ORIGINAL ARTICLE

The association between the serum levels of matrix metalloproteinase 9 and colorectal cancer

Ismar Rašić[1], Azra Rašić[2], Goran Akšamija[1], Svjetlana Radović[3], Nedžad Šehović[4]

[1]Clinic for General and Abdominal Surgery, [2]Clinic for Oncology; Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [3]Department of Pathology, School of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [4]Regional Hospital Haugesund, Gastro Surgical Department, Haugesund, Norway

ABSTRACT

Aim To determine the serum levels of matrix metalloproteinase 9 (MMP-9) concentration and their association with the stage and histopathologic sizes of colorectal cancer (CRC).

Methods One hundred and two patients with clinically diagnosed and histologically confirmed colorectal cancer ready for surgical treatment were included in the study. In each patient, preoperative peripheral venous blood samples were taken for determination of the concentration of MMP-9 using ELISA immunoassay test. Resected tumour specimens were studied pathologically according to the criteria of the TNM classification. All patients were divided into groups according to the TNM classification. The control group presented 30 subjects of the appropriate age and gender with no family history of cancer, clinical signs of malignancy or inflammatory bowel disease.

Results The serum levels of MMP-9 were progressively increased in patients with CRC reaching the highest value in the fourth stage of CRC. It was also confirmed that the serum concentrations of MMP-9 were significantly higher in patients with pericolonic lymph nodes involvement compared to the patients with no involvement of lymph nodes, 456.4 (445.9-464.7) ng/mL vs. 438.4 (418.4-447.8) ng/mL ($p<0.001$). Significantly higher serum levels of MMP-9 were found in the patients with metastatic CRC, 458.5 (452.0-468.1) ng/mL compared with the CRC patients without metastasis, 445.8 (436.9-456.5) ng/mL ($p<0.001$).

Conclusion It was confirmed that serum concentration of MMP-9 presented the significant independent risk factors for the progression of CRC.

Key words: colorectal cancer, proteolytic enzyme, serum, risk, progression

Corresponding author:
Ismar Rašić
Clinic for General and Abdominal Surgery, Clinical Centre of the University of Sarajevo, Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina
Phone: +387 33 297 179;
Fax: +387 33 221 518;
E-mail: rasicismar@gmail
ORCIDE ID: http://www. orcid.org/0000-0003-3675-4173

Original submission:
04 April 2017;
Revised submission:
20 April 2017;
Accepted:
28 April 2017.
doi: 10.17392/908-17

Med Glas (Zenica) 2017; 14(2): 229-235

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in human pathology, which was estimated as the third cause of mortality due to cancer disease in the United States in 2016 and the second most common cause of death from cancer in the European Union (EU) according the statistics for 2015 (1,2). More than a half of colorectal cancers are still diagnosed only when the disease involves regional or distant organs (1). This cancer is a heterogeneous disease that occurs only by complex and partially known sequence of molecular events. It is believed that a significant role in the pathogenesis of this disease has disrupted the relationship of apoptosis and proliferation of tumour cells, increased oxidative stress and impaired antioxidant protection (3-5). In addition, proteolytic enzymes play a sophisticated role in cancer development and progression due to their abilities to degrade various substrates (6). Matrix metalloproteinases (MMP) are multigenic family of structurally similar proteolytic enzymes. These are zinc-dependent endopeptidases, which have the capacity to degrade almost any extracellular matrix component (7). It is believed that tumour cells perform overexpress of protease enzyme activity causing the action of enzymes in the adjacent stromal cells for the purpose of degradation of the basement membrane and invasion of the surrounding tissue (8).

Higher activity of MMP and their over-expression has been confirmed in several malignant conditions, such as colon cancer (9), lung cancer (10), pancreas cancer (11), ovarian cancer (12), prostate cancer (13), breast cancer (14) and brain cancer (15), and its correlation with tumour aggressiveness and its malignant potential. Some studies have presented conflicting results regarding the expression of the most commonly related MMP-2 (gelatinase A), MMP-7 (matrilysin) and MMP-9 (gelatinase B) with the prognosis in patients with colorectal cancer (16,17). Recent publications about this cancer indicate that serum levels of matrix metalloproteinases 9 (MMP-9) are elevated in the patients with colorectal cancer (18,19) and can act even in non-proteolytic way (20). Immunohistochemical staining confirmed that the MMP-9 is very positive in the colorectal cancer cells and confirmed that tumour associated macrophages are significant sources of MMPs in the process of carcinogenesis (21). However, the question of the association of serum levels of MMP-9 with the different histopathologic size and progression of colorectal cancer still remains open (22).

