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PREDICTIVE POWER OF OXIDATIVE STRESS BIOMARKERS IN RECURRENCE AND SURVIVAL IN ADVANCED CERVICAL CANCER

The **aim** of our study was to measure the levels of 8-hydroxy-2-deoxyguanosine, malondialdehyde, and antioxidant enzymes in patients with locally advanced cervical cancer prior to treatment to determine how these evaluated biomarkers are associated with cervical cancer recurrence and to estimate their potential in further research and clinical use. **Materials and Methods.** The study included 45 female patients with newly diagnosed advanced cervical cancer who underwent concomitant chemoradiotherapy. The blood and urine samples were collected prior to treatment, between December 2013 and April 2016, and subsequent laboratory analysis was performed. After the medium follow-up of 29 months, the patients were divided into 3 groups according to the time of disease recurrence. A statistical analysis was performed in order to evaluate the relationship between the previously measured biomarkers and recurrence. **Results.** Taken individually, the parameters of oxidative stress did not reveal significant differences between the three groups in our study. Nevertheless, the catalase and glutathione S-transferase activities were the best predictors of the recurrence. Based on the activities of these two oxidative enzymes, it was possible to separate the group of patients without recurrence after follow-up from the other two groups of patients with recurrent disease. **Conclusions.** The parameters of oxidative stress have a certain predictive value on the outcome of patients with advanced cervical cancer after concomitant chemo-radiotherapy.

Keywords: biomarkers, cervical cancer, cancer recurrence, oxidative stress, antioxidative enzymes, 8-hydroxy-2-deoxyguanosine.

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Free radicals are produced in the human body as part of different physiological and pathological processes. The largest part of the oxygen produced by the metabolic processes in cells is reduced to water or transformed during enzyme-catalyzed reactions. The remaining, small part of the oxygen, forms reactive oxygen species (ROS) [1]. Even in small concentrations, these free radicals/ROS are toxic as they react with different biomolecules. In order to prevent oxidation and repair the damaged biomolecules, the organism uses various antioxidants, notably antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione S-transferase (GST) [2].

The oxidative stress occurs when the production of free radicals exceeds the capacities of the antioxidant protection system. The oxidative stress can cause a serious disturbance to cell metabolism, namely, discontinuation of DNA chains, an increase in intracellular free calcium ions, damage to the membrane ion transporter, and other specific proteins and lipid peroxidation that can consequently lead to cell death [3].

Cervical cancer presents a global healthcare issue, as it is the fourth most common cancer in women by the incidence and mortality. The incidence and mortality vary highly between the developed and developing countries, with 80% of newly diagnosed cases of cervical cancer taking place in the latter [4]. Patients with advanced cervical cancer (FIGO stages IIb—IV) usually undergo concomitant chemo-radiotherapy as a therapeutic modality and have a poorer prognosis and higher recurrence rates when compared with early stages. The persistent human papillomavirus (HPV) infection plays the most important role in cervical cancer pathogenesis: this virus has been isolated in 99.7% of cervical cancer patients [5]. The chronic infection activates inflammatory monocytes/macrophages that produce large quantities of ROS [6]. The high levels of ROS lead to the defects and breakage of DNA chains in cervical epithelium cells providing fragile places for the HPV genome integration. Thus, the oxidative stress acts as a co-carcinogen [7]. It acts not only in the initiation but also in the promotion and progression of carcinogenesis by stimulating modifications in the genome expression and suppressing cell apoptosis [8, 9].

The most common biomarkers used for the quantification of the oxidative stress are: antioxidant enzymes (SOD, CAT, GPx, GR, and GST); the product of DNA oxidation, 8-hydroxy-2-deoxyguanosine (8-OH-2dG); and the product of lipid peroxidation, malondialdehyde (MDA) [10].

The previous studies have shown alterations in the levels of oxidative biomarkers in patients with cervical cancer, compared to healthy controls, suggesting a role of the oxidative stress in cancer pathogenesis and a possible diagnostic potential for the measured biomarkers [11—14]. It has been suggested that oxidative stress biomarkers could be used as predictors of the response to the treatment, recurrence, and survival of patients with cervical carcinoma [15—17]. Yet, not much is known today about the potential association between the oxidative stress biomarkers and the cervical cancer response to treatment and the susceptibility to recurrence. The studies of the oxidative stress in cervical cancer were mostly focused on carcinogenesis and cancer biomolecular diagnostics.

