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Original paper

CA125 and CA242 markers' role in colorectal cancer diagnosis and management – a 30 year review

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Abstract Tumor markers were discovered in the second half of the 20th century and became a huge subject of interest for many scientists as they had the potential of becoming a universal diagnostic tool for specific cancers. Most of them have proven to be not as useful as believed in the beginning because of low specificity and/or sensibility. For colorectal cancer, markers such as CEA, CA19.9, CA125 and others are still being researched alone and in different combinations in the hope of finding a solution that has both specificity and sensibility as close to 100% as possible. Our review aimed to describe progress made in the past 30 years in the research of two particular tumor markers, CA125 and CA242, and their role in the screening, diagnosis and follow-up of colorectal cancer.

Keywords CA242, CA125, colorectal cancer, tumor markers.

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Introduction

Gastrointestinal tract neoplasms have always been major causes for concern in the medical community duet o their high morbidity and mortality rates as well as the lagging ability for early diagnosis (ATTALLAH A.M. et al [1]). Colorectal cancer (CRC), in particular, is the third type of neoplasm as incidence worldwide after lung and breast cancers and the second one in what concerns the overall mortality after lung cancer (GLOBOCAN 2018 [2]). Because it has such high incidence, prevalence and mortality, colorectal cancer should on the list for large cancer screening programs in every country. The most used test for screening is the fecal occult blood test, followed by colonoscopy and rectosigmoidoscopy. Unfortunately, these approaches have poor rates of compliance and are not widely known by target populations, so a serum marker would be more suitable for the detection of early-stage neoplasms provided that it has suittable sensitivity and specificity levels (EINARSSON P.R. [3]; HUNDT S. et al [4]).

Since their discovery more than 50 years ago, tumor markers have represented a subject of interest for many researchers hoping to transform them into a universal diagnostic tool for specific cancers, especially in the gastrointestinal area (ATTALLAH A.M. et al [1]). The development and progression of a tumor from a microscopic level to a point of distant metastases is a lengthy process that proceeds through multiple phases of localized, treatable cancer. Survival rates are favorable for patients with tumors that were detected in the early stages. Thus, early detection of colorectal cancer is crucial to reducing the mortality of the disease (ZHONG W. et al [5], THOMAS D.S. et al [6]). Tumor markers were seen as a potential tool for fulfilling this desire. Unfortunately, this is not the case as there are little to none specific or sensitive enough tumor markers even after all this time. Some antigens point towards specific directions, but they can only be used in monitoring rather than diagnosing neoplasms. However, even though the enthusiasm has been curved in the last years, some hope can be found in combining available tumor markers to obtain more accurate results. One example of such markers is CEA, the most widely used tumor marker for colorectal cancer, being the most frequently elevated in this type of neoplasm (EINARSSON P.R. [3]; HAGLUND C. et al [7]; CARPELAN-HOLMSTRÖM M. et al [8]; TSAVARIS N. et al [9]). Even though its usefulness in the management of colorectal neoplasms has been researched since its discovery (1969 – THOMSON et al.), its value in diagnosing primary cancer is still questionable (ATTALLAH A.M. et al [1]). Other "related" markers that have shown hope towards discovering an algorithm that may revolutionize the way we approach colorectal cancers today are C242 and C125.

In the last decade, there has been an explosion of information regarding the management of colorectal cancer, as it is a heterogeneous disease with many genetic, epigenetic, biochemical and molecular alterations associated with its evolution (MENTER D.G. et al [10]). Regarding the specific use of tumor markers in the diagnosis, treatment and surveillance of colorectal neoplasms, the latest available guidelines mention only CEA, CA19.9 and CA125 as of potential use. According to the latest Evidence-based Guideline for CRC from the German Guideline Program in Oncology (GGPO), with a strong expert consensus degree, the CEA value should be assessed pre-operatively and it is especially reliable as an indicator of cancer relapse, CA19.9 does not increase the conclusiveness of a relapse compared to determining only the CEA value and the relevance of CA 125 in the diagnosis of ovarian metastases and as a course parameter for further treatments of confirmed peritoneal carcinosis is currently unknown, but it is used as a marker for peritoneal cancer (GESELLSCHAFT FÜR VERDAUUNGS- und STOFFWECHSELKRANKHEITEN D. et al [11]). At the same time, the NCCN Clinical Practice Guidelines in Oncology (2020) recommends only CEA measurements for patients with TNM stage II, III and IV every 3-6 months for 2 years, then every 6 months for a total of 5 years. If a CEA elevation occurs during this time, the guidelines recommend further investigations (NCCN [12]).