The aim of the study was to analyse the serum concentration of MMP-9 in the patients in various depth of wall invasion, lymph nodes involvement and stage of colorectal cancer, estimated on the basis of preoperative, intraoperative findings and histological findings made after surgical resection of tumour altered organ, and to determine predictive significance of MMP-9 in the disease progression.

PATIENTS AND METHODS

Patients and study design

The research was designed as a cross-sectional study conducted from January 2014 to December 2015 at the Clinic for General and Abdominal Surgery, Clinical Centre of the University of Sarajevo (CCUS). A total of 102 patients of both genders with clinically diagnosed and histologically confirmed colorectal cancer who met the inclusion criteria were included in the study. Inclusion criteria were clinically diagnosed and histologically confirmed colorectal cancer and a need for surgical treatment of CRC. Exclusion criteria were evidence of neoplasm on an organ that is not linked to colorectal cancer, patients treated by preoperative radiotherapy or chemotherapy, those with inflammatory bowel disease or a known history of familial adenomatous polyposis and refusing surgical treatment.

A control group included 30 healthy volunteers of the appropriate age and gender without family history of cancer or clinical signs of malignant or inflammatory bowel disease, who went for preventive examinations at the Gastroenterology Counselling Centre. Informed consents were obtained from all participants. The study was approved by the Ethics Committee of the Clinical Centre and the Ethics Committee of the School of Medicine, University of Sarajevo.

Methods

Preoperative confirmation of the diagnosis of colorectal cancer was prepared on the basis of clinical examination, colonoscopy with biopsy following the histological evidence of tumour

lesions and additional radiological findings (chest X-ray, ultrasound and computed tomography of the abdomen and pelvis, and if necessary, other radiological imaging). Complete preoperative diagnostics was carried out in the institutions of the Clinical Centre of the University in Sarajevo.

A sample of 5 mL of peripheral venous blood was collected from each CRC patient for MMP-9 determination. Blood sample was taken before the surgical treatment of colorectal cancer in BD Vacutainer test tube with no additive, while the control blood was taken on the day of physical examination. Each test tube with blood sample was labelled with patient's number and promptly transported to the laboratory, where it was immediately centrifuged at 1.006 x g for 10 minutes at room temperature followed by separation of serum. All serum samples were stored at -80°C until analysis of the serum concentration of MMP-9. Serum concentration of MMP-9 was quantified on duplicate aliquots of each sample using the technique of enzyme-linked immunosorbent assay (ELISA) at the Department of Clinical Immunology of CCUS according to the manufacturer's instructions (R&D Systems, Inc; RD-DMP900). Reading of the results was carried out spectrophotometrically at 450 nm on a plate reader BioTek ELX50, with the correction wavelength at 540 nm or 570 nm. The measurement concentration of MMP-9 was expressed in nanograms per millilitre (ng/mL).

Surgical treatment of colorectal cancer (right hemicolectomy, left hemicolectomy or resection of the rectum, synchronous operation colon with metastasectomies) was performed as part of the therapeutic process under general anaesthesia. Oncology surgery principle "en bloc" resection of colon cancer with associated lymph-vascular arcade was complied with during the operative treatment. After surgical resection and macroscopic examination of surgically obtained samples of colon cancer, samples of the tumour mass and lymphatic nodes were taken for microscopic analysis.

Resected tumour specimens were studied histologically. Histological examination included determination of histological type of malignancy according to the categorization of the World Health Organization, the depth of tumour invasion in the intestinal wall (pT) and the number of pericolic lymph nodes infiltrated with cancerous tissue (pN) (23). The TNM classification of the American Joint Committee on Cancer of 2010 (24) was used for staging of colorectal cancer, in which "T" marks the degree of invasion of the intestinal wall, "N" level of involvement of lymph nodes and "M" means metastases and spread staging. Staging of the colorectal cancer was marked with numbers I to IV. All patients were divided into groups according to the TNM classification (24).

