Original article

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TROSATIVE STRESS PARAMETERS IN COLON CANCER TUMOR, ADJACENT AND HEALTHY TISSUE

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Colorectal cancer is one of the most frequent human malignant diseases and one of the most common causes of malignant diseases death. Oxidative and nitrosative stress have an important role in cancer initiation and propagation. That is why this study is focused on the determination of oxidative and nitrosative stress markers in tumor, adjacent and health tissue, which are important for the estimation of tumor proliferative and angiogenic potential. The study encompassed 50 patients who underwent surgery due to colorectal cancer. In the tissue samples from resected colon preparation (tumor, adjacent and healthy tissue, at least 10 cm distant from tumor), oxidative and nitrosative stress markers, malondialdehyde (MDA) and nitric oxide (NO) were determined. The obtained results prove the presence of oxidative stress in tumor tissue. Highly significantly ($p<0.001$) increased MDA concentrations in both tumor and adjacent tissue (12.43±9.39 and 11.57±5.56 nmol/mg proteins) compared to healthy one (7.25±5.52) reflect higher tumor aggressiveness and metastatic capacity. Higher NO concentrations in adjacent tissue (85.100±37.972 nmol/mg prot.) compared to the tumor one (58.608±22.789) point out high angiogenic potential of tumor surrounding tissue, which could have the clinical importance in the assessment of tumor invasiveness and the probability of local recurrence. In conclusion, the determination of the intensity of reactive oxygen and nitrogen species generation in tumor and adjacent colon tissue of patients with colorectal carcinoma could be useful in the estimation of the cancer invasive and metastatic capacity related to the prognosis of the disease and the choice of adjuvant therapy. *Acta Medica Medianae 2016;55(1):44-50.*

Key words: colon cancer, oxidative stress, nitrosative stress, nitric oxide

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Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer morbidity in world population, with the highest incidence rates in western coun-tries (1). It is the third most common cancer worldwide with a fatal outcome in one third of patients.

The complex process of carcinogenesis comprises the influence of numerous factors, such as angiogenesis stimulators and growth signals and the specific interactions of different mecha-nisms, leading to apoptosis regulation disturbance, replicative potential modification and the loss of response to growth signals stimulation.

In the last decades, the growing body of evidence indicates the role of reactive oxygen species (ROS) in the development of colorectal cancer (2, 3). Oxidative stress, implicated in the etiology of cancer, results from an imbalance in the production of ROS and cell's antioxidant defense. When free radicals are produced in excess, both they and their derivatives react with various bio-molecules, such as lipids, proteins and DNA, chan-ging their function, and may modulate the expres-sion of genes that play a key role in the develop-ment of cancer (4, 5). The molecules involved in cellular response to oxidative stress are the key players in the process of metabolic reprogram-ming which underlies cancerogenesis.

It has been already known that chronic inflammation promotes cancerogenesis (6, 7). Oxidative reactions are an integral part of the inflammatory response, and can be associated with CRC development. Inflammation leads to the generation of ROS, and, in consequence, to oxidative stress, leading to initiation of tumor changes (8). In excess, ROS deregulate the redox homeostasis and promote tumor formation by initiating an aberrant induction of signaling networks that cause tumorigenesis.

Nitric oxide (NO), one of the simplest molecules in nature (9), is produced through the oxidation of L-arginine by nitric oxide synthases (NOSs). NO is free radical, and a fundamental signaling molecule, regulating virtually every critical cellular function, as well as a potent mediator of cellular damage in a wide range of conditions (10). Nitric oxide directly influences cell redox status through the reactions with other free radicals, forming more reactive derivatives, such as peroxynitrite, formed in the reaction of NO with superoxide (O2-). This radical reacts with DNA, lipids and proteins via direct oxidative reaction or indirect, radical-mediated mechanisms. Chronic inflammatory diseases and cancers are among the many pathogenic mechanisms mediated by peroxynitrite.

