INDEX COPERNICUS INTERNATIONAL

Carcinoembryonic antigen and matrix metalloproteinase 2 serum and peritoneal washes concentration in staging and prognosis in colorectal cancer patients

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Tomasz Guzel[1ABDEFD], Dagmara Mirowska-Guzel[2BC], Gustaw Lech[1DF], Marek Wroński[1DF], Marzena Iwanowska[3B], Maciej Słodkowski[1F]

[1]Department of General, Gastroenterological and Oncologic Surgery, Medical University of Warsaw, Warsaw, Poland
[2]Chair and Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland
[3]Central Laboratory of the Central Clinical Hospital, Medical University of Warsaw, Warsaw, Poland

Article history: Received: 25.10.2017 Accepted: 22.06.2018 Published: 31.10.2018

ABSTRACT:

PURPOSE: The aim of the study was to determine the significance of carcinoembryonic antigen and matrix metalloproteinase 2 peritoneal washes and serum concentration in patients suffering from colorectal cancer concerning tumor staging and 5-year survival rate in these patients.

METHODS: 80 patients who underwent curative surgery for colorectal cancer were included in the study. Preoperative serum and intraoperative peritoneal washes CEA and MMP-2 concentrations were measured.

RESULTS: Regarding tumor penetration, CEA-s and CEA-p concentrations were higher in subsequent stages from T2 to T4. Both CEA-s and CEA-p concentrations were lower in T2 compared to T3 and T4. Significant difference of CEA-s and CEA-p was noted between T2 and T4 stages. MMP-2-s concentration was higher in T3 compared to T2, the highest MMP-2-p concentration was in T4, with no statistical significance. Regarding nodular status, a significant difference of CEA-s was noted between N0 and N1. For CEA-p, significance was found between N0 and N2 as between N1 and N2. MMP-2-s concentration was the highest in N1, MMP-2-p concentration was the highest in T4, with no statistical significance. The 5-year survival rate for all patients was 63.53%. There were significant differences in CEA-s and CEA-p concentrations between patients with negative and positive 5-year survival.

CONCLUSION: Intraoperative peritoneal washes concentration of CEA may potentially serve as an important factor for more precise colorectal cancer staging. CEA-p and CEA-s concentrations correlate with survival rate in patients suffering from colorectal cancer and can be useful as an additional prognostic factor. The usefulness of MMP-2 measurement still requires further studies.

KEYWORDS: colorectal cancer, CEA, MMP-2, peritoneal washes

The presented paper shows a significantly higher concentration of CEA-s and CEA-p in subsequent stages according to TNM classification and a significant correlation with the presence of nodular metastases. It may potentially serve as a valuable complementation of TNM classification.

INTRODUCTION

Cancer in general becames one of the most dynamically increasing diseases in the global population. In 2012, more than one and a quarter milion people died from cancer in the European Union (EU), which accounted for 25.8% of the total number of deaths. Cancer accounted for a higher share of deaths among men (29.2%) than among women (22.5%). In the same year, more than 150,000 poeople died in Europe from colon and rectum cancer (crc) which accounted for 11.9% of all deaths from cancer and 3.1% of the total number of deaths from any cause [1]. Colorectal cancer is the second most commonly diagnosed cancer, after breast cancer, that affects both men and women. It is also the second, after lung cancer, leading cause of deaths in Europe and the United States [1, 2, 3, 4]. In the EU, the 5-year relative survival for patients diagnosed in 2000–2007 was 57% and it ranged from 61% in Central Europe to 52% in Ireland and United Kingdom (UK) and 49% in Eastern Europe [5].

With its increasing morbidity and mortality, especially in developed countries, crc is claimed to be the main problem of health care services [6]. Despite screening programs, many patients are diagnosed with an advanced disease. There is not much to offer to the patient who reports with 4th degree disease staging.

This is the reason for great interest in colorectal cancer markers. The best known and most useful prognostic marker in crc patients is carcinoembryonic antigen (CEA) described by Gold and Freedman in 1965 [7]. It is known that CEA serum concentration depends on staging, tumor localization, liver condition (carcinoembryonic antigen is metabolized in liver cells) but also on smoking cigarettes. Antigen concentration was described to be higher in poorly-differentiated tumors and tumors located in the left colon [7, 8]. There was a higher serum concentration in smoking patients in comparison to non-smokers [9]. Routinely, CEA is measured before and after operation and during the follow-up period because its increasing serum concentration is usually the first sign of recurrent disease [10, 11, 12, 13]. CEA concentration was also previously measured in peritoneal washes in cancer patients [14, 15, 16, 17]. Lee et al. confirmed the correlation between CEA-p concentration and depth of tumor invasion, presence of metastases and TNM staging [18]. Kanellos et al. also proved a correlation with high risk of local recurrence [19]. In gastric cancer patients, the authors confirmed correlation of CEA-p concentration with

DOI: 10.5604/01.3001.0012.1269

high risk of intraperitoneal dissemination and presence of nodal metastases [20, 21]. The role of serum concentration in matrix metalloproteinases (MMPs) in colorectal cancer patients is not established and still requires assessment.