Statistical analysis

All data were expressed as the mean ± standard deviation (SD) or as median and interquartile range. The normality of data distribution was determined by Kolmogorov-Smirnov test or Shapiro-Wilk test. Comparison of mean values between two groups was performed using Student's t-test for variables with normal distribution and using Mann Whitney U test for variables without normal distribution. Kruskall-Wallis test was used for statistical evaluation of more than 3 groups. A model of regression analysis was applied to examine the impact of MMP-9 on stage, depth of CR-wall invasion (pT) and carcinoma infiltration lymph nodes. The level of significance was set at $p<0.05$.

RESULTS

Clinical and histopathologic colorectal cancer was more commonly confirmed in older people, mean age was 66.2 (range 47-78) years of which 61 (60%) were males. Adenocarcinoma was found in 100% of cases, predominantly grade 2, in 72 (70.6%) patients. The most common location of colorectal cancer was in the area of rectum, 34 (33.3%), and the rarest in the area of cecum, three (2.9%). According to the depth of tumour invasion of the intestine, histopathological pT3 was most common, in 65 (63.3%), while pT2 was the least common, in nine (8.9%) patients. Distant metastasis was found in 29 (28.4%) patients, mostly liver metastasis, in 26 (25.4%) patients. The serum concentration of MMP-9 was significantly higher in patients with CRC compared to the control group, 446.8 (433.2-454.3) vs. 323.6 (236.2-374.1) ng/mL ($p<0.001$) (Table 1).

Table 1. Demographic and clinical characteristics of the control group and colorectal cancer group patients

Demographic and clinical parameter	Control (n=30)	CRC (n=102)	p
Age (years) (median; min, max)	64.1 (47-78)	66.2 (51-78)	0.06
Males (No, %)	14 (46.7%)	61 (60%)	0.20
MMP-9 (ng/mL) (median and interquartile range)	323.6 (236.2-374.1)	446.8 (433.2-454.3)	0.001
Localization of CR cancer (No, %)			
Cecum		3 (2.9%)	-
Ascendens		15 (14.7%)	-
Transversum		3 (2.9%)	-
Descendens		6 (5.9%)	-
Sigmoid		22 (21.5%)	-
Rectosigmoid		19 (18.6%)	-
Rectum		34 (33.3%)	-

MMP-9, matrix metalloproteinase 9; CRC, colorectal cancer

Statistically significant differences in serum MMP-9 concentration in different stages of colorectal cancer and pericolonic lymph nodes infiltrated with cancerous tissue was found ($p < 0.01$) (Table 2). The serum level of MMP-9 was statistically significantly higher in the third stage of CRC as compared to the second stage of CRC, 454.8 (447.0-461.6) and 437.9 (403.7-444.8) ng/mL, respectively ($p<0.001$). Registered dynamics of the change of this parameter according to the depth of the CR-wall invasion (pT) indicated that the concentration of MMP-9 in serum is significantly higher in pT4 group as compared to pT3 group of the CRC patients, 459.5 (453.1-464.6) and 447.0 (436.8-457.0) ng/mL, respectively ($p<0.001$).

Table 2. Serum concentration of matrix metalloproteinase 9 (MMP-9) according to the stage of colorectal cancer (CRC), depth of CR-wall invasion (pT), lymph node involvement and metastatic disease

Characteristics	MMP-9 (ng/mL) (median and interquartile range)	p
Stage of CRC		
I stage	436.1 (409.9-442.8)	
II stage	437.9 (403.7-444.8)	
III stage	454.8 (447.0-461.6)*	<0.01
IV stage	458.5 (452.0-468.1)*	
	stage II vs stage I	0.145
	stage III vs stage II	0.000
	stage IV vs stage II	0.000
	stage IV vs stage III	0.102
Depth of CR-wall invasion (pT)		
pT2	450.4 (438.8-454.8)	
pT3	447.0 (436.8-457.0)	<0.01
pT4	459.5 (453.1-464.6)*	
	pT3 vs. pT2	0.396
	pT4 vs. pT2	0.081
	pT4 vs. pT3	0.000
Lymph node involvement		
N0	438.4 (418.4-447.8)	
N1	456.4 (445.9-464.7)*	<0.01
N2	456.6 (449.8-464.5)*	
	N1 vs. N0	0.000
	N2 vs N1	0.543
	N2 vs N0	0.000
Metastatic disease		
M0	445.8 (436.9-456.5)	
M1	458.5 (452.0-468.1)	<0.001

*p<0.001, the difference between stages III – II and stages IV - II, between pT4 and pT3, between N1 and N0, and between N2 and N0.