The aim of our study was to measure the levels of 8-OH-2dG, MDA, and the antioxidant enzymes in patients with locally advanced cervical cancer prior to treatment and compare the results obtained from three groups of patients after follow-up, based on the survival and the disease recurrence, in order to establish how these evaluated biomarkers are associated with the cervical cancer recurrence and estimate their potential in further research and clinical use.

Materials and Methods

Patients. This study included 45 female patients with newly diagnosed advanced cervical cancer

(FIGO stages IIb—IV). There were 31 patients in FIGO stage IIb, 9 patients in FIGO stage IIIb, 3 in FIGO stage IVa, and 2 in FIGO stage IV. The mean patients' age was 52.18 years. Three patients had adenosquamous carcinoma, while 41 patients had planocellular carcinoma. The inclusion criteria for the patients were: age above 18 years, the signed written consent, the negative pregnancy test, ECOG 0—1 the negative test for HIV, hepatitis C and B and the histological confirmation of cancer. The exclusion criteria for the patient groups was an acute inflammatory process in the body, the previous interventions on the cervix, the previous history of cancer, the previous radio- or chemotherapy. All patients underwent the same treatment (concomitant chemo-radiotherapy) after initial diagnosing and sample collection. The standard protocol for chemoradiation at our institution consists of cisplatin in doses of 40 mg/m^2, once per week, half an hour before EBRT (external beam radiotherapy), the latest one administered in 25 fractions to the cumulative dose of 45 Gy. The EBRT is followed by boost brachytherapy, given in 2—5 fractions until the cumulative radiation dose reaches 85 Gy.

Patients were grouped as follows: group 0 — patients who are alive and without disease recurrence at the time of follow-up; group 1— deceased or with disease recurrence within 6 months of receiving treatment; and group 2 — deceased or with disease recurrence between 6 months of receiving treatment and the date of follow-up (Table 1).

The study and informed consent were approved by the Ethical Committee of the Oncology Institute of Vojvodina (Ethical approval No. 2067/5 from 18.10.2013.). The samples were collected from December 2013 to April 2016. The medium follow-up period was 29 months.

Blood collection and erythrocyte lysate preparation. Five-milliliter blood samples were drawn into EDTA tubes by venipuncture. For the analysis of GPx, we used an amount of 0.4 mL of blood. For the determination of other antioxidative enzymes, 1 mL blood samples were centrifuged for 10 min at 1375 g. After plasma removal, red blood cells were washed thrice with physiologic saline. The ice-cold distilled deionized water was added to the erythrocytes up to 4 mL, and the obtained hemolysates were used for the analysis of SOD, GST, GR, and CAT. To analyze MDA, the plasma samples were separated from the remaining blood samples after they were centrifuged for 10 min at 1375 g.

Chemicals and equipment. All chemicals used in this study were purchased from Sigma Aldrich and were of analytical grade. A Beckman Coulter automated hematology analyzer was used for the analysis of the blood samples. An Agilent 8453 UV-visible spectrophotometer was used for measuring MDA concentration and the activity of the antioxidative enzymes. The concentration of 8-OH-2dG was determined by gas chromatography with mass detection (GC-MS) with an Agilent GC 7890A, 5975C VL MSD device. The identification of 8-OH-2dG was performed using commercial mass spectrometric libraries (Fiehn. L and NIST8.L) and confirmed by the use of the AMDIS software package and characteristic ions m/z 383 (T); 368 (Q1), and 311 (Q2) (T-target; Q1 and Q2-qualifier ions).

Superoxide dismutase. The xanthine/xanthine oxidase system was used as a basis for the total (Cu-Zn and Mn) SOD activity measuring method, as described by Jelic et al. [18]. The enzyme amount causing 50% inhibition in the cytochrome C reduction rate was defined as one unit of SOD, and the results were expressed in U/g Hgb.

Table 1. **Distribution of patients into groups**

Group	No	%
0	15	33
1	15	33
2	11	24
Loss-to-follow-up	4	9

Catalase. CAT activity was measured after the dilution of the sample with 50 mmol/L phosphate buffer, pH 7.00, just prior to measurements, by the same method used in the previous paper [18]. The reaction mixture was 30% H_2O_2, 50 mmol/L phosphate buffer pH 7.00, and 10 μL erythrocyte lysate. The reduction rate of H_2O_2 was followed at 240 nm for 3 min at 25 °C. CAT activity was expressed in U/g Hgb.