MMPs are a heterogenous group of zinc-dependent proteases that rebuild the extracellular matrix [22, 23]. They play an important role in many physiological processes such as tissue rebuilding, angiogenesis, wound healing, pregnancy and childbirth, and in pathogenesis of many diseases like atherosclerosis, arthritis, cancer invasion [24, 25].

Their expression is regulated by inflammatory cytokines, hormones, growth factors [26]. The activity of MMPs is inhibited by structurally related proteins - tissue inhibitors of matrix metalloproteinases (TIMPs) [27].

Matrix metalloproteinase-2 and 9 are gelatinases which participate in degradation of colagen type IV and play a role in development of tumor and metastasis [28, 29]. Expression of these proteinases in the epithelium of various cancers, such as endometrial cancer or crc is associated with poor prognosis and can promote tumor invasion [30, 31].

Several studies revealed the important role of MMP-2 and MMP-9 in colon cancer [32, 33, 34, 31]. Nevertheless, so far there are no published studies which assess the concentration of peritoneal washes MMP-2 or MMP-9 in crc patients. The role of MMP-2 and MMP-9 in tumor development and cancer progression is less described in literature than MMP-9 despite the fact that they are both gelatinases and have similar characteristics [35].

The current study was conducted to investigate the usefulness of CEA and MMP-2 serum (CEA-s, MMP-2-s) and peritoneal washes (CEA-p, MMP-2-p) concentrations in patients with different staging of colorectal cancer.

MATERIALS AND METHODS

Materials

From January 2010 to August 2011, 80 consecutive patients (37 women and 43 men) who underwent curative resection for colon or rectum cancer were included in the study.

In all patients, oncologic disease was confirmed by histopathology (colonoscopy biopsy) and concentration of CEA serum was measured before surgery. Patients with complications from cancer (bleeding, perforation) who required an emergency surgery and patients with free fluid in the abdominal cavity were excluded from the study.

Methods

Surgical methods and collection of material

All patients were operated according to schedule by laparotomy. At the beginning of each surgical procedure, before abdominal cavity exploration, 20 ml of saline were inserted into the abdomen and, after 5 minutes of lavage, 10 ml of washes from the pelvic region were aspired.

Histopathological assessment

Updated TNM classification was used for disease staging [36]

Tumors size was calculated as length x width of tumor's cross section which was established during histopathological examination. Patients were divided into 2 groups according to tumor size: below and over the median tumor cross section.

CEA and MMP-2 concentrations

CEA concentration was measured with the Chemiluminescent Microparticle Immunoassay (CMIA) method by Architect i2000 Chemiflex protocol. In the diagnostic laboratory where concentration of CEA serum was assessed, in routine practice CEA concentration between 0 to 5 ng/ml was set as a normal range. Concentration of CEA peritoneal washes was set between 0 to 5 ng/ml as previously described [37].

Concentrations of MMP-2 were measured with the Enzyme Linked Immunosorbent Assay (ELISA) method by commercially available Quantikine Human/Mouse/Rat MMP-2 Immunoassay, R&D Systems, US as per the manufacturer's instruction. CEA-s, CEA--p and MMP-2-p was measured in all patients, MMP-2-s was determined only in 20 cases.

Ethics

The study was approved by the local Ethics Committee in the Medical University of Warsaw. Written informed consent was obtained from each study participant before enrolling to the study.

Statistical analysis

Statistical analysis was performed with the statistical platform Statistica 7.1 by Statsoft (Krakow, Poland, 2013). TheMann-Whitney U test was used for comparison of independent samples. Spearman rank correlation test was used for correlations. The significant level of p value was <0.05.

RESULTS

Demographic and histopathological characteristics of patients

Eighty patients (43 men and 37 women) at a mean age of 66 years were qualified to the study. Half of them had colon cancer. Adenocarcinoma was found in the majority of cases. The medium size of tumor's cross section was 25.12 cm^2. Comparing the tumor size in different TNM, stages the biggest tumors were found in stage III (29.21 ± 17.66) and the smallest in stage I (18.68 ± 15.93). A trend (p=0.06) was noted when stage I tumors were compared to stage III and stage IV tumors. No other statistical differences were noted.

Exact demographic and histopathological data is presented in table I. M staging was not presented as M1 directly reflects the TNM stage IV and M0 stage I, II or III according to TNM classification.

Biochemical results

Overall, concentrations of CEA-s, CEA-p, MMP-2-s and MMP--2-p are presented in table I. The only statistically significant dif-

Tab. I. Demographic characteristic, histopathological data and biochemical results of patients.