Statistically significant differences were confirmed in the average level of MMP-9 in sera in cohort group of patients according to the existing infiltration of the lymph nodes ($p<0.01$). Mean value of the MMP-9 serum concentration was higher in the group N1 (the abstraction of 1-3 regional lymph node with cancer tissue) compared to N0 group of patients with no lymph node presentation in cancerous tissue, as well as in group N2 (metastases to 4 or more regional lymph nodes) compared to N0 group without lymph nodes involvement. It was also confirmed that the serum level of MMP-9 was significantly higher in patients with metastatic CRC than in those without metastasis, 458.5 (452.0-468.1) vs. 445.8 (436.9-456.5) ng/mL ($p<0.001$).

The model of regression analysis showed that MMP-9 serum concentrations were an independent predictor for the stage of colorectal cancer ($p<0.001$) as well as of the carcinoma infiltration lymph nodes ($p<0.05$) (Table 3).

Table 3. Matrix metalloproteinase 9 (MMP-9) as an independent predictor of colorectal cancer (CRC) progression

	B	SE	Beta	t	p	CI 95.0% (lower – higher)	
Constant	-1.711	0.692		-2.472	0.015	-3.083	-0.339
MMP-9	0.007	0.001	0.351	6.390	0.000	0.005	0.009
The dependent variable: the stage of CRC							
Constant	-2.143	1.149		-1.865	0.066	-4.426	0.141
MMP-9	0.006	0.002	0.246	2.632	0.010	0.002	0.011
Dependent variable: carcinoma infiltration of the lymph nodes							

SE, standard error; CI, confidence interval; B, regression coefficient

DISCUSSION

Matrix metalloproteinases are involved in the remodelling of extracellular matrix in a variety of normal and pathological processes, such as morphogenesis, angiogenesis, tissue repair. In some solid tumours this enzyme enhances tumour invasion and metastasis ability (25). Several studies have shown that matrix metalloproteinase can play an important role as indicators of colorectal cancer and its progression (26,27). The question of the significance of these enzymes, particularly MMP-9

and their serum levels correlation with progression of colorectal cancer remains open (22).

The results of our study indicate that the concentration of MMP-9 in the serum of patients with colorectal cancer was significantly higher than in the control group. Significant increase in serum levels of MMP-9 was observed with disease progression. Although the highest value was found in patients in the fourth stage of colorectal cancer, we found that serum MMP-9 levels were significantly increased in stage III patients compared to stage II patients, as well as in stage IV patients compared to stage II patients. Biasi et al. reported a statistically significant increase in the serum enzymatic activity and protein levels of MMP-9 only for the second and the third stage of colorectal cancer, comparable to the tendency we found (28). They also confirmed by immunohistochemistry that MMP-9 was clearly produced in large amounts in tumours at stage two and third.

Metastasis of cancer is a complex, multifactorial and multistage process, involving stromal invasion, penetration into the bloodstream from the primary site, the secondary site extravasation and growth of new tumours (29). These processes require degradation of extracellular matrix by proteolytic enzymes, among which the most important are the matrix metalloproteinases (6). In our research, it was found that the concentration of matrix metalloproteinase 9 in patients with colorectal cancer was significantly higher in patients with metastatic form of the disease, suggesting that MMP-9 is included in the cancer invasion and formation of metastases. A study of Hurst and colleagues also indicates elevated serum levels of MMP-9 in patients with colorectal cancer (18). Wilson et al. demonstrated that higher serum MMP-9 concentrations were significantly associated with the presence of colorectal neoplasia, with the suggestion that MMP-9 probably has the highest predictive value when used as part of a panel of biomarkers (19).

