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Expression of Soluble Intercellular Adhesion Molecule 1 in Colorectal Cancer and Potential Use as Treatment Response Index

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Abstract

Background: It has been previously demonstrated that there is a positive correlation between serum concentrations of soluble intercellular adhesion molecule (sICAM-1) with stage of colorectal cancer (CRC) progression and metastases. The present study was performed primarily to examine whether sICAM-1 levels are indeed affected by chemotherapy treatment in patients with metastatic CRC and secondly to examine whether such values can be used compared to CEA as a more reliable alternative treatment indices for patient monitoring with metastatic CRC during systemic chemotherapy.
Methods: The serum concentration of sICAM-1 and CEA in blood samples from 20 patients with advanced colorectal cancer were measured using enzyme-linked immunosorbent assay (ELISA) and electro-chemiluminescence immunoassay (ECLIA), respectively, and compared with those from 12 healthy adults volunteers.
Results: Despite the tendency of serum sICAM-1 to fall during systemic chemotherapy, there was no significant reduction in serum sICAM-1 concentration between pre-chemotherapy levels and after five chemotherapy courses in patients with metastatic CRC (411.9 $\pm$ 196.6 ng/mL vs. 353.0 $\pm$ 124.1 ng/mL, p = 0.011). On the contrary, there was a statistically significant reduction in the expression of serum CEA levels during the same time period in the study group (330.5 $\pm$ 474.3 ng/mL vs. 167.1 $\pm$ 359.7 ng/mL, p = 0.005). No statistically significant correlation was observed between serum concentrations of both sICAM-1 and CEA and patient gender. Finally, the mean value of serum concentrations of sICAM-1 is elevated significantly in patients with advanced CRC compared to healthy volunteers with the p- value lower than 0.001.
Conclusions: Despite the declining tendency of serum sICAM-1 levels during systemic chemotherapy in patients with advanced CRC, there was not a statistically significant difference in serum levels of sICAM-1 before and after five courses of systemic chemotherapy. Further research is required to assess the correlation between soluble intercellular adhesion molecule sICAM-1's kinetic and effectiveness of systemic chemotherapy in metastatic colorectal cancer patients.

Keywords
Colorectal cancer, sICAM-1, CEA, biomarker

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1. Introduction

Colorectal cancer (CRC) is the third most common newly diagnosed internal cancer in males after lung and prostate cancer and second in females after breast cancer. CRC is classified into familial, hereditary and nonhereditary (sporadic) types. CRC usually spreads through embolisation either via blood vessels (haematogenous route) or via lymphatic vessels. Other mechanisms of spread include contiguous, transperitoneal, transluminal, and perineural

spread [1, 2].

In these pathways of the metastatic spread of CRC, adhesion molecules (CAMs) are thought to play a key role in:

i. tumour cells release from the primary tumour site (by overcoming local adhesive interactions)

ii. tumour cells intravasation (by facilitating penetration of tumour cells into blood or lymph vessels)

iii. tumour cells extravasation (by facilitating initially tumour cells adherence to target capillary endothelium of distant organs and subsequently migration of them through the vessel wall)

iv. tumour cells colonization of distant organs and formation of secondary metastatic foci [3].

In recent years carcinoembryonic antigen (CEA), an adhesion molecule and member of immunoglobulin gene super family (IgSF), has been used as the gold standard diagnostic modality both for the detection of early local recurrent or distant metastatic disease in patients with CRC stage II-III after curative surgery and for patient monitoring with metastatic CRC during systemic chemotherapy regardless of patient gender [4, 5, 6, 7]. Unfortunately, significant limitations such: a) its dependence on the site of metastases (for example, the minority of patients with lung metastases from CRC have elevated CEA levels), b) its significant overexpression in other malignancies (like gastric, gallbladder, pancreas, small cell lung carcinomas etc.) as well as c) in non-cancerous pathologies, such as cirrhosis, bronchitis and renal failure in smokers, continue to prevent it from being a highly reliable diagnostic tool for monitoring patients with CRC [8].