	ALL PATIENTS N=80	MEN N=43	WOMEN N=37	P VALUE
Age (mean±SD)	66.5±12.35	66.65±12.43	66.27±12.44	#ns
Tumor localization:				
Colon, n(%)	40 (50%)	21 (49%)	19 (51%)	*ns dla wszystkich porównań
Sigmoid colon, n(%)	24 (30%)	12 (28%)	12 (32%)	
Rectum, n(%)	16 (20%)	10 (23%)	6 (16%)	
Tumor size (mean±SD)	25.12 ± 16.04	28.41 ± 17.16	21.18 ± 13.82	#0.032
Histopathology:				
Adenocarcinoma	72 (90%)	39 (91%)	33 (89%)	*ns for all comparisons
Adenocarcinoma partim gelatinosum	7 (8.75%)	4 (9%)	3 (8%)	
Adenocarcinoma mucinosum	1 (1.25%)	0	1 (3%)	
T stage^				
T2	12	8	4	*ns for all comparisons
T3	54	28	26	
T4	3	1	2	
N stage˘				
N0	36	22	14	*ns for all comparisons
N1	20	12	8	
N2	16	5	11	
TNM classification				*ns for all comparisons
I	11 (14%)	7 (16%)	4 (11%)	
II	21 (26%)	12 (28%)	9 (24%)	
III	23 (29%)	14 (33%)	9 (24%)	
IV	25 (31%)	10 (23%)	15 (41%)	
CEA-s mean	116.57	40.76	363.74	#ns
Median	2.1	2.72	6.38	
Q1; Q3	1.71; 3.88	1.82; 4.15	1.64; 149.5	
CEA-p mean	105.61	77.14	178.82	#0.03
Median	1.37	1.04	4.36	
Q1; Q3	0.5; 5.13	0.5; 12.94	1.04; 68.62	
MMP-2-s mean	126.48	188.46	143.46	#ns
Median	150.6	150.6	128.93	
Q1; Q3	143.84; 163.19	134.3; 182.1	115.34; 199.12	
MMP-p mean	106.31	125.21	132.17	#ns
Median	38.11	23.73	64.54	
Q1; Q3	5; 194.56	4.50; 151.48	10.96; 207.52	

p value counted with Mann-Whitney U test for comparison between men and women
* p value counted with chi-square test for comparison between men and women
^ T1 was not present in histopathological material
˘ N3 was not present in histopathological material
ns – not statistically significant
CEA-s – concentration of carcinoembryonic antigen serum
CEA-p – concentration of carcinoembryonic antigen peritoneal washes
MMP-2-s – concentration of matrix metalloproteinase 2 serum
MMP-2-p – concentration of matrix metalloproteinase 2 peritoneal washes

ference in concentration of markers between the men's and women's group was found for CEA-p (p=0.03).

Concentration of CEA and MMP-2 according to tumor localization and size

Concerning tumor localization, there was no significant differences in serum or concentrations of peritoneal washes CEA and MMP-2 = (Tab. II). The highest CEA-s concentration was found in the sigmoid and CEA-p in rectal tumors. The highest MMP-2-s concentration was in the sigmoid and MMP-2-p in colonic tumors. In the group of patients with tumors with an over 29 cm^2 tumor size, there was a significantly higher MMP-2-p concentration (p=0.025).

Concentrations of CEA and MMP-2 according to T and N stages

Nodular metastases and distant metastases were investigated according to TNM classification of tumor staging. Concentrations of CEA-s and CEA-p were higher in T3 (for CEA-s p=0.024 and for CEA-p p=0.025) and T4 (for CEA-s p=0.01 and for CEA-p p=0.02) compared to T2 grade. The presence of nodular metastases was confirmed in over 50% patients in IV stage of TNM staging. Concentrations of CEA-s and CEA-p was the highest in N1. A significant difference of CEA-s was noted between N0 and N1 (p=0.03). For CEA-p, significance was found between N0 and N2 (p<0.0001) as between N1 and N2 (p=0.006) for CEA-p. We found a positive correlation of CEA-s and CEA-p with count and percentage of metastasized lymph nodes and CEA-p with the surface of the tumor cross section (Tab. III).

Tab. II. Concentrations of serum and peritoneal washes of CEA and MMP-2 according to tumor localization.

TUMOR LOCALIZATION	CEA-S (NG/ML)	CEA-P (NG/ML)	MMP-2-S (NG/ML)	MMP-2-P (NG/ML)
colon, mean	44.35	87.85	174.66	149.58
median	2.98	3.76	140.04	52.5
Q1; Q3	1.16; 15.36	0.56; 48.98	121.18; 190.6	15.83; 177.84
sigmoid colon, mean	310.19	85.58	241.94	107.92
median	2.86	1.15	256.12	24.8
Q1; Q3	1.87; 29.93	0.5; 6.08	2.76; 463.93	4.83; 206.83
rectum, mean	116.57	105.61	126.48	106.31
median	2.1	1.37	150.6	38.11
Q1; Q3	1.71; 3.88	0.5; 5.13	143.84; 163.19	5; 194.56

CEA-s – concentration of carcinoembryonic antigen serum
CEA-p – concentration of carcinoembryonic antigen peritoneal washes
MMP-2-s – concentration of matrix metalloproteinase 2 serum
MMP-2-p - concentration of matrix metalloproteinase 2 peritoneal washes
Q1 – first quartile
Q3 – third quartile

Tab. III. Concentrations of serum and peritoneal washes of CEA and MMP-2 according to T and N stage.