Many lines of evidence suggest the involvement of NO in some critical steps of the complicated process that leads from normal tissue to malignancy (11). NO affects tumor angiogenesis, metastasis, blood flow and immune surveillance. Both forms of NOSs (inducible and endothelial) can modulate cancer-related events, such as angiogenesis, apoptosis, cell cycle, invasion and metastasis (12). But, the role of reactive nitrogen species (RNS) in colon cancerogenesis is multifactorial and literature data are contradictory (13). RNS cause resistance to apoptosis, mutations and damage of DNA, enhanced proliferation and tumor vascularity, as well as increased metastatic potential (14).

Considering all the literature data, the idea for this study was to examine the level of oxidative/nitrosative stress parameters in the specimens of colorectal cancer tissue, adjacent and healthy tissue obtained during surgical colon resection due to colorectal cancer.

Patients and methods

The patients and tumor specimens

he study encompassed 50 patients who underwent surgery for colon resection due to colorectal cancer. The patients were hospitalized at the Department of Colorectal Surgery of Clinic of Surgery, Clinical Centre Niš. The cancer speci-mens were taken by surgery, together with the specimen of tumor surrounding tissue (adjacent tissue), as well as normal colonic mucosa (healthy tissue) more than 10 cm from tumor border (at the incision margin), during colon resection due to colorectal cancer. Cancers were diagnosed by rou-tine surgical and histopathological examination.

Sample preparation

T Directly after surgery, the tissue specimens were washed in cold saline and frozen at -20^{o}C. Then the tissues were cut into small pieces and homogenized on homogenizer with teflon pestle. The homogenates were frozen until biochemical analyses were performed.

Biochemical analyses

The biochemical part of the research was done at the Research Centre for Biomedicine and Institute for Biochemistry, Faculty of Medicine, University of Niš. In the samples of cancer tissue, as well as adjacent and healthy tissue, the following parameters were determined: malondial-dehyde (MDA) and nitrite + nitrate (NO_2+NO_3) concentrations.

- MDA determination in tissue homogenates
- The lipid peroxidation level was measured spectrofotometrically by the estimation of MDA concentration (nmol/mg of proteins) based on the reaction with thiobarbituric acid (15).
- NO_2+NO_3 determination in tissue homogenates
- In the presence of oxygen NO is rapidly oxidized to stable products nitrites and nitrates. Therefore, the concentration of NO_2+NO_3 has been used as marker of nitric oxide synthase activity and endogenous NO production in biological systems. Tissue NO_2+NO_3 concentration was determined using method of Navaro-Gonzalvez et al. (16), based on Griess reaction.
- Protein determination in tissue homogenates
- Tissue proteins were determined according to the method of Lowry et al. (17).

Results

Demographic characteristic of the patients involved in the study are presented in Table 1.

The percentage of cancer clinical stages representation is shown in Figure 1. The most frequent tumor stage was T3, registered in 66% of the patients, while the rarest represented were T1 and T4 stages found in only 6% of the patients. NO_2+NO_3 concentration in colon cancer tissue (58.608±22.789 nmol/mg prot.) was statistically

Table 1. The sex distribution of the investigated patients with colorectal cancer

	Number	Percent	Age X±SD	Age 95% CI for mean
Men	37	74.0	67.9±11.6	63.1-72.7
Women	13	26.0	68.1±5.9	64.3-71.9
Total	50	100.,0	68.0±10.1	64.6-71.3