Intercellular adhesion molecule (ICAM-1), also known as CD54, another member of IgSF CAMs family plays a pivotal role in neovascularisation process by exciting endothelial cell migration, endothelial cell differentiation, and sprouting of aortic rings and thus facilitates tumour growth [9]. ICAM-1 is shed from the surface of leukocytes, fibroblasts and endothelial cells to the serum, where it can be determined as soluble form (sICAM-1), whereas the concentration levels of sICAM-1 in the serum were easily measured with the ELISA method. Also, sICAM-1 has been detected in other biological fluids like urine, synovial fluid, cerebrospinal fluid, bronchoalveolar lavage fluid and sputum [10]. So, sICAM-1 was evaluated in the present study based on two criteria. Firstly, sICAM-1 represents the direct pathway of angiogenesis which has been previously shown to play a crucial role both in tumour growth and in the metastatic spread of CRC and therefore it is strongly related to the disease [11]. Secondly, sICAM-1 would be easy to measure using a standardized and inexpensive method.

2. Materials and methods

2.1 Patients

The study included 20 patients with metastatic colorectal cancer (12 men and 8 women, mean age 69.8 $\pm$ 6.6 years) and healthy individuals – control group (6 men and 6 women, mean age 39.1 $\pm$ 8.7 years) between May 6, 2013 and Oct 31, 2013 under simple random sampling. Patients with concurrent autoimmune disorder, inflammatory bowel disease, second primary malignancy, renal disease, hematologic malignancies and patients who participate in other clinical trials were excluded from the study.

The diagnosis of metastatic CRC was based on clinical presentation, colonoscopy, radiology, abdominal ultrasonography and computed tomography (CT) scan of thoracic and abdominal cavity in order to evaluate number, size and location of metastases. All the patients were diagnosed and treated in the First Department of Clinical Oncology, the Third Department of Clinical Oncology and in the Gastroenterology Department of Theagenio Cancer Hospital, Thessaloniki.

All the patients enrolled in the study gave a written informed consent for participation. The study was approved by the Ethical Committee of the Scientific Council of Theagenio Cancer Hospital, Thessaloniki, Greece according to the guidelines for good clinical practice (GCP).

2.2 Assays

Peripheral venous blood samples of patients with metastatic CRC were collected into BD Vacutainer®Tubes in the morning after an overnight fasting of 8 hours during regular clinical visits for the 1st, 3rd and 6th cycle of systemic chemotherapy. In the control group, the blood samples were collected in the same manner with the study group.

The blood samples were allowed to clot for 30 minutes before centrifugation at 3500 rpm for 15 minutes. The serum was then separated and stored at -80°C prior to the assay, but no more than 6 months. The analysis took place in the lab of 2nd Propaideutic Department of Internal Medicine of Aristotle University of Thessaloniki prior to which blood samples were slowly thawed and mixed gently.

2.3 sICAM-1 Measurement

Enzyme-linked immunosorbent assay (ELISA) for determination of sICAM-1 in serum was performed by using a commercially available ELISA kit (Human sICAM-1/DCD540) according to the manufacturer's recommendations (R&D Systems, Abingdon Science Park, Abingdon, UK).

2.4 CEA Measurement

Electro-chemiluminescence immunoassay ECLIA for determination of CEA in serum was performed by using a commercially available COBAS®CEA Kit REF 11731629, according to manufacturer's recommendations (Roche Diagnostics, Konzern-Hauptsitz Grenzacherstrasse, Basel, Switzerland).

2.5 Statistical Analysis

Data are presented as means ± standard deviation (SD). Analysis of variance (ANOVA) with repeated measures was used to test statistical significance of the studied variables at the 3 cycles. Receiver operating characteristic (ROC) curves are used to determine a cutoff value for sICAM-1. A p value < 0.01 was considered statistically significant.

3. Results

Demographic and clinical characteristics of the 20 patients with advanced colorectal cancer are illustrated in Table 1 below. The patient sample consisted of 12 males and 8 females (1.5 male to female ratio) with a median age of 69.8 ± 6.6 years. Most of the patients were in ECOG performance status 0 or 1 who experienced first-line chemotherapy for advanced disease.

Serum mean concentrations of sICAM-1 in subjects with metastatic colorectal cancer were 411.9 ± 196.6 ng/mL at the beginning of the treatment, 374.7 ± 155.6 ng/mL and 353.0 ± 124.1 ng/mL, at the third and sixth cycle of chemotherapy respectively. Meanwhile, serum mean concentrations of CEA in the same patients were 330.5 ± 474.3 ng/mL, 241.8 ± 459.2 ng/mL, 167.1 ± 359.7 ng/mL during the same time intervals. What was noticed was that there was a 14.4% downward trend for sICAM-1 serum levels and a 49.5% downward trend for CEA serum levels, respectively. Unfortunately, in the present study it was not feasible to perform a change evaluation in both sICAM-1 and CEA serum levels based on tumour volumetric image analysis of computed tomography scans.