T/N STAGE	CEA-S (NG/ML)	CEA-P (NG/ML)	MMP-2-S (NG/ML)	MMP-2-P (NG/ML)
T2 mean	3,96	3,33	57,41	119,33
median	1,80	0,5	25,63	39,23
Q1; Q3	0,77; 2,10	0,5; 0,73	2,76; 143,84	3,97; 239,8
T3 mean	158,95	104,05	181,57	98,23
median	2,86	2,46	150,71	35,32
Q1; Q3	1,71; 6,84	0,5; 8,51	128,93; 199,12	6,25; 106,07
T4 mean	218,37	197,03	*	191,53
median	81,86	99 100		213,01
Q1; Q3	6,01; 557,23	1,15; 490,83		2,74; 358,83
No mean	16,73	4,54	120,70	104,19
median	2,17	0,58	134,30	30,84
Q1; Q3	1,36; 3,60	0,5-2,86	25,63; 167,27	3,99; 111,90
N1 mean	333,31	131,89	247,20	101,43
median	4,01	1,80	163,19	35,32
Q1; Q3	2,25; 25,79	0,91; 6,08	150,83; 329,12	5,48; 190,63
N2 mean	174,92	222,66	150,60#	114,6
median	6,01	51,32		37,48
Q1; Q3	1,61; 311,80	4,15; 438,56		16,59; 158,20

CEA-s – concentration of carcinoembryonic antigen serum
CEA-p – concentration of carcinoembryonic antigen peritoneal washes
MMP-2-s – concentration of matrix metalloproteinase 2 serum
MMP-2-p – concentration of matrix metalloproteinase 2 peritoneal washes
Q1 – first quartile
Q3 – third quartile
* no patients
# MMP-2 determined in only 1 patient

Comparisons of MMP-2 concentrations revealed no statistically significant differences. Concentrations of all markers were presented in table IV.

Concentrations of CEA and MMP-2 according to TNM stages

Concentrations of CEA-s, CEA-p, MMP-2-s and MMP-2-p are presented in table IV. The highest concentration of serum and peritoneal washes was found in both markers in stage four of TNM. For the concentration of CEA serum, statistically significant differences in subsequent TNM stages (from I° to IV°) were noted with ANOVA test (for CEA-s p=0.035 and for CEA-p p=0.0027).

Correlations of biochemical and histological parameters

We have noted positive correlations between CEA-s and CEA-p (r=0.42). Both CEA-s and CEA-p correlated positively with T (r=0.37, r=0.35, respectively), N stage (r=0.28, r=0.57, respectively), M stage (r=0.39, r=0.48, respectively) and TNM (r=0.48, r=0.54, respectively), p<0.05 for all correlations. In case of MMP-2, the only correlation was noted for MMP-2-s, M stage (r=0.55) and TNM (r=0.52). Interestingly, CEA-p correlated with MMP-2-p (r=0.29).

Survival and mortality rate

The 5-year survival rate was 63.5% and 1-year survival rate was 78.8%. The mortality rate within a 5-year period was 37.5% for rectal cancer and 36.2 % for colon cancer. A significantly higher CEA-s (p=0.02) and CEA-p (p=0.0002) concentration was measured in patients who died before 5 years after surgery. CEA-p was also significantly higher in patients who died less than 1 year after surgery in comparison to those who survived more than 5 years (p=0.008). For patients with concentration if CEA-s <5ng/ml, the 5-year survival rate was 71.4%, for patients >5ng/ml was 38.5%. For CEA-p, the 5-year survival rate for both groups was 75% and 37.9%.

Tab. IV. Concentration of serum and peritoneal washes of CEA and MMP-2 according to TNM staging.

TNM STAGING	CEA-S (NG/ML)	CEA-P (NG/ML)	MMP-2-S (NG/ML)	MMP-2-P (NG/ML)
I°(n11), mean	1.63	1.58	57.41	128.68
median	1.73	0.30	143.84	62.06
Q1; Q3	0.77; 2.05	0.30; 0.62	143.84; 143.84	3.63; 240.87
II°(n21), mean	3.42	6.48	144.43	106.30
median	2.80	0.77	140.05	38.64
Q1; Q3	1.53; 3.91	0.30; 3.87	121.18; 183.20	6.25; 106.07
III°(n23), mean	7.35	16.71	184.53	82.86
median	2.89	1.80	150.83	35.74
Q1; Q3	1.71; 6.01	0.91; 19.56	150.60; 163.19	5.79; 103.40
IV°(n25), mean	950	249.96	300.95	188.82
median	40.01	32.28	312.27	71.24
Q1; Q3	2.14; 343.83	2.77; 438.56	148.71; 453.19	19.56; 293.08

