localization both in men, and in women, at world level. The most usual biomarkers for colorectal carcinoma with prognostic and predictive importance for diagnosis and treatment are the CEA and CA19-9.*

Cuvinte cheie: *cancer de colon, markeri tumorali*

Rezumat: *Cancerul colorectal reprezintă o localizare neoplazică frecventa atât la barbaţi cât şi la femei, pe plan mondial. Cei mai uzuali biomarkeri din cancerele colorectale cu rol prognostic şi predictiv pentru diagnostic şi tratament sunt CEA şi CA19-9.*

INTRODUCTION

The tumour markers in colorectal carcinoma (CCR) represent a practical utility when talking about the evaluation of the illness from the moment of diagnosis, as well as when referring to recurrence and metastasis. Serial determinations of more than one marker at once are in a great relation with the clinical evolution of the illness, being important as a prognosis test.(1,4) The most important immunological markers known in colorectal carcinoma (CCR) are: *Carcino-embrionary Antigen (ACE) and CA19-9. As a pre-surgery prognosis index* ***ACE*** *is helpful in establishing the stage of the illness.* It has an important role in *monitoring the metastasis illness during the treatment*: ACE is determined at the beginning of the treatment; even two high values over the initial value during the treatment are enough to consider the illness in evolution, even though there is no correlation with the imaging data.(10,13) When talking about the metastasis illness, 85% of the cases will register high ACE values. ACE is considered to be the election marker when monitoring the treatment (5). On the other hand, a high value of the ACE during the therapy indicates an evolution of the illness. **CA19-9** has the same role: it is an antigen which measures the mucin from the tumour secretion; it is produced in pancreases, stomach and colon adenocarcinomas.

AND Proliferation Index and AND ploidy (index): are determined through flow cytometry, or through analysis of the fresh tumour tissue or fixed in paraffin.(6)

P53 is a tumoral suppressor gene which prevents the separation of the altered ADN cells.(8) In colorectal carcinoma, p53 gene is mutant, or even is absent.(12) It is not recomended to use it as routine test. ***Oncogena ras*****,** mutant or hiper-expressed, leads to the activation of p21, whose abnormal expression is associated with a wide variety of neplasis ilnesses, including colorectal carcinoma.(4,7) ***LASA (lipid associated sialic acid)***: is a complex marker which measures the quantity of sialic acid in the serum. It is also found in colorectal carcinoma, with a high value.

MATERIAL AND METHOD

A transversal prospective test was made on 156 patients who were in the records of Sibiu County Oncology Hospital's Oncology Clinic, during 1.01.2006-31.12.2009. We studied the existence of a possible correlation between immunological markers' value and the stage of the illness, the specific treatment, the moment of the local recurrence and the appearance of the metastasis.

STUDY INCLUSION CRITERIA

TNM stages; histo-pathological confirmation; information regarding the extension degree of the tumour and ganglion infestation; patients with specific oncological treatment; the value of the immunological markers at the beginning and during the treatment; objective documentation regarding the metastasis and the local recurrence.

Observed tumour markers: CEA (carcino-embrionary antigen); CA 19-9

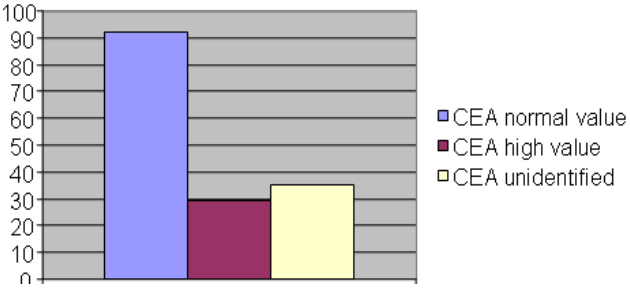
RESULTS AND DISCUSSIONS

During the present study we analyzed a group of 156 patients, **average age – 58 years old. 103** patients **(66%) were radically operated, 45 patients (28.8%) were incomplete operated** and **8** patients **(5.1%) were not operated at all. A number of 61 patients (39.1%)** registered **evolution of the illness** (osseous, of the lungs, hepatic metastasis, or local recurrence) and the rest of **95** patients **(60.89) presented no evolution** of the illness.