Conversely, some authors did not show clear association of MMP-9 with significant colorectal pathology despite robust sampling protocols in evaluation of accuracy of a serum matrix metalloproteinase 9 test in indicating colorectal cancer or its precursor conditions in a symptomatic population (30). Recent study of Jonsson et al. demonstrated significant differences regarding concentrations of some matrix metalloproteinases including MMP-9, using plasma vs serum (31). In this study all MMPs expressed higher concentration in serum compared with plasma. The authors of this study considered that measurements in serum could reflect the release of proteases by involved blood cells during the clotting process and that the use of anticoagulant in the collected blood prevent this artefact, and therefore they recommended the use of plasma samples for future studies of these proteases.

Herszényi et al. showed that the matrix metalloproteinases and their tissue inhibitors (TIMPs) are particularly important in the process of tumour invasion, progression and metastasis of colorectal cancer (32). The results of our study also suggest that MMP-9 plays an important role during the metastasis of colorectal cancer. Research by Ting and associates suggests that genetic variations in MMP-2 and MMP-9 may be potential predictors of survival without the existence of distant metastases after curative surgery (33). Recent studies have also shown that the level of gene expression and enzyme activity of MMP-2 and MMP-9 correlates with the initiation, progression, angiogenesis, metastasis and recurrence of colorectal cancer (34-36). In a study Said et al. (37) the level of expression of MMP-1, -2, -7, -9 and -13 is correlated with poor outcome, and MMP-12 may be protective. Such findings suggest that the matrix metalloproteinase can be an attractive therapeutic target.

The results of linear regression analysis in our study indicate that serum MMP-9 concentration is statistically significant independent positive predictor of stages of colorectal cancer and carcinoma infiltration of pericolonic lymph nodes.