Glutathione reductase. GR was determined by measuring the reduction rate of oxidized glutathione (GSSG) with NADPH as a suitable enzyme substrate at 340 nm, as described earlier [18]. GR activity was defined in nmol of NADPH/min/gHgb.

Glutathione peroxidase. The enzymatic activity of GPx was determined in erythrocyte lisate after dilution. The reaction mixture was 1 mol/L Tris buffer, pH 8.00, containing 5 mmol/L of Na_2EDTA, 2 mmol/L NADPH, 250 IU/mL of glutathione reductase (GR), and 0.1 mol/L reduced glutathione (GSH). After the reaction mixture was incubated for 10 min at 37 °C the reaction was initiated with 7 mmol/L t-butylhydroperoxide. The formation rate of oxidized glutathione (GSSG) and concomitant oxidation of NADPH to $NADP^+$ were monitored spectroscopically at 340 nm. The activity of GSH-Px was expressed in nmol of NADPH/min/g Hgb.

Glutathione-S-transferase. The conjugation of the –SH group of reduced glutathione with 1-chloro-2,4-dinitrobenzene (CDNB) was used for the determination of glutathione-S-transferase (GST). The measurement of GST enzyme activity was performed with 20 mmol/L GSH as the first, and 25 mmol/L CDNB as the second electrophilic substrate in 0.5 mol/L potassium phosphate buffer, pH 6.50. The absorbance of the conjugate CDNB-glutathione was measured at 340 nm. The activity of GST was represented in nmol of CDNB-glutathione conjugate/min/g Hgb.

Thiobarbituric acid reactive substances. The formation of thiobarbituric acid reactive substances (TBARS) was used to estimate lipid peroxidation, as described by Jelic et al. [18]. The deproteinization of the samples was carried out with 15% trichloroacetic acid, after which the samples were treated with 0.375% thiobarbituric acid. The mixture was heated in a boiling water bath for 15 min. After cooling to room temperature, it was centrifuged at 3500 g for 10 min, and the developed pink color was measured at 535 nm. The values were defined in nmol of MDA/L.

8-OH-2dG. After 3-mL urine sample was centrifuged at 3500 g 1 mL of supernatant was taken for analysis. 1 mL of the sample was injected into the column, after the column had been conditioned. Later, the column was washed and centrifuged at 3500 g and 8-OH-2dG was eluted with methanol. Before analysis, the eluate was quantitatively transferred in GC-inserts, evaporated, and after re-dissolution derivatized by dissolving the residue in 20 mL of acetonitrile (HPLC grade) and adding 20 mL of bis-trimethylsilyl trifluoroacetamide (BSTFA). Then it was incubated for at least 30 min at room temperature and analyzed by GC-MS (EI ionization). The values were represented as the concentration of 8-OH-2dG/mg creatinine.

Statistical analysis. The statistical analysis included the Kruskal — Wallis test followed by, when necessary, a multiple comparison test of medium ranges. *P*-values at the level of 0.05 were considered statistically significant. The canonical discriminant analysis (CDA) was used for the assessment of discrimination between the examined groups of patients, based on the values obtained for the markers of the oxidative stress, while the determination of the resemblance between the groups was performed by the hierarchical cluster analysis based on Mahalanobis distances. Microsoft Excel 2007 and the Statistica 13 software package (StatSoft Inc., USA), University License (University of Novi Sad) were used for statistical analysis.

Intra- and inter-assay precision. The validation of the analytical methods required for the

determination of lipid peroxidation intensity, SOD activity, CAT activity, GST activity, GPx activity, and GR activity included the determination of the repeatability (intra-assay) and the reproducibility (inter-assay) coefficients, which were summarized in the form of the expanded measurement uncertainty (EMU). Specifically, each tenth sample analyzed for one day was assessed in triplicate (ur), while on different days randomly chosen samples were analyzed in triplicates (Ur), which was used for the determination of the combined measurement uncertainty. As it concerns the analytical method required for the determination of 8-OH-2dG, the intra- and inter-assay precisions were determined by analyzing real samples spiked at three concentration levels with the analytical standard in triplicate on the first day and on the two subsequent days. The previously determined coefficients combined with the recovery test were used for the calculation of the combined measurement uncertainty and EMU with covering factor k = 2.