CEA-s – concentration of carcinoembryonic antigen serum
CEA-p – concentration of carcinoembryonic antigen peritoneal washes
MMP-2-s – concentration of matrix metalloproteinase 2 serum
MMP-2-p – concentration of matrix metalloproteinase 2 peritoneal washes
Q1 – first quartile
Q3 – third quartile
CEA-s I a II p = 0,024; CEA-s I a III p = 0,018, CEA-p I a III p = 0,008; CEA-s I a IV p <0,001; CEA-p I a IV p <0,0001; CEA-s II a IV p = 0,003; CEA-p II a IV p = 0,0003
CEA-s III a IV p=0,009; CEA-p III a IV p = 0,023

There were no significant differences in the concentration of MMP-2-s and MMP-2-p among these patients.

DISCUSSION

Colorectal cancer, with its increasing morbidity and mortality, still requires investigation and new treatment strategies. Many authors report a correlation between the concentration of CEA, MMP serum and tumor staging [38, 39, 40, 41, 42, 43]. The present study confirms a positive correlation between investigated markers, T staging and presence of nodular metastases. Concerning nodular metastases, CEA-s significantly differed only between N0 and N1, whereas CEA-p both between N0-N2 and N1-N2. All markers had the highest presence of distal metastases. We noted a significantly increasing concentration of CEA-s and CEA-p in subsequent stages of TNM classification.

Our results are similar to those published before. Lee et al. reported a close correlation between the concentration of CEA peritoneal washes and the presence of peritoneal metastases, reccurence and peritoneal metastases reccurence in crc patients. The autors confirmed a correlation between the concentration of CEA washes and positive cytology in peritoneal effusion fluid; however, they haven't proven any correlations with local advance and nodal metastases [18]. Bala et al. reported a significantly higher concentration of CEA-p in D2 Duke's staging, which remains in accordance to our findings [44]. Interesting results were presented by Kanoh et al. who compared the concentration of CEA in metastatic and negative lymph nodes in crc patinets. The authors revealed a significantly higher CEA concentration in metastatic lymph nodes [45]. In opposite to our results, they did not confirm any significant correlation between CEA-p and the presence of nodular metastases.

In our study, we also confirmed a significant positive correlation of CEA-s and CEA-p concentration with the percentage of lymph nodes with metastases.. To our knowledge, such a result has not been published before.

What is more, we found a higher concentration of CEA peritoneal washes in colon tumors with the largest surface of the cross section. The same tendency was found in the concentration of MMP-2 washes. These results are in accordance to previous investigations confirming a higher concentartion of these antigents in crc tissues compared to normal tissues, thus the concentration of paritoneal washes may also be higher [21, 30, 31, 46]. Bala et al. revealed a higher concentration of CEA washes in colonic tumors, compared to rectal tumors, which was explained by extratperitoneal rectum localization [44]. In our study, we did not find significant differences of both markers according to tumor localization.

We did not find statistical differences of MMP-2-s and MMP-2-p according to different features of tumor invasion or overall TNM classification. Interestingly, the highest MMP-2-s concentration was observed in the sigmoid where tumor size was the smallest, and in MMP-2-p in colonic tumors in which the cross section surface was the largest. As there is no previous evidence of the concentration pg MMP-2 washes in crc patients, this phenomenon might be explained by vasculogenic mimicry which is vascularization without endothelium cells, also presented in crc [47]. One can speculate that large tumors secret MMP-2 and this can cause a high concentration of washes, whereas growing tumors, due to vascularization, may probably influence a higher serum concentration.

In the stud,y we also indicate certain correlations between MMP-2 and tumor size as well as localization that might be essential for cancer progression. Our findings might have important implications, as some authors the on antiprogressive effect of MMP-2 ihibition [48]. Our results are complementary to those previously performed and may indicate direction of further research.

Concerning the concentration of MMP-2 serum and peritoneal washes as well as TNM classification, our findings are not in accordance with the results of other studies. However, they are also inconclusive. Groblewska et al. revealed a decreasing concentration of MMP-2 serum with bowel wall infiltration (T), nodular involvment (N) and distant metastases [49]. Langenskiold et al. investigated the expression of MMP-2 plasma and revealed lower expression in T4 tumors vs T2 and T3 tumors [22]. In turn, a positive correlation between tissue MMP-2 concentration and

bowel wall inflitration, as well as invasion of vascular and lymph vessels has been reported by other authors [50, 51].

Previously, the activity of MMP-2 was measured in healthy and colon cancer tissues. Li et al. confirmed a higher activity of MMP-2 in crc tissue which rose with depth of tumor invasion and presence of nodular metastses [33]. Liabakk et al. compared MMP-2 concentration in colon cancer, colonic adenoma and normal colon tissue. Results showed a higher concentration in cancer and adenoma compared to normal tissue [34].