Materials and Methods

Available well-known databases were searched using the following search formula: [(CA125 OR CA242) AND ((colorectal or rectal or colonic) AND (cancer or disease or neoplasm))]. Eligibility criteria were CRC-specific, CA125 and/or CA242 specific and the English language. All studies published after 1990 that met the criteria were taken into account.

In what concerns the study of the relationship between CA 242 and colorectal cancer, 17 research articles were found and included in our review, of which 9 were published in the 1990s and the rest of 8 after the year 2000. For CA125, 20 articles were found and analyzed. The trend went in the opposite direction in what concerns research on this tumor marker, as most articles on the theme were published after the year 2000 (17 compared to only 4 articles in the 1990s).

Results

CA 125 marker

CA125 is a glycoprotein identified for the first time in 1981, after the development of a monoclonal antibody against an ovarian serous carcinoma cell line (HUANG C.J. et al [13]). It is a tumor marker used mostly in cases of ovarian cancer, but research about its usefulness in the management of colorectal tumors has been made since its discovery (ZHANG M. et al [14]). Also, elevated levels appear in a variety of other clinical settings, such as ovarian metastatic disease from colorectal adenocarcinoma, making it more difficult for the physician to accurately diagnose the primary tumor due to its low specificity (LEWIS M.R. et al [15]; JOHNSON C.C. et al [16]). Abnormal serum CA125 levels might also be associated with pathological changes in different tissues

induced by a specific disease, particularly high levels in patients with cirrhosis, lung fibrosis, nephrotic syndrome and pancreatic cancer and lower levels in healthy patients aged >65 years, those suffering from rectal cancer, cerebrovascular disease or gastritis (ZHANG M. [14]).

CA125 correlation with tumor type and stage

According to available medical literature, multiple research teams have found a connection between CA125 and tumor stage as well as tumor type (benign or malignant). A study from 30 years ago, published in 1991 by C. Haglund et al., aimed to research exactly how CA125 behaves in cases of gastrointestinal cancers in a group of 162 patients with various digestive tract cancers. They found that while CA125 serum levels increased for 20% of patients suffering from primary colorectal cancer, it was mostly the case for those with advanced disease (DUKED C and D). On the other hand, in the case of benign disease, the marker's serum levels grew only for 2 patients out of a total of 33 diagnosed. Also, they concluded that its specificity was higher than that of CEA in the case of colorectal malignancy (HAGLUND C. et al [17]). YANG X.Q. et al. concluded, in a recent study from 2011 on a group of 80 patients with colorectal cancer, that preoperative serum status of CA125 had correlations with tumor stage (YANG X-Q et al [18]). Yangfeng G. et al. evaluated serum CEA125 (as well as CEA, CA 19.9, CA 72-4 and Ferritin) as diagnostic markers and factor of clinical importance in colorectal cancer. In this particular setting, CA125 had the lowest sensitivity (only 10.04%) and the highest specificity (99%). Again, a positive correlation between CA125 and tumor stage was found (GAO Y. et al [19]). In 2015, Thomas D.S. et al. aimed to evaluate whether serum CA125 could be a tool in the early detection, using longitudinal preclinical samples from 40 women subsequently diagnosed with colorectal cancer, 20 women subsequently diagnosed with benign disease at this level and 40 matched non-cancer controls. They collected samples up to 4 years before diagnosis. Their study showed that it did not differ significantly between cases and controls for any of the time groups, even though they found that serum levels were significantly higher in the late stage than those in early-stage case samples measured 2-3 and 3-4 years before having the disease diagnosed (THOMAS D.S. et al [6]).