Results

There were no statistically significant differences between the three evaluated groups of patients, with respect to the activities of SOD, CAT, GPx, GR, GST, and the values of TBARS and 8-OH-2dG (Kruskal—Wallis test). The obtained results for each of the tested parameters are presented in Fig. 1.

On the other hand, when canonical discriminant analysis was applied to the variables describing the markers of the oxidative stress in patients, the results showed that the values obtained for catalase and glutathione S-transferase activities significantly contributed to the discrimination among patients (the tested variables were: CAT, GST, LP, GPx, GR, SOD, and C (8-OH -2dG)/mg Cr) (Table 2).

The canonical analysis showed that the first canonical axis (CA1) describes 89.18% of the discriminations among the examined patients, while the second canonical axis (CA2) describes 10% of the discriminations among the patients (Table 3).

Table 3 demonstrates the loadings of the first two canonical axes including all the antioxidant enzymes as variables, thus showing the correlation between the originally measured variables and the newly formed canonical variables.

The position of the examined patients in the space defined by the first two canonical axes shows the grouping of patients without relapse (group 0) in the negative part, *i.e.*, the grouping of patients with relapses (groups 1 and 2) in the positive part (Fig. 2).

The hierarchical cluster analysis on the Mahalanobis distances obtained by discriminant analysis demonstrates the separation of patients without relapse from the group of patients in whom relapse occurred within 6 months or later (Fig. 3).

Discussion

The variations in the prognosis and the survival of patients with advanced cervical cancer are the result of the multiple factors (FIGO stage, histopathology, therapeutic modalities, follow-up interval). These differences can partially be explained by an altered oxidative-antioxidant system in cancer cells, which leads to treatment resistance or tumor progression, in some patients, and longer survival without recurrence, in the others.

These alterations have been well documented in a study where enhanced lipid peroxidation and lower activities of antioxidant enzymes were estimated in pre-treatment samples, taken from patients with advanced cervical cancer and compared to the control group of healthy patients [15]. The results obtained in this study correspond to the ones published in two other studies, where the high levels of the lipid peroxidation products and the low activities of anti-