In conclusion, a significant increase in serum concentrations of MMP-9 in relation to the stage of CRC, depth of CR-wall invasion, lymph nodes involvement and present of metastatic disease indicates the involvement of MMP-9 in carcinogenesis and progression of human colorectal cancer. The search for non-invasive markers and useful parameters progression of neoplastic diseases of the colon is of great importance. Our findings suggest that serum MMP-9 could establishes itself as a "liquid biopsy" parameter, but there is a need for additional clinical studies with a large group of patients with CRC and meta-analysis to determine the "cut-off" values for different stages of colorectal cancer.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66:7-30.
2. Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? Ann Oncol 2015; 26:779-86.
3. Fearonn ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61:759-67.
4. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interac 2006; 160:1-40.
5. Gopčević KR, Rovčanin BR, Tatić SB, Krivokapić ZV, Gajić MM, Dragutinović VV. Activity of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in different stages of colorectal carcinoma. Dig Dis Sci 2013; 58:2646-52.
6. Herszényi L, Barabás L, Hritz I, István G, Tulassay Z. Impact of proteolytic enzymes in colorectal cancer development and progression. World J Gastroenterol 2014; 20:13246–57.
7. Iyer RP, Patterson NL, Fields GB, Lindsey ML. The history of matrix metalloproteinases: milestones, myths, and misperceptions. Am J Physiol Heart Circ Physiol 2012; 303:H919-30.
8. Roy R, Yang J, Moses MA. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. J Clinl Oncol 2009; 27:5287-97.
9. Hong SW, Kang YK, Lee B, Lee WY, Jang YG, Paik IW, Lee H. Matrix metalloproteinase-2 and -7 expression in colorectal cancer. J Korean Soc Coloproctol 2011; 27:133-9.
10. El-Badrawy MK, Yousef AM, Shaalan D, Elsamanoudy AZ. Matrix metalloproteinase-9 expression in lung cancer patients and its relation to serum MMP-9 activity, pathologic type, and prognosis. J Bronchology Interv Pulmonol 2014; 21:327-34.
11. Mroczko B, Lukaszewicz-Zajac M, Wereszczynska-Siemiatkowska U, Groblewska M, Gryko M, Kedra B, Jurkowska G, Szmitkowski M. Clinical significance of the measurements of serum matrix metalloproteinase-9 and its inhibitor (tissue inhibitor of metalloproteinase-1) in patients with pancreatic cancer: metalloproteinase-9 as an independent prognostic factor. Pancreas 2009; 38: 613-8.
12. Zhang W, Hu X-x, Yang X-z, Wang Q, Cheng H, Wang S-m, Yan-ling Hu, Yang Z-j, Li L. Combined detection of serum matrix metalloproteinase 9, acetyl heparinase and cathepsin L in diagnosis of ovarian cancer. Chin J Cancer Res 2012; 24: 67–71.
13. Zhang L, Shi J, Feng J, Klocker H, Lee C, Zhang J. Type IV collagenase (matrix metalloproteinase-2 and -9) in prostate cancer. Prostate Cancer Prostatic Dis 2004; 7:327-32.
14. Provatopoulou X, Gounaris A, Kalogera E, Zagouri F, Flessas I, Goussetis E, Nonni A, Papassotiriou I, Zografos G. Circulating levels of matrix metalloproteinase-9 (MMP-9), neutrophil gelatinase-associated lipocalin (NGAL) and their complex MMP-9/NGAL in breast cancer disease. BMC Cancer 2009; 9:390.
15. Hormigo A, Gu B, Karimi S, Riedel E, Panageas KS, Edgar MA, Tanwar MK, Rao JS, Fleisher M, DeAngelis LM, Holland EC. YKL-40 and matrix metalloproteinase-9 as potential serum biomarkers for patients with high-grade gliomas. Clin Cancer Res 2017; 23:1422-31.
16. Herszényi L, Hritz I, Lakatos G, Varga MZ, Tulassay Z. The behavior of matrix metalloproteinases and their inhibitors in colorectal cancer. Int J Mol Sci 2012; 13:13240-63.
17. Yang B, Su K, Gao J, Rao Z. Expression and prognostic value of matrix metalloproteinase-7 in colorectal cancer. Asian Pac J Cancer Prev 2012; 13:1049-52.
18. Hurst NG, Stocken DD, Wilson S, Keh C, Wakelam MJ, Ismail T. Elevated serum matrix metalloproteinase 9 (MMP-9) concentration predicts the presence of colorectal neoplasia in symptomatic patients. Br J Cancer 2007; 97:971-7.
19. Wilson S, Damery S, Stocken DD, Dowswell G, Holder R, Ward ST, Redman V, Wakelam MJ, James J, Hobbs FD, Ismail T. Serum matrix metalloproteinase 9 and colorectal neoplasia: a community-based evaluation of a potential diagnostic test. Br J Cancer 2012; 106:1431-8.
20. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 2010; 141:52-67.
21. Chu D, Zhao Z, Zhou Y, Li Y, Li J, Zheng J, Zhao Q, Wang W. Matrix metalloproteinase-9 is associated with relapse and prognosis of patients with colorectal cancer. Ann Surg Oncol 2012; 19:318–325.
22. Emara M, Cheung P-Y, Grabowski K, Sawicki G, Wozniak M. Serum levels of matrix metalloproteinase-2 and -9 and conventional tumor markers (CEA and CA 19-9) in patients with colorectal and gastric cancers. Clin Chem Lab Med 2009; 47:993–1000.
23. Hamilton SR, Aaltonen LA. (Eds). Pathology and Genetics of Tumours of the Digestive System. In: Kleihues P, Sobin LH. (series eds.) World Health Organization Classification of Tumours. Lyon: IARCPress, 2000:104.
24. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual (7th ed). New York: Springer-Verlage, 2010.
25. Sun J. Matrix metalloproteinases and tissue inhibitor of metalloproteinases are essential for the inflammatory response in cancer cells. J Signal Transduct 2010; 2010:985132.