Differential diagnosis between ovarian and colorectal carcinomas

One great dilemma is differentiating ovarian carcinomas from colorectal carcinoma. It seems that CA125 might be useful in such situations. In 1992, Yedema CA et al. measured levels of CA125 and other tumor markers (CEA, CA15.3, CA19.9, CA M29, CA M26) in two groups of women diagnosed with one disease or the other. The results showed that a ratio between CA125/CEA greater than 25 proved to have a high discriminative power with a specificity of 100% and a sensitivity of 91% (overall test accuracy of 94%), making it a useful tool in the preoperative differential diagnosis between adenocarcinomas of ovarian/colorectal origin (YEDEMA C.A. [20]). Colleagues Lewis M. et al. researched a group of 26 female patients suffering from ovarian cancer who had an elevated level of CA125, with 10 patients having a history of colorectal adenocarcinoma. In three cases metastatic colorectal carcinoma was initially diagnosed as a primary ovarian tumor, while in one other case it was taken into consideration before favoring a diagnosis of endometrioid adenocarcinoma. The authors concluded that the possibility of metastasis from a colorectal adenocarcinoma does merit consideration in the differential diagnosis of a female patient with an adnexal mass and elevated serum CA125. However, the possibility of metastasis from a colorectal tumor cannot be dismissed solely on the elevated serum level of the CA125, even if the patient does not have a history of gastrointestinal malignancy (LEWIS M.R. et al [15]).

On the other hand, tumor marker levels can be influenced by other factors than the presence of a neoplasm. In our research results were contradictory, thus demanding further research on the subject. Johnson et al. performed an epidemiological investigation on a wide lot of subjects, measuring levels of CA125 in a group of 25,608 post-menopausal women aged 55-74 years, without any history of lung, colorectal or ovarian cancer. They found that in post-menopausal women without any history of ovarian cancer, CA125 levels were influenced by several factors such as race/ethnicity, age, hysterectomy, smoking history and obesity. High levels (>35U/ml) were associated with increased age and former smoking, while hysterectomy and obesity were protective factors. Also, mean levels were higher with increasing age, ever use of hormone therapy, former smoking and history of breast cancer and lower with non-white status, previous hysterectomy, current smoking and obesity (JOHNSON C.C. et al [16]). On the other hand, Colleagues Zhong et al. investigated the possible association between multiple serological biomarkers (among which we can find CA125) with patient characteristics and disease outcomes in colorectal cancer. Their research found that high CA125 is not associated with age, gender, pathological type and location of cancer, but is associated with poor tumor differentiation, higher tumor invasion, a greater degree of abdominal lymph node metastasis and higher TNM as well as Duke stage tumors. Thus, CA125 expression in colorectal patients appears to indicate more advanced disease and disease recurrence (ZHONG W. et al [5]).

Prognostic value

One of the biggest desiderates envisioned by researchers for tumor markers was their prognostic value. 3 research articles have found that a high CA125 level measured preoperatively could indicate a poor prognosis for the patient. A research paper by Yang X.Q. et al. published in 2011 found that a set of 3 tumoral markers (CA125+CA19.9+CEA) measured preoperatively can be used as an independent prognostic factor for the 5-year recurrence-free survival rate in colorectal cancer patients, as those with simultaneously positive serum CA19.9, CEA and CA125 values had a recurrence rate of 100% and the shortest recurrence-free survival (of only 4 months)

(YANG X.Q. [21]). Again, Yang X.Q. et al. concluded, in another study on a group of 80 patients with colorectal cancer, that preoperative serum CA125 level is an independent negative prognostic marker for overall survival in colorectal cancer, as patients with elevated CA125 serum levels before surgery had worse survival rates compared to those with normal levels (statistically significant). Moreover, the same study did a multivariate analysis showing that the only two parameters that were indeed independent prognostic factors for the overall survival of patients with colorectal cancer were CA125 serum levels and tumor stage (YANG X.Q. et al [18]). Webb A. et al. did a univariate analysis on a group of 81 patients with colorectal cancer and found that an elevated level of CA125 was a measure of poor prognosis at both the lower cut of 35 U/ml and the higher cut of 350 U/ml. Similar results arise in the multivariate analysis, where CA125 proved to be an independent prognostic marker at both cut-off values (WEBB A. et al [22]).