1. CEA:

From the total amount of 156 patients, in the case of 92 (59%), in the moment of diagnosis, the CEA was over the normal value, for 29 patients (18.58%) the CEA was normal, and in the case of 35 patients (22.4%) the CEA was not identified.

Picture no. 1. CEA value at the moment of diagnosis



From the 156 studied patients, in the moment of

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diagnosis, **47 patients (30,12%)** presented heredo-collateral antecedents, as neoplasias and/or gastrointestinal pathology (gastric ulcer, haemorrhoids, intestinal polyposis, ulcero-haemorrhagic rectocolitis); **34 patients (21,79%)** presented **gastrointestinal pathological personal antecedents** (intestinal polyps, irritable bowel, diarrhoea or constipation, haemorrhoids etc) and **66 patients (42.30%) presented cardiac or metabolic personal antecedents** (obesity, diabetes mellitus, ischemic heart disease, high blood pressure).

The analisys showed that the existence of the heredo-colateral antecedents, of the gastrointestinal pathological personal antecedents and of the general pathological personal antecedents correlates with the high value of the CEA in a great number of patients: 35 patients (26.71%) with AHC, 28 patients (21.37%) with APP and 42 patients (32.06%) with APP. These data are not statistically important.

Table no. 1. Correlation between CEA in the moment of diagnosis and in the stages of the illness

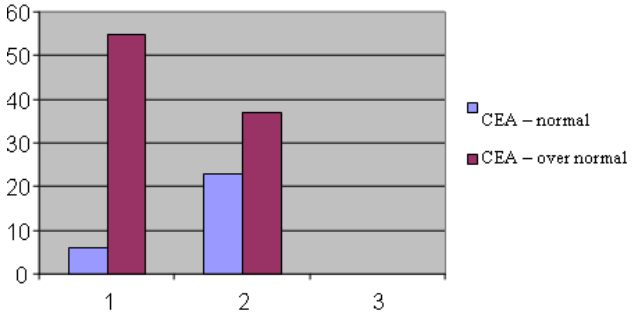
CEA	Normal values	Over normal values	Unidentified	Total
2nd Stage	17	10 (6.4%)	22	49
3rd Stage	10	50 (32.1%)	11	71
4th Stage	2	32 (20.5%)	2	36
Total	29	92	35	156

P = 0.000* likelihood ratio (99% accuracy)

Although CEA is not recommended as screening test for colorectal carcinoma – taking into account the fact that international studies registered false-positive results – we can say that the value of CEA identified in the moment of diagnosis is important to sustain the diagnosis, especially in the advanced stages of the illness, as statistically important indicator.

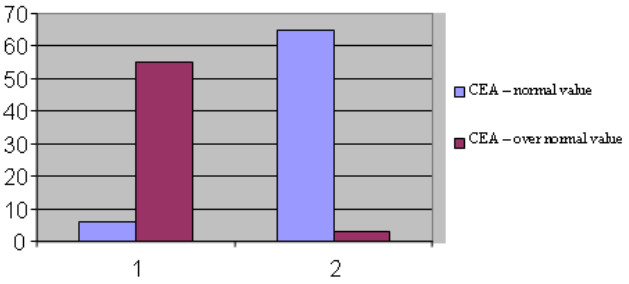
We observed that a number of **92 patients (59%)** registered in the moment of diagnosis an **over normal value of CEA**; from these **55 patients (41.96%)** registered an **evolution of the illness** (local recurrence, metastasis), and 37 patients (28.24%) did not register an evolution of the illness. **29 patients (18.6%) registered normal CEA value** in the moment of diagnosis: **6 patients (4.5%) registered evolution of the illness** (local recurrence, metastasis) and 23 patients (17.55%) did not register an evolution of the illness.

Picture no. 2. Correlation between the CEA in the moment of diagnosis and the evolution of the illness (local recurrence and metastasis)



In dynamics, **CEA** was identified to a number of **128 patients**. **70 patients (44.9%) registered in dynamics a normal CEA value: 5 patients (3.9%)** registered **evolution of the illness** (local recurrence and metastasis) and the rest of 65 patients (50,7%) did not register an evolution of the illness. **58 patients (37.2%) registered an over normal CEA value in dynamics**: **55 patients (42.96%) registered evolution of the illness** (local recurrence, metastasis), and the rest of 3 patients (2.3%) did not register an evolution of the illness.