26. Bendardaf R, Lamlum H, Pyrhönen S. Prognostic and predictive molecular markers in colorectal carcinoma. Anticancer Res 2004; 24:2519-30.
27. Vihinen P, Kähäri V. Matrix metalloproteinases in cancer: prognostic markers and therapeutic targets. Int J Cancer 2002; 99:157-66.
28. Biasi F, Guina T, Maina M, Nano M, Falcone A, Aroasio E, Saracco GM, Papotti M, Leonarduzzi G, Poli G. Progressive increase of matrix metalloprotease-9 and interleukin-8 serum levels during carcinogenic process in human colorectal tract. PLoS ONE 2012; 7: e41839.
29. Talmadge JE, Fidler IJ. AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 2010; 70:5649-69.
30. Damery S, Nichols L, Holder R, Ward ST, Warmington S, Wilson S, Wakelam MJ, James J, Ismail T. Assessing the value of matrix metalloproteinase 9 (MMP9) in improving the appropriateness of referrals for colorectal cancer. Br J Cancer 2013; 108:1149-56.
31. Jonsson A, Hjalmarsson C, Falk P, Ivarsson ML. Levels of matrix metalloproteinases differ in plasma and serum - aspects regarding analysis of biological markers in cancer. Br J Cancer 2016; 115:703-6.
32. Herszényi L, Hritz I, Lakatos G, Varga MZ, Tulassay Z. The behavior of matrix metalloproteinases and their inhibitors in colorectal cancer. Int J Mol Sci 2012; 13:13240-63.
33. Ting WC, Chen LM, Pao JB, Yang YP, You BJ, Chang TY, Lan YH, Lee HZ, Bao BY. Genetic polymorphisms of matrix metalloproteinases and clinical outcomes in colorectal cancer patients. Int J Med Sci 2013; 10:1022-7.
34. Asano T, Tada M, Cheng S, Takemato N, Kuramae T, Abe M, Takahashi O, Miyamato M, Hamada J, Moriuchi T, Kondo S. Prognostic values of matrix metalloproteinase family expression in human colorectal carcinoma. J Surg Res 2008; 146:32-42.
35. van der Jagt MFP, Wobbes T, Strobbe LJA, Sweep FCGJ, Span PN. Metalloproteinases and their regulators in colorectal cancer. J Surg Oncol 2010; 101:259-69.
36. Zucker S, Vacirca J. Role of matrix metalloproteinases (MMPs) in colorectal cancer. Cancer Metastasis Rev 2004; 23:101-17.
37. Said AH, Raufman J-P, Xie G. The role of matrix metalloproteinases in colorectal cancer. Cancers 2014; 6:366-75.

Udruženost između serumskih nivoa matriks metaloproteinaze 9 i kolorektalnog karcinoma

Ismar Rašić[1], Azra Rašić[2], Goran Akšamija[1], Svjetlana Radović[3], Nedžad Šehović[4]

[1]Klinika za opću i abdominalnu hirurgiju, [2]Klinika za onkologiju; Klinički centar Univerziteta u Sarajevu, Sarajevo, Bosna i Hercegovina, [3]Katedra za patologiju, Medicinski fakultet, Univerzitet u Sarajevu, Sarajevo, Bosna i Hercegovina, [4]Regional Hospital Haugesund, Gastrosurgical Department, Haugesund, Norwey

SAŽETAK

Cilj Utvrditi nivoe koncentracije matriks metaloproteinaze 9 (MMP-9) u serumu i njihove povezanosti sa stadijem i patohistološkom veličinom kolorektalnog karcinoma (KRK).

Metode Stotinu i dva pacijenta sa klinički i patohistološki potvrđenom dijagnozom kolorektalnog karcinoma, koji su bili za hirurško liječenje, uključeni su u studiju. U svakog pacijenta preoperativno su uzeti uzorci periferne venske krvi za određivanje koncentracije MMP-9 pomoću ELISA-testa. Resecirani uzorci tumora proučavani su patološki prema kriterijima TNM klasifikacije, te su i pacijenti podijeljeni u grupe prema TNM klasifikaciji. Kontrolnu grupu predstavljalo je 30 ispitanika odgovarajuće dobi i spola, bez porodične historije karcinoma, kliničkih znakova maligniteta ili upalne bolesti crijeva.

Rezultati Serumski nivoi MMP-9 progresivno su se povećavali u pacijenata sa KRK-om dostigavši najveću vrijednost u četvrtom stadiju bolesti. Također je potvrđeno da su koncentracije MMP-9 u serumu bile značajno više u bolesnika sa zahvaćenim u odnosu na bolesnike bez zahvaćenih perikoličnih limfnih čvorova 456,4 (445,9-464,7) ng/mL nasuprot 438,4 (418,4-447,8) ng/mL ($p<0,001$). Statistički značajno veći serumski nivoi MMP-9 nađeni su u pacijenata sa metastatskim kolorektalnim karcinomom, 458,5 (452,0-468,1) ng/mL, u odnosu na pacijente bez metastatske bolesti, 445,8 (436,9-456,5) ng/mL ($p<0,001$).

Zaključak Potvrđeno je da je serumska koncentracija MMP-9 predstavljala značajan neovisan faktor rizika za progresiju KRK-a.

Ključne riječi: karcinom debelog crijeva, proteolitički enzim, serum, rizik, progresija