CA125 in particular situations

CA125 is a useful marker for the diagnosis of peritoneal carcinomatosis (GESELLSCHAFT FÜR VERDAUUNGS- und STOFFWECHSELKRANKHEITEN D. et al [11]). In the past 30 years, efforts have been made towards discovering whether its usefulness could find a place in other particular situations such as diagnosing liver metastases and predicting response to different therapies for patients in advanced stages of the disease. Zhang D. et al. measured the predictive value of CA125 (among other blood tumoral markers) in liver metastases from colorectal cancer, finding positive results. Not only CEA, CA19.9, and CA125 on their own were independent prognostic factors for liver metastases, but authors also found that the combination of these 3 markers would enhance their sensitivities, thus increasing their value in predicting liver metastases from colorectal cancer (ZHANG D. et al [23]). A study published by Chang S.J. et al. in 2018 chose a narrower area of research: they selected a group of stage III colorectal cancer patients and tried to identify factors that could predict adjuvant chemotherapy benefits for them. CA125 level was one of the factors investigated, concluding that a low serum level (<35u/ml, p=0.0015) was strongly associated with a better 2-year disease-free survival for this lot of patients (CHANG S-J et al [24]). One study by Huo Y.R. et al. measured the prognostic value of CA125 (among other markers) for patients with peritoneal carcinomatosis from colorectal cancer, treated by cytoreductive surgery and intraperitoneal chemotherapy. Thus, their group of study consisted of patients with very advanced disease. The research concluded that CA125, as well as CEA, remained independent predictors of survival after adjusting for peritoneal cancer index (PCI). Also, patients with high CEA and low CA125 or vice versa had an approximately triple risk of death and in patients with both CEA and CA125 elevated the risk of death increased by a six-fold (HUO Y.R. [25]). In the same year, a study by Huang C.J. et al. tried to evaluate whether the serum concentration of CA125 can be a predictor for peritoneal dissemination of colorectal cancer, following previous reports about its usefulness in diagnosing peritoneal dissemination in gastric cancer. The study concluded that CA125 concentration was a better tumor marker than CEA concentration in predicting peritoneal dissemination in colorectal cancer, in both sexes. Moreover, the same study showed that the primary tumor site did not change the predictive ability of CA125 concentration. However, authors mention the small number of patients in the peritoneal dissemination group as a shortcoming, thus encouraging further studies on the matter in order to improve results (HUANG C.J. et al [13]).

Follow up

Tumoral markers can be ideal tools to use in the follow-up of patients in remission because they are easy to obtain and cheaper as well as less dangerous than other methods such as Computer Tomography. Unfortunately, there are not many markers proven to have high enough sensibility and specificity to fulfill this desiderate. For now, only CEA is used in the follow up of patients who have successfully been treated for a CRC (NCCN [12]). A study published by Shannon B.N. et al. evaluated preoperative and postoperative CA125 serum levels in patients undergoing complete cytoreduction surgery and hyperthermic intraperitoneal chemotherapy in order to understand the time frame before values normalize. The authors tried to establish whether CA125 could be used as a surveillance tool for these patients. They concluded that aside from immediate measurement, CA125 is misleading and should not be measured postoperatively for the first 3 months after surgery. After 3 months, its use as a surveillance marker can be resumed (SHANNON N.B. et al [26]). In 2016, Basu A. Et al. did a comparative study of tumor markers in 51 male patients with CRC before and after chemotherapy, finding that CA125 serum levels decreased significantly after the treatment (BASU A. et al [27]). In what concerns the usefulness of CA125 in the follow up of patients with colorectal cancer, colleagues Tsavaris N. et al. found that, in their lot of patients, even though serum levels of CA125 were increased in 37% of cases at the beginning of the therapy, the marker did not demonstrate any utility. Moreover, it had significant rates of false-positive (9%, p<0.008) and false negative (8.1%, p<0.008) results when measured in the evaluation of chemotherapy response. According to this study, CEA is a better option for the follow-up of patients suffering from colorectal cancer (TSAVARIS N. et al [9]). Another more recent study by Jain P. et al. on a group of 90 patients with colorectal cancer concluded that preoperative serum of CA125 is not an efficient tool for prognostication in colorectal cancer (JAIN P. et al [28]).

CA 242 marker

CA 242 is a tumor marker defined by the monoclonal antibody known as C-242 (EINARSSON P.R. et al [3]). It is of carbohydrate nature related to type I chain, but different from other antibodies of the same nature such as CA 19-9 or CA 50. CA242 is a tumor marker discovered at the end of the 20th century in relation to many

gastrointestinal neoplasms as well as other diseases from te colorectal, gastric, hepatic, biliary or pancreatic areas.