Picture no. 3. Correlation between CEA in dynamics and the evolution of the illness (metastasis or local recurrence)



1 – Evolution; 2 – No evolution

Linking the marker's value in the moment of diagnosis with the one during the evolution of the illness, it has been found that a high CEA value in the moment of diagnosis is associated with a high value in the dynamics of the illness evolution; it is associated with the evolution of the illness both through local recurrence and metastasis. We can conclude that these variables are significantly associated (with 99% accuracy).

The majority of the studied patients followed: surgical treatment and cytostatic adjuvant therapy +/- radiotherapy. From the 103 patients who received radical surgical therapy, a larger number registered, at the end of the therapy, normal values of the tumour marker versus 45 patients who received sub-optimal surgical therapy: 26% versus 3%.

We can say that CEA value in dynamics may be used as a statistically significant indicator of the efficiency of the radical surgical therapy (with 99% accuracy).

From the 138 patients who received adjuvant chemotherapy: 28 patients (20.3%) registered a normal CEA value in the moment of diagnosis, 81 patients (58.7%) registered a high CEA value in the moment of diagnosis and in the case of 29 patients (21%) CEA was not identified.

From the 18 patients who received cytostatic adjuvant therapy: 1 patient (5.6%) registered a normal CEA value in the moment of diagnosis, 11 patients (61.1%) registered a high CEA value in the moment of diagnosis and in the case of 6 patients (33.3%) CEA was not identified.

CEA value registered in dynamics correlated with cytostatic adjuvant therapy does not appear to be a statistically significant indicator of the effectiveness of the therapy (p>0.05).

2. CA19-9

From the 156 studied patients: 34 patients (21.8%) registered high CA19-9 value in the moment of diagnosis, 79 patients (50.6 %) registered a normal CA19-9 value in the moment of diagnosis and in the case of 43 patients (27.6%) CA19-9 was not identified.

Table no. 2. CA 19-9 values in the moment of diagnosis correlated with the stage of the illness

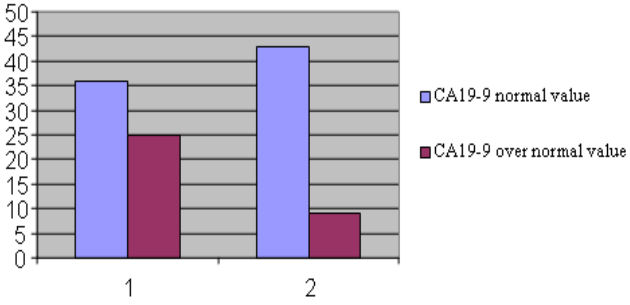
CA19-9	1st Stage	2nd Stage	3rd Stage	4th Stage	Total
Normal values	0	23 (14.7%)	41 (26.3%)	15 (9.6%)	79 (50.6%)
Over normal values	0	5 (3.2%)	15 (9.6%)	14 (9%)	34 (21.8%)
Unidentified	0	21 (13.5%)	15 (9.6%)	7 (4.5%)	43 (27.6%)

P=0,005*likelihood ratio 156(100%)

We can say that CA19-9 value identified in the moment of diagnosis has no importance for the diagnosis itself, no matter the stage of the illness, statistically significant result (with 95% accuracy).

From the patients who registered normal CA19-9 values, the majority – 45 patients (39.82%) – did not register evolution of the illness. 32 patients (28.81%) from those who registered high CA19-9 values, registered also evolution of the illness.

Picture no 3. CA19-9 value in the moment of diagnosis correlated with the evolution of the illness

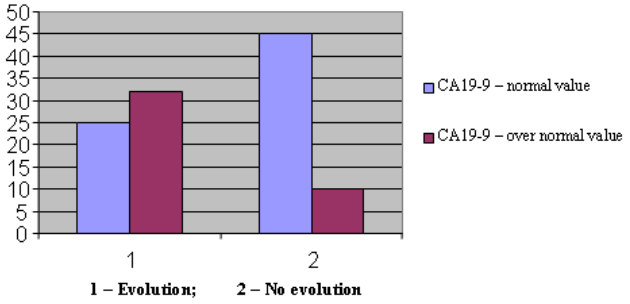


1 - Evolution 2 – No evolution

CA19-9 identified both in the moment of diagnosis and during the treatment may be correlated with the evolution of the illness, both through local recurrence or remote metastasis, the variables are significantly associated (with 99% accuracy).