NS for all parameters

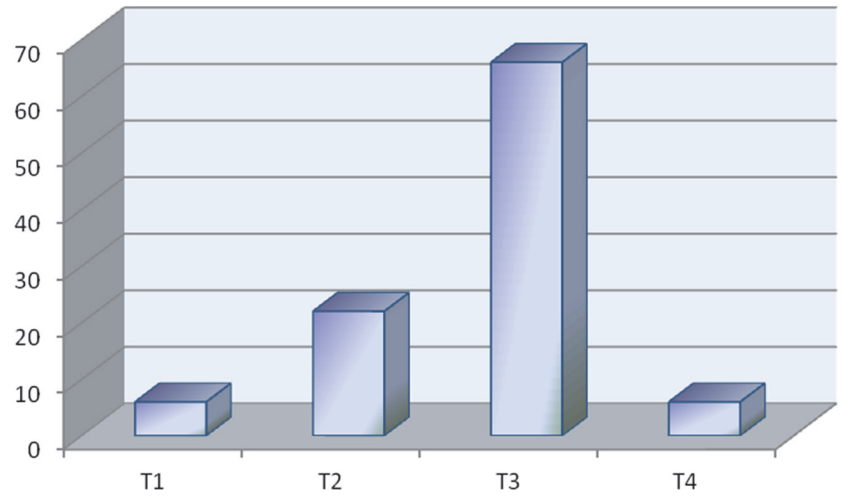
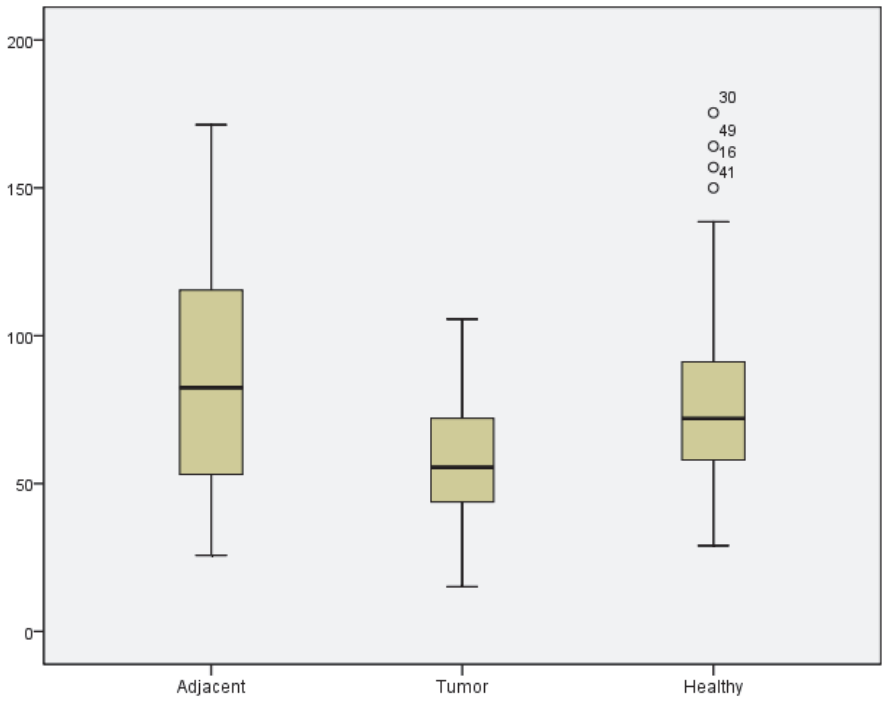