It seems that CA242 levels, as well as in the case of CA125, correlate with tumor stage and aggressivity. The marker was found to be more prevalent and of higher values in patients with advanced-stage CRC, as well as in those with metastatic disease. On the other hand, one particular study found that, after treatment, CA242 levels diminished more rapidly for patients with advanced CRC. In what concerns colorectal neoplasms, studies as old as the 1991s show that it can be found in the serum of patients with small tumors (DUKES A and B), of those with advanced cancers (DUKES C and D) as well as at some patients with benign diseases. The same results were obtained by Spila A. et al in a study published in 1999, showing that CA242 levels correlated with the stage of the disease. Also, they found a consistent relationship between the efficacy of surgery and the reduction of CA242 serum levels as they diminished immediately post-operatory, while levels remained high in patients undergoing palliative surgery (SPILA A. et al [29]). In another study published by the same authors in 2001 (following the encouraging results from the initial one), they aimed to compare CA 242 and CA 19.9 serum levels in patients who had colorectal cancer, finding similar results and concluding that the first one does not offer a particular advantage over the latter. The results also showed that CA242 levels were found the most in metastatic disease (58.2%) (SPILA A. et al [30]). A more recent research paper published in 2001 by Engaras B et al. showed that in their lot of 90 patients who had undergone surgery with curative intent, the levels of the CA 242 marker diminished during the first 2 years after surgery in an inverse relationship to the Dukes staging (meaning that the highest levels were measured for patients who had a Dukes A type of tumor) (ENGARÅS B. et al [37]).

In comparison with other well-known tumoral markers used in the surveillance and management of gastrointestinal diseases such as CA19-9 and CEA, CA242 had lower levels in patients with benign diseases, thus representing an advantage in differentiating these cases (SPILA A. et al [29]; KUUSELA P. et al [31]; NILSSON O. et al [32]). One study from 1995 compared preoperative serum levels of CEA and CA 242 in patients with colorectal neoplasms, finding promising results especially for patients with Dukes D colorectal cancer, both markers having similar sensitivities at specificity rates higher than 90%. On the other hand, no correlation between their serum levels was found (ATTALLAH A.M. et al [1]). Also, CA242 has shown promising results as well as a superior sensitivity for colorectal cancer than CA19-9 and CA50 [7]. Von Kleist S. et al compared four tumor markers (CA242, CA19-9, TPA and CEA) in 308 patients with colorectal carcinoma, benign digestive disease (128 patients) and a healthy control group of 45 patients, concluding that CA242 was the most specific marker in hepatobiliary diseases, having a similar performance as CEA particularly for colon cancer (Von KLEIST S. et al [33]).

In 2003, colleagues Palmqvist et al. compared the levels of CEA and CA242 in patients suffering from colorectal cancer and found that an elevated level of CA 242 was not significantly related to colorectal cancer risk (PALMQVIST R. et al [38]). On the other hand, a more recent study from 2006 found promising results: in the particular case of colon cancer, serum levels of CEA, CA19-9 and CA242 were significantly ($p<0.001$) higher than controls, with CA242 being the most sensitive and specific serum marker (ATTALLAH A.M. [1]).

Colleagues Eskelinen M. Et al. tried to develop a diagnostic score using CEA and CA 242 levels, resulting in a tool with a specificity of 0.88 and an efficiency of 0.67 in detecting colorectal cancer, thus proving that the two markers have diagnostic value in the preoperative evaluation of these patients (ESKELINEN M. et al [34]). Wu J et al., in 1995, showed that the combined determination of CEA and CA 242 was superior to single CEA determination in what concerns sensitivity and accuracy in the detection of colorectal cancer, as well as Attalash A. et al. who proved that using the two markers concomitantly increased the overall sensitivity to 72% (ATTALLAH A.M. et al [1]; WU J. et al [35]; YOu W. et al [36]).

In what concerns its role in patients' surveillance following curative resection for colorectal cancer, Hall N.R. et al. found that CA 242 alone is not superior to CEA in measuring recurrences, but their combined use has a high sensitivity (88%) and specificity(78%), as well as an even higher negative predictive value (97%), thus making them useful in reducing unnecessary investigations in follow-ups or even as a guide to the initiation for further treatment in case of recurrent disease. Also, the same study concluded that patients with high preoperative concentrations of CA 242 had worse outcomes than those with lower serum levels (HALL N.R. et al [39]).