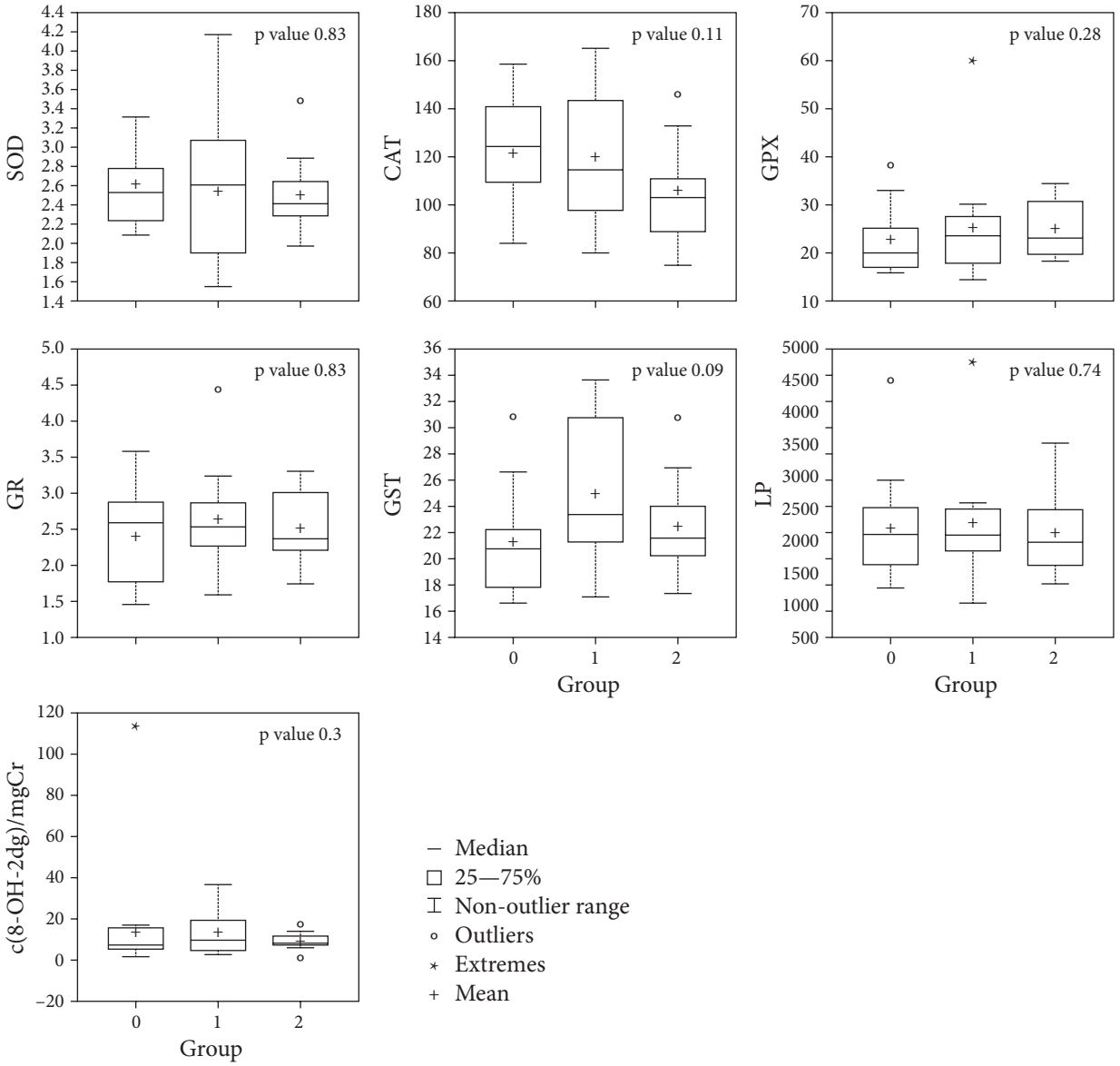

Fig. 1. Differences in the activity of antioxidative enzymes SOD, CAT, GPx, GR, and GST and values of TBARS and 8-OHdG between groups 0, 1 and 2: SOD — superoxide dismutase; CAT — catalase; GPx — glutathione peroxidase; GR — glutathione reductase; GST— glutathione S-transferase; TBARS — thiobarbituric acid reactive substances; 8-OHdG — 8-hydroxy-2-deoxyguanosine; group 0 — patients that are alive and without disease recurrence at the time of follow-up; group 1 — deceased or with disease recurrence within 6 months of receiving treatment; and group 2 — deceased or with disease recurrence between 6 months of receiving treatment and the date of follow-up

oxidant enzymes were observed [13, 16]. In our previous study, the high activity of antioxidant enzymes and high concentrations of TBARS and 8-OH-2dG were observed in patients with cervical cancer [18].

In accordance with our previous findings [18], the study by Zahra et al. [19] demonstrates an increased level of lipid peroxidation, higher levels of 8-OHdG, and an altered antioxidant defense system in the blood of cervical cancer

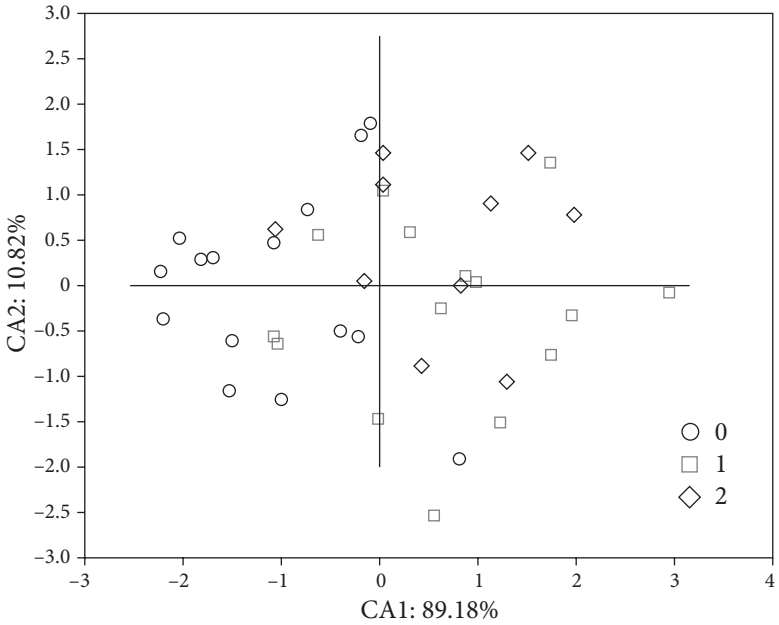

Fig. 2. Position of the patients in the area defined by first two canonical axes: CA 1 — canonical axis 1, CA 2 — canonical axis 2; group 0 — patients that are alive and without disease recurrence at the time of follow-up; group 1 — deceased or with disease recurrence within 6 months of receiving treatment; and group 2 — deceased or with disease recurrence between 6 months of receiving treatment and the date of follow-up