MMP-2 seems to be an interesting factor in evaluating staging and survival prognosis of crc patients. Metaanalysis made by Shi et al. concluded that MMP-2 overexpression is asocciated with a poor overall and progression-free survival in crc patients [52].

A valuable part of present investigation is a correlation between the concentration og CEA-s, CEA-p, MMP-2-s and MMP-2-p and colorectal cancer development estimated with survival rate after surgery. In the presented study, the 5-year survival rate was 63.5% (62.5% for colon and 63.7% for rectal cancer) which is in accordance with US and EU cancer statistics [1, 4]. In the study, we confirmed a significantly higher concentration of CEA-s and CEA-p in patients with a negative 5-year survival rate. These results are in accordance with other authors. The concentration of CEA peritoneal washes was investigated by Abe et al. in ga roup of 54 crc patients who were divided into CEA positive/CEA negative groups. The authors concluded a significantly worse 5-year survival rate in the CEA positive group; they also proved depth of tumor invasion significantly correlated with CEA-p levels [15]. Lee et al. reported significantly reduced the survival rate in patients with CEA-p>4ng/ml concentration. In gastric cancer there were a higher CEA-p concentration as a negative prognostic factor for the 5-year survival [21, 53]. Regadring the relation of MMP-2 concentration and 5-year survival, our study is inconclusive. We noted a higher concentration of MMP-2-s and MMP-2-p in patients with a negative 5-year survival rate but without any statistical significance. To our knowledge, there were no studies concerning the concentration of MMP-2 peritoneal washes in crc patients. Langers et al. assessed MMP-2 and MMP-9 levels in normal colorectal mucosa in crc patients and suggested these levels are prognostic for 5-year survival, independent from TNM classification [54]. Also, Hilska et al. reported a high expression of MMP-2 in the malignant epithelium and stroma which was associated with reduced survival of crc patients [31]. On the other hand, Hong et al. reported that the expressions of MMP-2 or MMP7 did not significantly correlate to an advanced level of cancer and showed no correlation with the prognoses for patients [55]. To assess the usefulness of this observation, further studies are required; however, establishing new prgnostic factors in crc development might be another step in cancer treatment and new therapeutic strategies.

REFERENCES:

1. Eurostat Statistics Explained: Cancer statistics-specific cancers. Available at: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics_-_specific_cancers#Colorectal_cancer
2. National Cancer Institute: Surveillance, Epidemiology, and End Results Program (SEER). Available at: https://seer.cancer.gov/statfacts/html/colorect.html
3. Jemal A., Bray F., Center M.M., et al: Global cancer statistics. Ca. Cancer J. Clin., 2011;61:69-90
4. The American Cancer Society Statistics. Available at: www.cancer.org.
5. Holleczek B., Rossi S., Domenic A., et al: On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 – results from the Eurocare-5 study. Europ. J. Cancer, 2015;51:2158-2168
6. Carpentier M.Y., Vernon S.W., Bartholomew L.K., et al: Receipt of recommended surveillance among colorectal cancer survivors: a systematic review. J. Cancer Surviv., 2013;7(3):464-483
7. Gold P., Freedman S.O.: Specific carcinoembryonic antigens of the human digestive system. J. Exp. Med., 1965;122(3):467-481