Conclusions

Occurrence and progression of colorectal cancer is triggered by a combination of multiple factors, among which family history, age, gender, geographical location, and personal history are the main risk factors. Genetic changes including microsatellite instability and mutations in tumor suppressor genes are the main culprits closely rlinked to CRC development (MIHALCEA [40], Murarasu [41], BOLOCAN [42], MURARASU [43]). The interest in studying serum tumor marker CA242 has diminished from the 1990s as the number of research articles has decreased, while the interest in CA125 grew over time. Elevated antigen levels of CA125 and CA242 alone may be indicative of colorectal cancers, but while their specificity is high, sensibility levels remain low, thus prohibiting them from being used as tests for mass screening or follow up for the moment. However, both sensitivity and specificity grew when measured together with other tumoral markers (such as CA19.9 or CEA) CA125 was assessed by numerous investigators regarding its utility as a marker of stage, disease status, prognosis or even in the screening of

ovarian cancer. Unfortunately, low sensitivity and specificity prohibit its use as a single marker for screening purposes. There is a possibility of using CA242 in monitoring disease status for patients with colorectal cancer, being useful in differentiating benign vs. malignant disease as well as metastatic vs. non-metastatic cancer. The concomitant determination of CEA and CA242 has had superior sensitivity and specificity compared to CEA alone. For now, the only useful tumor marker in the surveillance of CRC is CEA. Further research is necessary and encouraged.

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References

1. ATTALLAH AM, AL. E. Clinical Value of Serum CEA, CA19-9, CA 242 and AFP in Diagnosis of Gastrointestinal Tract Cancers. *Int J Cancer Res*. 2006; 2(1):50-56.
2. International Agency for Research on Cancer. Colorectal cancer Source: Globocan 2018 Number of new cases in 2018, both sexes, all ages. 2018; 876:1-2. http://gco.iarc.fr/today.
3. EINARSSON PR. Oncology analyte Serum tumour marker CA242 in colorectal cancer Oncology Diagnosis of colorectal cancer and case studies. *Int J Cancer*. 2006; (April).
4. HUNDT S, HAUG U, BRENNER H. Blood markers for early detection of colorectal cancer: A systematic review. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(10):1935-1953. doi:10.1158/1055-9965.EPI-06-0994
5. ZHONG W, YU Z, ZHAN J, et al. Association of Serum Levels of CEA, CA199, CA125, CYFRA21-1 and CA72-4 and Disease Characteristics in Colorectal Cancer. *Pathol Oncol Res*. 2015; 21(1):83-95. doi:10.1007/s12253-014-9791-9
6. THOMAS DS, FOURKALA EO, APOSTOLIDOU S, et al. Evaluation of serum CEA, CYFRA21-1 and CA125 for the early detection of colorectal cancer using longitudinal preclinical samples. *Br J Cancer*. 2015; 113(2):268-274. doi:10.1038/bjc.2015.202
7. HAGLUND C, KUUSELA P, J H, ROBERTS PJ. Preoperative serum levels of CEA and CA 242 in colorectal cancer. 1995; 872:868-872.