patients. The oxidative stress was involved not only in the pathogenesis, but also in the progression of cervical cancer, since this imbalance became more pronounced in the advanced stages due to the increased tumor burden. Another study revealed that the compromised antioxidant system in the blood samples of cervical cancer patients of Bangladesh was associated with damage to various biomolecules and ultimately impaired cellular functions and suggested that these parameters can be used in the early diagnosis of cervical cancer [20].

The high levels of lipid peroxidation are due to the cancer cell-intrinsic production of free radicals, or an impaired antioxidant system. Lipid peroxidation, which occurs at a primary

Table 2. **Canonical discriminant analysis – model summary. Evaluated variables: SOD, CAT, GPx, GR, GST, TBARS, and 8-OH-2dG. Whole model statistics: F (14.62) = 1.6637; *p* = 0.0872**

Variable	Wilks' (Lambda)	Partial (Lambda)	F-remove (2.31)	*p*	Tolerance
CAT	0.733432	0.720457	6.014115	0.006208	0.494195
GST	0.796480	0.663427	7.863534	0.001729	0.293710
GPX	0.535766	0.986263	0.215885	0.807029	0.793223
GR	0.529115	0.998660	0.020791	0.979438	0.843448
SOD	0.601730	0.878145	2.150841	0.133438	0.522918
c(8-OH-2dG) / mg Cr	0.530508	0.996038	0.061652	0.940325	0.909752
LP	0.533728	0.990029	0.156110	0.856133	0.873545

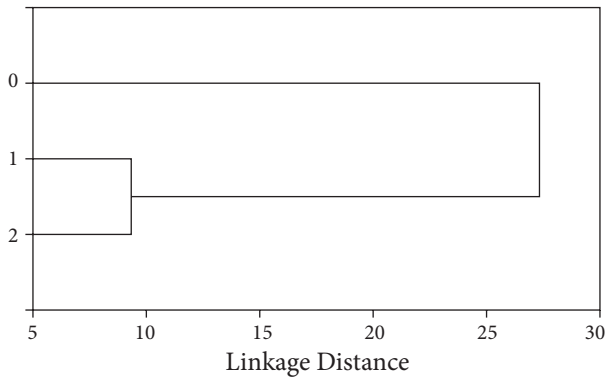

Fig. 3. Hierarchical cluster analysis on Mahalanobis distances (group 0 — patients that are alive and without disease recurrence at the time of follow-up; group 1 — deceased or with disease recurrence within 6 months of receiving treatment; and group 2 — deceased or with disease recurrence between 6 months of receiving treatment and the date of follow-up)

site can also be propagated to other tissues [15]. The activity of the antioxidant enzymes in cervical cancer patients varies in different studies depending on the response to the produced oxidants [21]. The high activity of the antioxidant enzymes is usually explained by the increased gene expression and the upregulation as a response to oxidant production, whereas the low activity might be due to the increased consumption of the antioxidant enzymes in an oxidant-rich environment such as cancer [22].

Table 3. **Canonical discriminant analysis — the loadings of the first two canonical axes (SOD, CAT, GPx, GR, GST, TBARS, and 8-OH-2dG)**

Variable	CA 1	CA 2
CAT	–1.11552	–0.676837
GST	1.61883	–0.642359
GPX	0.16519	0.264420
GR	0.02976	0.121549
SOD	–0.71672	0.428161
c(8-OH-2dG)/mg Cr	–0.07096	–0.164395
LP	–0.16203	–0.057807
Eigen value	0.73719	0.089393
Cumulative proportion	0.89185	1.000000

Free radicals act as mediators for chemotherapy and radiotherapy. Their increased production during treatment leads to cancer cell DNA damage and cell death [23]. Several studies indicate that the high activity of GST can be responsible for the multiple cytotoxic drug resistance acting as an inhibitor of the apoptotic MAP kinase pathway, or via the direct conjugation and subsequent inactivation of chemotherapeutics [24]. Lower concentrations of glutathione in peripheral blood erythrocytes were observed in patients with a complete and partial response to chemotherapy, compared to ones with stable or progressive cancers. This corresponds to an increased synthesis of glutathione in cancer cells with rapid proliferation, while glutathione reduction causes the sensitization of cancer cells to therapy and apoptosis [25, 26].