To evaluate whether both sICAM-1 and CEA serum levels are indeed affected by chemotherapy treatment in patients with metastatic CRC, repeated measures ANOVA were used. The reductions of tumour markers in relation to the effectiveness of chemotherapy are shown in Fig. 1. Contrary to the statistically significant reduction of CEA ($p = 0.005$), there was no statistically significant reduction in the expression of sICAM-1 ($p = 0.011$) during same time intervals.

The next step was to study whether gender influenced serum sICAM-1 levels with regard to CEA levels during systemic chemotherapy. This was because while the impact of gender has been well studied for CEA levels [5, 6, 7], sICAM-1 levels had remained understudied. Statistical analysis of repeated measures ANOVA, however, showed that during systemic chemotherapy there was no statistically significant reduction neither in the expression of sICAM-1 ($p = 0.299$) nor CEA ($p = 0.284$) with respect to gender (Table 2).

Serum levels of sICAM-1 were compared between patients with advanced colorectal cancer (before systemic chemotherapy) and healthy volunteers. The statistical analysis showed that the mean value for the patients is greater than the controls with the level of statistical significance less than 0.001 (412.0 ± 196.6 vs. 220.9 ± 34.6; $p<0.001$). Furthermore, the dispersion of advanced colorectal cancer patients with respect to controls was six times greater derived from the Levene's Test for Equality of Variances ($p = 0.017$).

Finally, ROC analysis between the patients and the control group showed an AUC of 96.7% (95% CI 83.5% − 99.9%) $p < 0.0001$. Considering a cutoff point > 264.5 ng/mL for sICAM-1, both sensitivity and specificity have been respectively calculated to 90% and to 100% (figure 2), while, both positive predictive value (PPV) and negative predictive value (NPV) have been respectively computed to 100% and to 99.5%.

Previously, Bagaria et al (2013) have shown that the mean value of CEA serum levels for the patients with CRC is greater than the controls with the level of statistical significance less than 0.05. The ideal threshold value based on the ROC curve for CEA was >3.34 ng/mL with a sensitivity of 76% (95% CI: 61.8–86.9) and a specificity of 100% in patients with CRC compared to controls [12].

4. Conclusions

Systemic chemotherapy remains the standard-of-care treatment for advanced colorectal cancer. Its efficacy is typically estimated on the basis of physical, radiological and biochemical findings. However, this does not always facilitate timely detection of early recurrence and new metastases. Therefore, there is an increasing need for highly reliable and convenient tools for estimating the effectiveness of chemotherapy treatment in view of improving colorectal cancer management on an individual basis.

In this simple random sampling study, there was not any statistically significant reduction in the serum levels of the sICAM-1 ($p = 0.011$) after five courses of systemic chemotherapy, despite the tendency of patient serum sICAM-1 levels to fall. Thus, based upon this pilot study results, sICAM-1 serum levels cannot be used as a biological surrogate marker of systemic chemotherapy efficacy in patients with metastatic colorectal cancer. Alexiou et al (2001), examined whether serum sICAM-1 levels in 63 patients with colorectal cancer changed following surgical resection. They observed a significant decrease of sICAM-1 levels only in patients without distant metastases at presentation who underwent curative radical resection of the primary tumour site. On the contrary, patients with metastatic disease showed no significant difference in sICAM-1 levels before and after surgery [13]. Unlike other types of cancer no research has been conducted as yet on whether sICAM-1 levels might be influenced by systemic chemotherapy for colorectal cancer. For example, Qian et al (2011), reported that serum sICAM-1 levels had significantly declined after two courses of chemotherapy compared with pretreatment levels in 115 patients with non-small cell lung cancer [14]. Whereas, Mills et al (2004),

Table 1. Demographic and clinical characteristics of patients with advanced colorectal cancer (CRC).