8. CARPELAN-HOLMSTRÖM M, LOUHIMO J, STENMAN U-H, ALFTHAN H, HAGLUND C. CEA, CA 19-9 and CA 72-4 improve the diagnostic accurary in gastrointestinal cancers. *Anticancer Res*. 2002; 22:2311-2316.
9. TSAVARIS N, VONORTA K, TSOUTSOS H, et al. Carcinoembryonic Antigen (CEA), α-fetoprotein, CA 19.9 and CA 125 in Advanced Colorectal Cancer (ACC). *Int J Biol Markers*. 1993; 8(2):88-93. doi:10.1177/172460089300800204
10. MENTER DG, DAVIS JS, BROOM BM, et al. Back to the Colorectal Cancer Consensus Molecular Subtype Future. *Curr Gastroenterol Rep*. 2019; 21(2):5. doi:10.1007/s11894-019-0674-9
11. Gesellschaft für Verdauungs- und Stoffwechselkrankheiten D, Krebsgesellschaft D. *Evidenced-Based Guideline for Colorectal Cancer Version 2.1 – Januar 2019*.; 2019. https://www.dgvs.de/wissen-kompakt/leitlinien/leitlinien-der-dgvs/kolorektales-karzinom/.
12. NCCN. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*.; 2020. doi:10.1007/978-1-4615-6165-1_18
13. HUANG CJ, JIANG JK, CHANG SC et al. Serum CA125 concentration as a predictor of peritoneal dissemination of colorectal cancer in men and women. *Med (United States)*. 2016; 95(47). doi:10.1097/MD.0000000000005177
14. ZHANG M, ZHANG Y, FU J. Serum CA125 levels are decreased in rectal cancer but increased in fibrosis-associated diseases and in most types of cancers. *Prog Mol Biol Transl Sci*. 2019; 162:241-252. doi:10.1016/BS.PMBTS.2018.12.012
15. LEWIS MR, EUSCHER ED, DEAVERS MT et al. Metastatic colorectal adenocarcinoma involving the ovary with elevated serum CA125: A potential diagnostic pitfall. *Gynecol Oncol*. 2007; 105(2):395-398. doi:10.1016/j.ygyno.2006.12.035
16. JOHNSON CC, KESSEL B, RILEY TL, et al. The epidemiology of CA-125 in women without evidence of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. *Gynecol Oncol*. 2008; 110(3):383-389. doi:10.1016/j.ygyno.2008.05.006
17. HAGLUND C, KUUSELA P, ROBERTS P, JALANKO H. Tumour marker CA 125 in patients with digestive tract malignancies. *Scand J Clin Lab Invest*. 1991; 51(3):265-270. doi:10.3109/00365519109091613
18. YANG X-Q, LI Y, CHEN C et al. Preoperative serum carbohydrate antigen 125 level is an independent negative prognostic marker for overall survival in colorectal cancer. *Med Oncol*. 2011; 28(3):789-795. doi:10.1007/s12032-010-9518-z
19. GAO Y, WANG J, ZHOU Y et al. Evaluation of Serum CEA, CA19-9, CA72-4, CA125 and Ferritin as Diagnostic Markers and Factors of Clinical Parameters for Colorectal Cancer. *Sci Rep*. 2018; 8(1):1-9. doi:10.1038/s41598-018-21048-y
20. YEDEMA CA, KENEMANS P, WOBBES T, et al. Use of Serum Tumor Markers in the Differential Diagnosis between Ovarian and Colorectal Adenocarcinomas. *Tumor Biol*. 1992; 13(1-2):18-26. doi:10.1159/000217748
21. YANG XQ, CHEN C, WANG FB et al. Preoperative serum carcinoembryonic antigen, carbohydrate antigen 19-9 and carbohydrate antigen 125 as prognostic factors for recurrence-free survival in colorectal cancer. *Asian Pacific J Cancer Prev*. 2011; 12(5):1251-1256.