8. Duffy M.J.: Evidence for the clinical use of tumor markers. Ann. Clin. Biochem., 2004;41(Pt 5):370-377
9. Duffy M.J.: Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin. Chem., 2001;47(4):624-630
10. Carpelan-Holmstrom M., Louhimo J., Stenman U.H., et al.: CEA, CA 242, CA 19-9, CA 72-4 and hCGbeta in the diagnosis of recurrent colorectal cancer. Tumor Biol., 2004;25(5-6):228-234
11. Goldstein M.J., Mitchell E.P.: Carcinoembryonic antigen in the staging and follow- up of patients with colorectal cancer. Cancer Invest., 2005;23(4):338-351
12. Ma C.J., Hsieh J.S., Wang W.M., et al.: Multivariate analysis of prognostic determinants for colorectal cancer patients with high preoperative serum CEA levels: prognostic value of postoperative serum CEA levels. Kaohsiung J. Med. Sci., 2006;22(12):604-609
13. McCall J.L., Black R.B., Rich C.A., et al.: The value of serum carcinoembryonic antigen in predicting recurrent disease following curative resection of colorectal cancer. Dis. Colon Rectum, 1994;37(9):875-881
14. Abe N., Watanabe T., Toda H., et al.: Prognostic significance of carcinoembryonic antigen levels in peritoneal washes in patients with gastric cancer. Am. J. Surg., 2001;181(4):356-361
15. Abe N., Watanabe T., Toda H., et al.: Carcinoembryonic antigen levels in peritoneal washes: a potential prognostic marker for patients with colorectal cancer. Hepatogastroenterology, 2003;50(52):1025-1028
16. Irinoda T., Terashima M., Takagane A., et al.: Carcinoembryonic antigen level in peritoneal washing is a prognostic factor in patients with gastric cancer. Oncol. Rep., 1998;5(3):661-666
17. Asao T., Fukuda T., Yazawa S., Nagamachi Y.: CEA levels in peritoneal washings from gastric cancer patients as a prognostic guide. Cancer Lett., 1989; 47(1-2):79-81.
18. Lee I.K., Kim do H., Gorden D.L., et al.: Prognostic value of CEA and CA 19-9 tumor markers combined with cytology from peritoneal fluid in colorectal cancer. Ann. Surg. Oncol., 2009;6(4):861-870
19. Kanellos I., Zacharakis E., Kanellos D., et al.: Prognostic significance of CEA levels and positive cytology in peritoneal washings in patients with colorectal cancer. Colorectal Dis., 2006;8(5):436-440
20. Asao T., Fukuda T., Yazawa S., et al.: Carcinoembryonic antigen levels in peritoneal washings can predict peritoneal recurrence after curative resection of gastric cancer. Cancer, 1991;68:44
21. Nishiyama M., Takashima I., Tanaka T., et al.: Carcinoembryonic antigen levels in the peritoneal cavity: useful guide to peritoneal recurrence and prognosis for gastric cancer. World J. Surg., 1995;19(1):133-7
22. Langenskiold M., Holmdahl L., Falk P., et al.: Increased plasma MMP-2 protein expression in lymph node-positive patients with colorectal cancer. Int. J. Colorectal Dis., 2005;20(3):245-252
23. Pesta M., Holubec L., Jr, Topolcan O., et al.: Quantitative estimation of matrix metalloproteinases 2 and 7 (MMP-2, MMP-7) and tissue inhibitors of matrix metalloproteinases 1 and 2 (TIMP-1, TIMP-2) in colorectal carcinoma tissue samples. Anticancer Res., 2005;25(5):3387-3391
24. Chaussain-Miller C., Fioretti F., Goldberg M., et al.: The role of matrix metalloproteinases (MMPs) in human caries. J. Dent. Res., 2006;85(1):22-32
25. Collins H.M., Morris T.M., Watson S.A.: Spectrum of matrix metalloproteinase expression in primary and metastatic colon cancer: relationship to the tissue inhibitors of metalloproteinases and membrane type-1-matrix metalloproteinase. Br. J. Cancer, 2001;84(12):1664-1670
26. Malemud C.J.: Matrix metalloproteinases (MMPs)in health and disease: an overview. Front. Biosci., 2006;11:1696-1701