CRC Patients' Characteristics	Value (%)
Enrolled patients	20
Sex	
Men	12 (60)
Women	8 (40)
Median age, Years	69.8 ± 6.6
<69.8	7 (35)
>69.8	13 (65)
Primary tumour	
Colon	14 (70)
Rectum	6 (30)
Location of metastases	
Liver	17(85)
Lung	6(30)
Intra-abdominal lymph nodes	2(10)
Stage	
Stage 0-IIIc	0 (0)
Stage IVA-IVB	20 (100)
Chemotherapy	
First-line Chemotherapy	11 (55)
Second-line Chemotherapy	9 (45)
Clinical Response	
CR	0 (0)
PR	13 (65)
SD	2 (10)
PD	5 (25)
Patient Performance Status	
0	9 (45)
1	5 (25)
2	6 (30)
3	0 (0)
4	0 (0)
5	0

Abbreviations: *CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; ECOG PS = Eastern Cooperative Oncology Group Performance Status;*

Table 2. Tests of Within-Subjects Contrasts.

Source	Type III Sum of Squares	df	Mean Square	F	p
sICAM1_factor1	25258.07	1	25258.07	2.067	0.168
sICAM1_factor1*gender	13994.95	1	13994.95	1.145	0.299
sICAM1_Error(factor1)	219943.16	18	12219.06		
CEA_factor1	221924.9	1	221924.9	8.691	0.009
CEA_factor1*gender	31117.5	1	3117.5	1.219	0.284
sICAM1_Error(factor1)	459652.5	18	25536.2		

showed that serum sICAM-1 levels had significantly risen after four courses of chemotherapy in 26 patients with breast cancer [15].

No significant gender related sICAM-1 levels fall during systemic chemotherapy was observed. This finding is consistent with previous studies in this field of research, such as Mantur et al (2009), concluding that patient's age and gender do not influence expression of serum sICAM-1