Figure 1. The percentage of cancer clinical stadiums representation

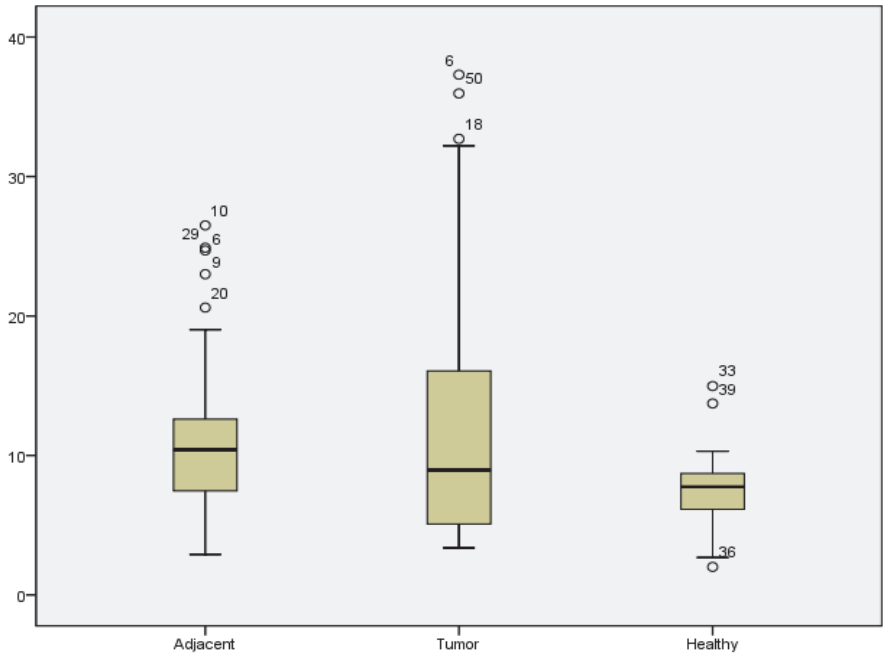


Vertical boxplot. The boundaries of the box are Tukey's hinges. The median is identified by a line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (o).

Figure 2. NO_2+NO_3 concentration in tumor, adjacent and healthy colon tissue

significantly lower ($p<0.001$) compared to healthy tissue (81.556±38.182). In adjacent tissue, NO_2+NO_3 concentration (85.100±37.972) was significantly ($p<0.001$) higher in comparison with tumor tissue, but without statistically significant difference compared to the values in healthy tissue (Figure 2).

MDA concentration in colon tumor tissue (12.43±9.39 nmol/mg proteins) was statistically significantly higher ($p<0.001$) compared to the values in healthy tissue specimens (7.25±5.52). MDA level in adjacent tissue was also significantly higher (11.57±5.56) ($p<0.001$) in comparison he correlation analysis revealed the similar trend of positive association between NO_2+NO_3 and MDA values in tumor, adjacent and healthy colon tissue, which was the most prominent in adjacent tissue (Figure 4).



Vertical boxplot. The boundaries of the box are Tukey's hinges. The median is identified by a line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (o).