27. Łukaszewicz-Zając M., Mroczko B., Szmitkowski M.: Gastric cancer – the role of matrix metalloproteinases in tumor progression. Clin. Chim. Acta, 2001;412(19-20):1725-30
28. Vihinen P., Kahari V.M.: Matrix metalloproteinases in cancer – prognostic markers and therapeutic targets. Int. J. Cancer, 2002;99(2):157-66
29. Mroczko B., Groblewska M., Okulczyk B., et al.: The diagnostic value of matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of matrix metalloproteinases 1 (TIMP-1) determination in the sera of colorectal adenoma and cancer patients. Int. J. Colorectal. Dis., 2010;25(10):1177-84
30. Di Nezza L.A., Misajon A., Zhang J., et al.: Presence of active gelatinases in endometrial carcinoma and correlation of matrix metalloproteinase expression with increasing tumor grade and invasion. Cancer, 2002;94(5):1466-1475
31. Hilska M., Roberts P.J., Collan Y.U., et al.: Prognostic significance of matrix metalloproteinases-1, -2, -7 and -13 and tissue inhibitors of metalloproteinases-1, -2, -3 and -4 in colorectal cancer. Int. J. Cancer, 2007;121(4):714-723
32. Murnane M.J., Cai J., Shuja S., et al.: Active MMP-2 effectively identifies the presence of colorectal cancer. Int. J. Cancer, 2009;125(12):2893-2902
33. Li B.H., Zhao P., Liu S.Z., et al.: Matrix metalloproteinase-2 and tissue inhibitor of metallo-proteinase-2 in colorectal carcinoma invasion and metastasis. World J. Gastroenterol., 2005;11(20):3046-3050
34. Liabakk N.B., Talbot I., Smith R.A., et al.: Matrix metalloprotease 2 (MMP-2) and matrix metalloprotease 9 (MMP-9) type IV collagenases in colorectal cancer. Cancer Res., 1996;56(1):190-196
35. Birkedal-Hansen H., Moore W.G., Bodden M.K., et al.: Matrix metalloproteinases: a review. Crit. Rev. Oral Biol. Med., 1993;4(2):197-250
36. TNM classification of malignant tumors seventh edition. (2010) Available at: www.uicc.org
37. Cascinu S., Del Ferro E., Barbanti I., et al.: Tumor markers in the diagnosis of malignant serous effusions. Am. J. Clin. Oncol., 1997;20(3):247- 250
38. Bannura G., Cumsille M.A., Contreras J., et al.: Carcinoembryonic antigen (CEA) as an independent prognostic factor in colorectal carcinoma. Rev. Med. Chil., 2004;132(6):691-700
39. Choi J.S., Min J.S.: Significance of postoperative serum level of carcinoembryonic antigen (CEA) and actual half life of CEA in colorectal cancer patients. Yonsei Med. J., 1997;38(1):1-7
40. Allende T., Garcia Muniz J.L., Vizoso F., et al.: Preoperative serum levels of the carcinoembryonic antigen (CEA) and prognosis in colorectal cancer. Rev. Esp. Med. Nucl., 2001;20(5):358-364
41. Arribas J.: Matrix metalloproteases and tumor invasion. N. Engl. J. Med., 2005;352(19):2020-2021
42. Finleton B.: Matrix metalloproteinases: roles in cancer and metastasis. Front. Biosci., 2006;11:479-491
43. Heslin M.J., Yan J., Johnson M.R., et al.: Role of matrix metalloproteinases in colorectal carcinogenesis. Ann. Surg., 2001;233(6):786-792
44. Bała D., Jawień A., Czechowicz W., et al.: Oznaczanie stężenia antygenu karcynoembrionalnego w popłuczynach otrzewnowych u chorych na raka jelita grubego. Pol. Merk. Lek., 2002;13(76):289
45. Kanoh T., Monden T., Tamaki Y., et al.: Extraction and analysis of carcinoembryonic antigen in lymph nodes: a new approach to the diagnosis of lymph node metastasis of colorectal cancer. Dis. Colon Rectum, 2002;45(6):757-763
46. Kiluk M.S., Rolkowski R., Zawadzki R.J., et al.: Przydatność markerów nowotworowych CEA, CA 15-3 i CA 125 w diagnostyce płynów wysiękowych w jamie brzusznej. Pol. Merk. Lek., 2002;13:298-301
47. Baeten C.I., Hillen F., Pauwels P., et al.: Prognostic role of vasculogenic mimicry in colorectal cancer. Dis. Colon Rectum, 2009;52(12):2028- 2035
48. Damodharan U., Ganesan R., Radhakrishnan U.C.: Expression of MMP-2 and MMP-9 (gelatinases A and B) in human colon cancers. Appl. Biochem. Biotechnol., 2001;165(5-6):1242-52
49. Groblewska M., Mroczko B., Gryko M., et al.: Matrix metalloproteinase 2 and tissue inhibitor of matrix metalloproteinases 2 in the diagnosis of colorectal adenoma and cancer patients. Folia Histochem. Cytobiol., 2010;48(4):564-571
50. Sis B., Sagol O., Kupelioglu A., et al.: Prognostic significance of matrix metalloproteinase-2, cathepsin D, and tenascin-C expression in colorectal carcinoma. Pathol. Res. Pract., 2004;200(5):379-387
51. Schwandner O., Schlamp A., Broll R., et al.: Clinicopathologic and prognostic significance of matrix metalloproteinases in rectal cancer. Int. J. Colorectal Dis., 2007;22(2):127-136
52. Shi M., Yu B.., Gao H, et al.: matrix metalloproteinase 2 overexpression and prognosis in colorectal cancer: a meta-analysis. Mol. Biol. Rep., 2013;40:617-623
53. Yamamoto M., Baba H., Kakeji Y., et al. :Prognostic significance of tumor markers in peritoneal lavage in advanced gastric cancer. Oncology, 2004;67(1):19-26
54. Langers A.M., Verspaget H.W., Hawinkels L.J., et al.: MMP-2 and MMP-9 in normal mucosa are independently independly associated with outcome of colorectal cancer patients. Br. J. Cancer., 2012;106(9):1495-8
55. Hong S.W., Kang Y.K., Lee B., et al.: Matrix metalloproteinase-2 and -7 expression in colorectal cancer. J. Korean Soc. Coloproctol., 2011;27(3):133-139

Word count: 4100 Page count: 8 Tables: 4 Figures: – References: 55

DOI: 10.5604/01.3001.0012.1269 Table of content: https://ppch.pl/issue/11379

Competing interests: The authors declare that they have no competing interests.

Corresponding author: Tomasz Guzel, Department of General, Gastroenterological and Oncological Surgery, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland; Tel. +48 506 168 239; Fax +48 22 599 20 57; e-mail: tomasz.guzel@gmail.com, tomasz.guzel@wum.edu.pl

Cite this article as: Guzel T., Mirowska-Guzel D., Lech G., Wroński M., Iwanowska M., Słodkowski M.; Carcinoembryonic antigen and matrix metalloproteinase 2 serum and peritoneal washes concentration in staging and prognosis in colorectal cancer patients; Pol Przegl Chir 2018: 90 (5): 36-43