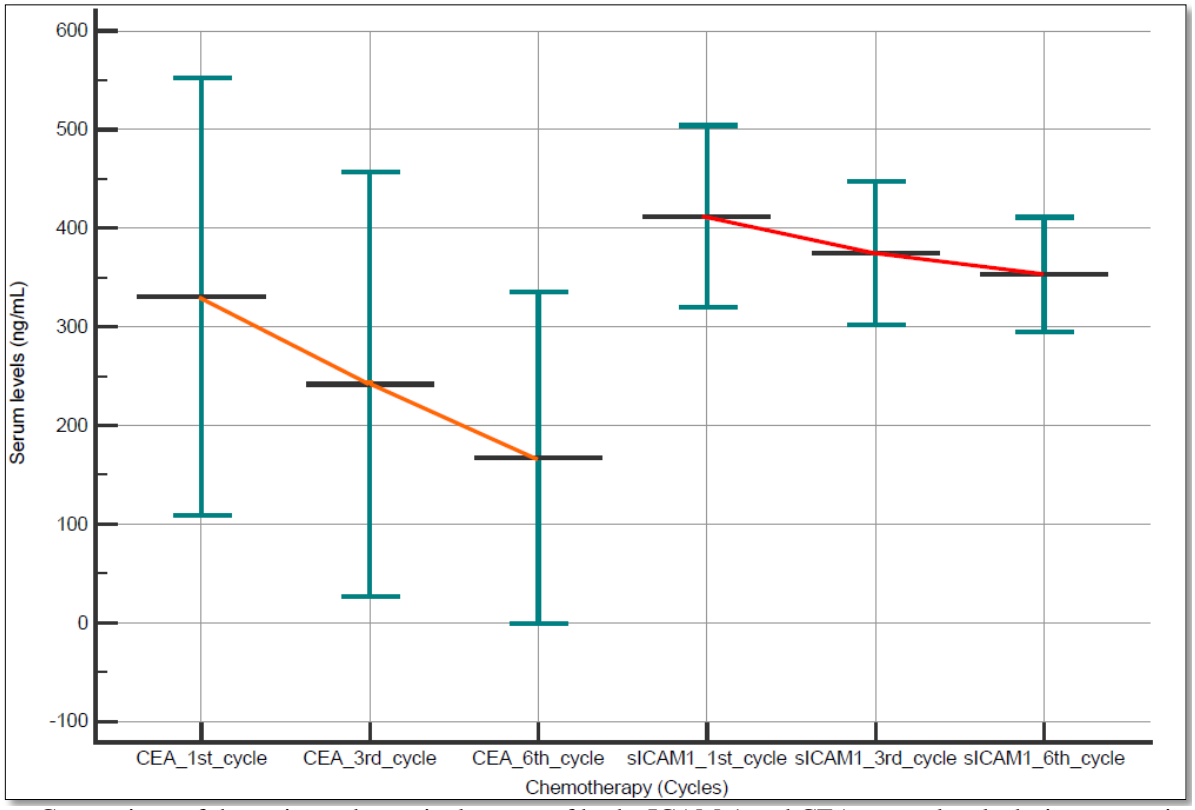

Figure 1. Comparison of the estimated marginal means of both sICAM-1 and CEA serum levels during systemic chemotherapy.

in patients with colorectal cancer. On the contrary, increased expression of soluble ICAM-1 was significantly dependent on primary tumour size, lymph node status and presence of distant metastases [16].

Although a significant decline in serum CEA levels was observed after five courses of systemic chemotherapy, which is consistent with ASCO 2006 guidelines statement that CEA represents the current golden standard biological marker for monitoring response to treatment in patients with metastatic CRC disease [17], some notable limitations of CEA levels interpretation for monitoring response to treatment during palliative chemotherapy should be mentioned. Besides CEA sensitivity and specificity dependence on the site of metastases [18], what was also observed is a transient CEA elevation in a minority of patients with advanced CRC receiving oxaliplatin-based regimen (FOLFOX) or irinotecan-based regimen (FOLFIRI) or 5-fluorouracil regimen despite their evident radiographic and clinical benefit [19, 20, 21, 22]. This therapy-related flare phenomenon is attributed to a positive effect of chemotherapy on CEA mRNA transcription and expression rather than to disease progression [23, 24, 25]. Moreover, Gangmi et al (2013), assessed CEA levels efficacy for the prediction of tumour progression during systemic chemotherapy in patients with advanced disease. They reported that sensitivity, specificity and diagnostic accuracy of CEA in predicting tumour progression were 50%, 77% and 69%, respectively [26]. On the other hand this study confirms previous studies which have demonstrated that gender does not influence CEA levels [6, 7].

In the present study, what is demonstrated that pre-chemotherapy mean concentration of sICAM-1 in the peripheral blood of patients with advanced CRC was significantly higher than that of healthy individuals with the p-value less than 0.001. This finding is consistent with previous studies (27-32), revealing higher serum concentrations of sICAM-1 in correlation with higher tumour load in patients with advanced CRC compared to healthy individuals. Furthermore, it was also observed that the dispersion of patients with advanced CRC is six times greater than healthy subjects derived from the Levene's Test for Equality of Variances.

In this study there have been, however, several limitations. First, it is a small scale pilot study, restricted by both time and cost, conducted as a master thesis requirement which would require a larger number of participants of greater diversity in order to establish a more representative and clearer state of whether or not sICAM-1 could be a reliable tumour marker for monitoring response to treatment in patients with advanced CRC. Although the mean age of the patients in the study group and the control were different, Koycheva et al (2011) concluded that there