We can conclude by saying that the CEA and CA19-9 values prove to be indicators of the negative prognosis of the illness, being able to highlight, several months earlier, the evolution moment of the illness.

Picture no. 5. CA19-9 value registered in dynamics correlated with the evolution of the illness



1 – Evolution; 2 – No evolution

Table no 3. CEA and/or CA19-9 values registered in evolution correlated with the evolution of the illness

CEA/CA19-9 markers' vakues in evolution	Evolution	No evolution	Total
Normal value	6	65	71
Over normal value	55	3	58
Total	61	68	129

P<0.05

CONCLUSION

CEA and **CA19-9** values correspond to advanced stages of colorectal neoplasias. **CEA** is useful, especially in monitoring the treatment (low values of the marker show an efficient treatment; the persistence of high values or increased levels of the markers during or after the therapy show a treatment with reduced efficiency or the lack of response to the treatment, case which requires a change in treatment). **CEA** and **CA19-9** may be used as prognosis markers for colorectal neoplasia. **High values of CEA** and **CA19-9** in the moment of diagnosis contribute to establishing the diagnosis in the case of colorectal carcinoma.

REFERENCES

1. Badulescu F. Oncologie generala. Elemente de curs. Reprografia Univ. Craiova, 1997:110-192.
2. Huang CW, Bai I. Clinical value of carbohydrate antigen 50 and carbohydrate antigen 242 in the diagnosis of colorectal carcinoma. Di Yi Jun Yi Da Xue Xue Bao, 2002 Dec;22(12):1116-8.
3. Lai IR, Lee WJ si colab. Comparison of serum CA72-4, CEA, TPA, CA19-9 and CA125 levels in gastric cancer patients and correlation with recurrence. Hepatogastroenterol, 2002 Joule-Aug; 49(46):1157-60.
4. Mandorwski S, Laurenco LG, Forones NM - CA72-4 and CEA in serum and peritoneal washing in gastric cancer. Arch Gastroenterol, 2002 Jan-Mar;39(1):17-21.
5. Ochi Y, Okabe H si colab. Tumour marker - present and future. Rinsho Byori, 1997 Sep; 45(9) 875-83.
6. Ubukata H, Katano M si colab. - Evaluation of CA72-4 as a tumour marker in patients with gastric cancer. Gan To Kagaku Ryoho, 2003 Oct; 30(11):1821-4.
7. Banfi G, Bravi S, Ardemagni A, Zerbi A - CA19-9, CA242 and CEA in the diagnosis and follow-up of pancreatic cancer. Int J Biol Markers, 1996 Apr-Jun;11(2): 77-81.
8. Huang CW, Bai I. Clinical value of carbohydrate antigen 50 and carbohydrate antigen 242 in the diagnosis of colorectal carcinoma. Di Yi Jun Yi Da Xue Xue Bao, 2002 Dec; 22(12):1116-8.
9. Lai IR, Lee WJ si colab. Comparison of serum CA72-4, CEA, TPA, CA19-9 and CA125 levels in gastric cancer patients and correlation with recurrence. Hepatogastroenterol, 2002 Joule-Aug; 49(46):1157-60.
10. Mandorwski S, Laurenco LG, Forones NM - CA72-4 and CEA in serum and peritoneal washing in gastric cancer. Arch Gastroenterol, 2002 Jan-Mar; 39(1):17-21.
11. Ochi Y, Okabe H si colab. Tumour marker - present and future. Rinsho Byori, 1997 Sep; 45(9):875-83.
12. Ubukata H, Katano M si colab. Evaluation of CA72-4 as a tumour marker in patients with gastric cancer. Gan To Kagaku Ryoho, 2003 Oct; 30(11):1821-4.
13. Ritts RE, pitt HA; CA19-9 in pancreatic cancer, Surg Oncol Clin N Am 1998;7(1):93-101 Review.