Figure 3. MDA concentraton in tumors, adjacent and healthy colon tissue

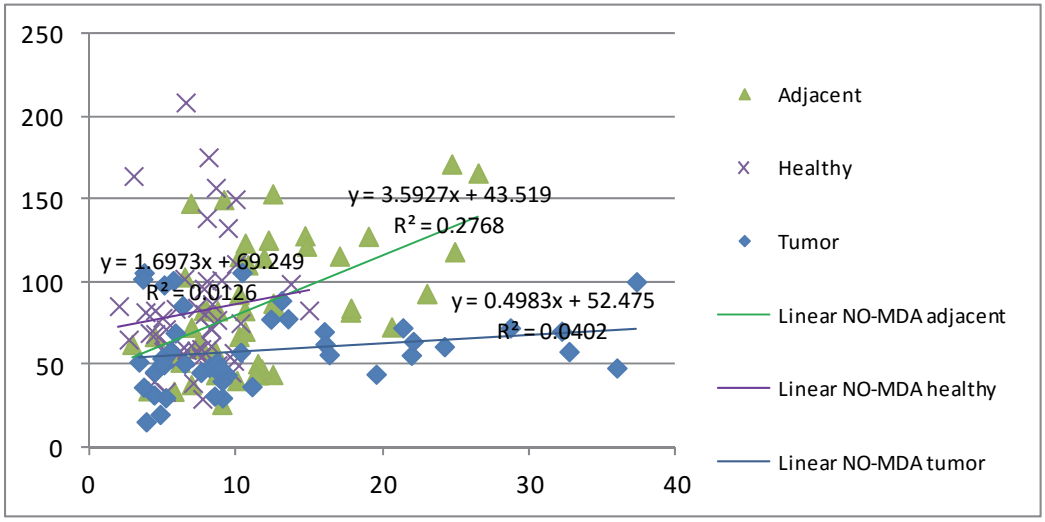


Figure 4. Correlation of NO_2+NO_3 and MDA values

Discussion

Although it is still not clear what is the initial event that leads to the activation of the cascade of the mechanisms underlying the transformation of normal colon mucosal cell into neoplastic one, there is a growing body of evidence that reactive oxygen and nitrogen species have important roles in cancerogenesis (18,19,20). Tumor redox microenvironment is a critical factor in cellular signaling and ROS play important roles as intracellular signaling molecules which regulate key cellular functions, such as proliferation, differentiation, growth, and apoptosis through cellular signaling. ROS and RNS are involved in all three phases of cancerogenesis: intiation, promotion and progression, from DNA damage and gene mutations in initiation phase to epigenetic changes, such as gene expression changes, modulation of second messengers etc. The results of these changes are either increase of cell proliferation or reduction of apoptosis rate, leading to cancer promotion. Finally, oxidative stress contributes to tumor progression by gene mutations accumulation (21).

The ROS production increase has been reported in both benign (adenoma) and malignant

(adenocarcinoma) colorectal tumors (22, 23). The literature data confirm that during disease progression there is lipid peroxidation increase, leading to the damage of cell membrane and DNA. The finding of significant MDA increase in tumor tissue in our study is in agreement with these re-sults. Also, high MDA level in adjacent tissue com-pared to healthy one points out the surrounding tissue tendency to malignant transformation. ROS are critical mediators in tumor capability for inva-sion into surrounding tissue. The microenviron-ment, rich in free radicals, facilitates successful adherence of tumor cells, since free radicals des-troy the integrity of endothelial barrier, which is followed by the formation of intercellular gaps, tu-mor cells bind to.

Increased ROS generation induces genome instability, tumor invasion and metastases. How-ever, it was reported that when the malignant phenotype was acquired, increased oxidative status induced antioxidant defenses in cancer cells, which is favourable for their aggressiveness. The modern concept of redox adaptation suggests that cancer cells use it in order to survive under oxidative stress. This contradictory behavior of cancer cells related to redox status is very impor-tant for potential anticancer therapies, since it se-ems that antioxidant therapy could be the best way to induce tumor growth suppression, increa-sing cancer cell capacity to metabolize ROS. Altho-ugh, there are literature reports that antioxidant therapy increased cancer incidence, possibly by reducing drug antitumor activity which is also me-diated by ROS (24-26).

It is well known that tumor cell, especially metastatic cells, has higher capacity for ROS production compared to normal ones. Our results are in agreement with this. It is also thought that the intensity of the synthesis of free radicals re-flects tumor phenotype aggression (27), since ROS and RNS initiate the cascade of cell processes which facilitate tumor growth and promotion. In this context, highly significant higher MDA con-centrations in both tumor and adjacent tissue in our specimens reflect high tumor metastatic capa-city. However, the correlation analysis didn't show the significant predictive value of MDA concen-tration in tumor and adjacent tissue for distant metastases appearance in five year period (unpu-blished data).

The recent data report NADPH oxidases (Nox enzymes) over expression as the important sources of ROS and RNS in cancer cells with a consequent induction of signaling pathways which facilitate metastasis (28). In tumor microenvi-ronment, nitric oxide could be produced by cancer and stromal cells, activated macrophages and endothelial cell of tumor blood vessels. Also, since inflammation could be a common substrate for colon cancerogenesis, proinflammatory cytokines and tumor necrosis factor - alpha could contribute to NO synthesis, increasing cellular arginine upta-ke and inducible NOS activity. The increased activity of all three isoforms of NOS has been proved in different cancer types (29-31). Although literature data proved positive correlation of increased iNOS expression with tumor progression (32), there was also an increasing number of stu-dies that reported negative correlation between NOS expression and cancer progression (33, 34).

There are also contradictory literature data about antineoplastic potential of NO. While Scott et al. (35) documented iNOS antineoplastic role in mice experimental model of familial adenomatous polyposis, other authors reported that in cell microenvironment high NO concentrations induced cytostasis and cytotoxicity in tumor cells. In this context, low NO concentrations proved in tumor tissue of the patients in our study could be inter-preted as unfavourable for tumor prognosis, which is supproted by the fact that the majority of the investigated patients in this study experienced disease progression in the period after sugery (36). Also, low NO levels could be the indicators of intensive tumor proliferation, since they can be explained by decreased availability of L-arginine for NO synthesis due to its direction into synthesis of polyamines, mediators of cell proliferation and differentiation (37). This was also proved by inve-stigations of polyamine concentrations in tumor and adjacent tissue of our patients, pointing out high proliferative potential of both tumor and adjacent tissue (38).