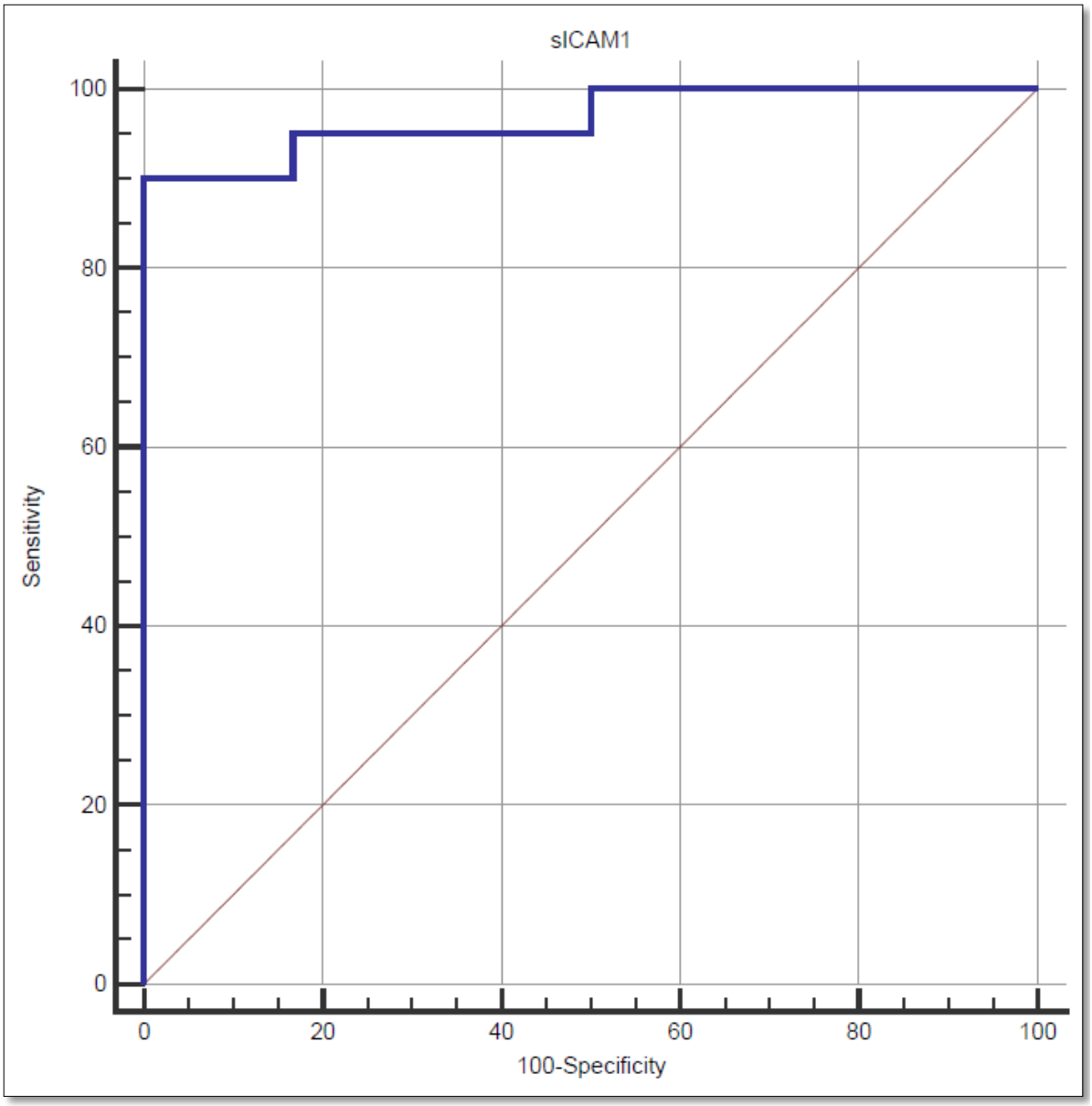

Figure 2. ROC curve of sICAM-1 between patients with advanced colorectal cancer and healthy volunteers.

was no age-related dependence for serum sICAM-1 concentrations in the 18–65 age range for both sexes in 110 healthy volunteers of the same geographic region [33]. Another limitation was the short observation period because it assessed both the effect of systemic chemotherapy on sICAM-1 and CEA serum levels in patients with advanced CRC after three months of systemic chemotherapy instead of the standard treatment period of six months [34]. A large number of previous published studies demonstrated statistically elevated serum levels of other cell soluble adhesion molecules like sE-selectin, sP-selectin and sVCAM-1 in patients with advanced CRC compared with healthy controls suggesting their being considered as biomarkers of neoplastic spread [35, 36, 37, 38, 39, 40, 41, 42, 43]. Hence, these findings could provide grounds for further investigating the use of these soluble adhesion molecules including sICAM-1 as predictors of treatment efficacy in patients with advanced CRC.

In conclusion, despite the declining tendency of serum sICAM-1 levels during systemic chemotherapy in patients with advanced CRC, there was no statistically significant difference in serum levels of sICAM-1 before and after five courses of systemic chemotherapy. Further research is required to assess the correlation between soluble adhesion molecules kinetics like sICAM-1 and effectiveness of systemic chemotherapy in metastatic colorectal cancer patients.

Collaborators: K. Tzanas managed the database and conducted statistical analyses. A. Mpalaska conducted the laboratory analysis of the blood samples. Dr. N. Croft critically reviewed and accepted the study proposal.

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