22. WEBB A, SCOTT-MACKIE P, CUNNINGHAM D, et al. The prognostic value of CEA, βHCG, AFP, CA125, CA19-9 and C-erb B-2, (βHCG immunohistochemistry in advanced colorectal cancer. *Ann Oncol*. 1995; 6(6):581-588. doi:10.1093/oxfordjournals.annonc.a059248
23. ZHANG D, YU M, XU T, XIONG B. Predictive value of serum CEA, CA19-9 and CA125 in diagnosis of colorectal liver metastasis in Chinese population. *Hepatogastroenterology*. 2013; 60(126):1297-1301. doi:10.5754/hge121125
24. CHANG S-J, GE X-S, XU Z-Y et al. Lower serum CA125 level, negative vascular invasion, and wild BRAF were strongly associated with better 2-year disease-free survival in patients with stage III colorectal cancer who received adjuvant chemotherapy. *Cancer Biomarkers*. 2018; 22:161-168. doi:10.3233/CBM-181179
25. HUO YR, HUANG Y, LIAUW W et al. Prognostic value of carcinoembryonic antigen (cea), afp, ca19-9 and ca125 for patients with colorectal cancer with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Anticancer Res*. 2016; 36(3):1041-1050.
26. SHANNON NB, TAN GHC, CHIA CS et al. CA-125: an inaccurate surveillance tool immediately after cytoreductive surgery and hyperthermic intraoperative chemotherapy (CRS-HIPEC)? *Int J Hyperth*. 2018; 34(5):585-588. doi:10.1080/02656736.2017.1342874
27. BASU A, SETH S, CHAUHAN AK et al. Comparative study of tumor markers in patients with colorectal carcinoma before and after chemotherapy. *Ann Transl Med*. 2016; 4(4):1-8. doi:10.3978/j.issn.2305-5839.2016.02.02
28. JAIN P, MONDAL SK, SINHA SK et al. Diagnostic and prognostic significance of different mucin expression, preoperative CEA, and CA-125 in colorectal carcinoma: A clinicopathological study. *J Nat Sci Biol Med*. 2014; 5(2):404-408. doi:10.4103/0976-9668.136207
29. SPILA A, FERRONI P, COSIMELLI M, D'ALESSANDRO R et al. Evaluation of the CA 242 tumor antigen as a potential serum marker for colorectal cancer. *Anticancer Res*. 1999; 19(2B):1363-1368.
30. SPILA A, FERRONI P, COSIMELLI M, et al. Comparative analysis of CA 242 and CA 19-9 serum tumor markers in colorectal cancer patients. A longitudinal evaluation. *Anticancer Res*. 2001; 21:1263-1270.
31. KUUSELA P, HAGLUND C, ROBERTS PJ. Comparison of a new tumour marker CA 242 with CA 19-9, CA 50 and carcinoembryonic antigen (CEA) in digestive tract diseases. *Br J Cancer*. 1991; 63(4):636-640. doi:10.1038/bjc.1991.146
32. O NILSSON, C JOHANSSON, B GLIMELIUS et al. Sensitivity and specificity of CA242 in gastrointestinal cancer. A comparison with CEA, CA50 and CA 19-9. *Br J Cancer Vol*. 1992; 65:215-221. doi:10.1177/001452469700800907
33. Von KLEIST S, HESSE Y KH. Comparative evaluation of four tumor markers, CA 242, CA 19/9, TPA and CEA in carcinomas of the colon. *Anticancer Res*. 1996; 16(4B):2325-2331.
34. ESKELINEN M, PASANEN P, KULJU A, et al. Clinical evaluation of serum tumour markers CEA, CA 50 and CA 242 in colorectal cancer. *Anticancer Res*. 1994; 14:1427-1432.
35. WU J, YU H, SHAO Y. Significance of CEA and CA242 in the diagnosis of colorectal carcinoma. *Zhonghua Zhong Liu Za Zhi*. 1995; 17:438-440. doi:10.1007/BF02954747
36. YOU W, SHENG N, YAN L, et al. The difference in prognosis of stage II and III colorectal cancer based on preoperative serum tumor markers. *J Cancer*. 2019; 10(16):3757-3766. doi:10.7150/jca.31660
37. ENGARÅS B, KEWENTER J, NILSSON O et al. CEA, CA 50 and CA 242 in patients surviving colorectal cancer without recurrent disease. *Eur J Surg Oncol*. 2001; 27:43-48. doi:10.1053/ejso.2000.1027
38. PALMQVIST R, ENGARÅS B, LINDMARK G, et al. Prediagnostic Levels of Carcinoembryonic Antigen and CA 242 in Colorectal Cancer: A Matched Case-Control Study. *Dis Colon Rectum*. 2003;46:1538-1544. doi:10.1097/01.DCR.0000089121.59268.D2
39. HALL NR, FINAN PJ, STEPHENSON BM et al. The role of CA-242 and CEA in surveillance following curative resection for colorectal cancer. *Br J Cancer*. 1994;70(3):549-553. doi:10.1038/bjc.1994.343
40. MIHALCEA A, STEFAN I, TICA V, IONICA E. The detection of mutations in the APC gene of Romanian patients with colorectal cancer through two independent techniques. *Rom Biotechnol Lett*. 2009, 14(5): 4747-4755
41. MURARASU D, PUIU L, ALDEA PITICA IM, MAMBET C, MIHALCEA CE, MARINCAS AM, CINCA S, BRASOVEANU L, DIACONU CC. TP53 somatic mutations and LOH profile in colorectal cancer in Romania. *Rom Biotechnol Lett*. 2018, 23(2): 13530-40
42. BOLOCAN A, PADURARU DN, NITIPIR C, HAINAROSIE R, PITURU SM, DIACONU C, SUCEVEANU A, PANTEA STOIAN A. Mixed adenoneuroendocrine carcinoma of the gastrointestinal tract-features, diagnosis, management and prognostics. *Rom Biotechnol Lett*. 2018, 23(6): 14193-202.
43. MURARASU D, PUIU L, MIHALCEA CE, ALDEA PITICA IM, MAMBET C, RADU EL, MATEI L, DRAGU DL, SIMION L, MARINCAS MA, CHIVU ECONOMESCU M, CINCA S, BRASOVEANU L, BLEOTU C, DIACONU CC. Characterization of TP53 polymorphisms in Romanian colorectal cancer patients. *Rom Biotechnol Lett*. 2018, 23(6): 14124-34