The important findings in our study are sig-nificantly high NO_2+NO_3 concentration in adjacent tissue compared to tumor tissue, but, also, in comparison with healthy tissue. This is a bad pro-gnostic factor and the sign of tissue preparation for angiogenesis and tumor invasion at the site. This hypothesis is supported by literature data showing that tumor tissue injected by cells with iNOS overexpression (which will produce high NO amounts) is better vascularized and grows faster than "the parent tumor" (39). Beside, Weiss et al. (40) suggest that inducible NOS and high NO concentrations don't influence tumor incidence, but have an impact on its invasive capacity and size.

The literature data undoubtedly confirm the important role of NO in carcinogenesis. Unfortuna-tely, this molecule exerts the specific dichotomy of its effects in these conditions, having sometimes tumor suppressor and the other time promoting tumor progression and distant metastasis occur-rence. Obviously, its behaviour depends on the microenvironment conditions and tumor heteroge-neity.

In conclusion, the determination of the in-tensity of ROS and RNS generation in tumor and adjacent colonic tissue of patients with colorectal carcinoma could be useful in the estimation of the cancer invasive and metastatic capacity related to the prognosis of the disease and the choice of adjuvant therapy.

Acknowledgments

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PARAMETRI NITROZATIVNOG STRESA U TUMORSKOM TKIVU KARCINOMA KOLONA I OKOLNOM ZDRAVOM TKIVU

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Karcinom debelog creva jedno je od najčešćih malignih oboljenja ljudske populacije i jedan od najčešćih razloga smrti od malignih oboljenja. Oksidativni i nitrozativni stres igraju važnu ulogu u pojavi i napredovanju ovog karcinoma. Zbog toga je ova studija usmerena na određivanje markera oksidativnog i nitrozativnog stresa u tumorskom, okolnom i zdravom tkivu, koji su od značaja za procenu proliferativnog i angiogenog potencijala tumora. U studiju je uključeno 50 bolesnika operisanih zbog karcinoma debelog creva. U uzorcima tkiva sa reseciranog preparata debelog creva (tkivo tumora, tkivo neposredno pored tumorske lezije i zdravo tkivo, udaljeno najmanje 10 cm od tumora) određivani su markeri oksidativnog i nitrozativnog stresa – koncentracije malondialdehida (MDA) i azot monoksida (NO). Dobijeni rezultati dokazuju prisustvo oksidativnog stresa u tumorskom tkivu. Visoko signifikantni porast ($p<0,001$) koncentracije MDA u tumorskom i okolnom tkivu (12,43±9,39 i 11,57±5,56 nmol/mg proteina) u odnosu na zdravo (7,25±5,52) odražavaju veliku agresivnost tumora i metastatski kapacitet. Visoke koncentracije NO u tkivu koje neposredno okružuje tumor (85,100±37,972 nmol/mg prot.) u odnosu na tumorsko tkivo (58,608±22,789) ukazuju na veliki angiogeni potencijal tkiva koje neposredno okružuje tumor, što ima klinički značaj u proceni invazivnosti tumora i verovatnoće za nastanak lokalnog recidiva. Može se zaključiti da određivanje intenziteta produkcije reaktivnih vrsta kiseonika i azota u tumorskom i tkivu koje ga neposredno okružuje može biti korisno za procenu invazivnosti i metastatskog potencijala kancera u odnosu na prognozu bolesti i izbor adjuvantne terapije. *Acta Medica Medianae 2016;55(1):44-50.*

Ključne reči: *karcinom debelog creva, oksidativni stres, nitrozativni istres, azot monoksid*