The Mn-SOD expression in cervical cancer cells is associated with a poorer prognosis, possibly due to an increased resistance to radiotherapy associated with its expression [27]. It has been suggested that the overexpression of Mn-SOD provides counteraction to the intracellular oxidative mechanisms that normally inhibit cancer cell growth and proliferation, thus providing these cancer cells with more aggressive behavior and resistance to therapy [28—30].

To our knowledge, only four studies have evaluated the oxidative stress in patients with cervical cancer, prospectively, focusing on the alterations of the oxidative stress biomarkers following treatment and follow-up and assessing their prognostic value. In the study by Sharma et al. [15], lipid peroxidation decreased and the antioxidative enzyme activity grew until it was normalized, about four months after treatment, and stayed normal after one year in patients who exhibited a complete response, while patients who exhibited only a partial response, or a stable disease, such normalization did not occur. Mila-Kierzenkowska et al. reported the normalization of glutathione peroxidase, catalase, and TBARS about 6 months after

brachytherapy [11]. In the study by Bhuvaraha-murthy et al. [16], these parameters returned to normal values at a different level after therapy depending on the therapeutic modality. Srista-va et al. [13] demonstrated that the antioxidant enzyme levels dropped further during follow-up, whereas the lipid peroxidation levels did not show significant changes.

In our study, the oxidative stress parameters taken individually did not show significant differences between the three groups of patients. Nevertheless, the analysis of all tested biomolecular markers of the oxidative stress in three groups of patients with advanced cervical cancer that underwent the same standard treatment showed that, among the others, the CAT and GST activities were the best predictors of the recurrence. Based on the activities of these two oxidative enzymes, it was possible to separate the group of patients without recurrence within the follow-up period from the other two groups of patients with the recurrent disease. In our study, the oxidative stress parameters have a certain predictive value on the outcome of patients with advanced cervical cancer after the concomitant chemoradiotherapy. It was not possible to subdivide the groups further because of the small number of patients, which could be the potential limitation of our study.

Furthermore, Prabhu et al. [31] studied the association of GST level and radiation response in cervical cancer patients and found that the high level of the antioxidant production by tumor tissue can be protective against the cytotoxic effects of radio/chemotherapy contributing to the recurrence. This is in accordance with our findings, since GST directly influences GSH concentration. Our assumption is that CAT plays an additional role in the enhanced antioxidant capacity of tumor tissues making them less susceptible to the oxidative stress and conferring specific growth advantage.

The oxidative stress biomarker values are variable in patients with cervical cancer. They differ in patients with cancer as opposed to healthy persons, as well as at a particular stage of the disease. They also change after cancer treatment. In order to translate future findings into the clinical use, a considerable scientific effort is needed to find the exact pattern of these variations and their background. Considering the prognostic value of oxidative stress biomarkers in cervical cancer (predominantly GST and CAT), prospective randomized studies with larger groups of patients and more sampling periods, during longer follow-up, are necessary do draw definite conclusions. The results of several studies conducted thus far, including ours, justify further research.

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ПРЕДИКТИВНЕ ЗНАЧЕННЯ БІОМАРКЕРІВ ОКИСНОГО СТРЕСУ У ВИЗНАЧЕННІ РЕЦИДИВІВ ТА ВИЖИВАНОСТІ ПРИ ПОШИРЕНОМУ РАКУ ШИЙКИ МАТКИ

Метою нашої роботи було дослідити рівні 8-гідрокси-2-дезоксигуанозину, малонового діальдегіду та антиоксидантних ферментів у пацієнток з місцево-поширеним раком шийки матки до лікування для визначення їх зв'язку із рецидивом захворювання, а також оцінити їхній потенціал у подальших дослідженнях і можливому клінічному застосуванні. **Матеріали та методи.** Робота ґрунтується на результатах обстеження та лікування 45 пацієнток із вперше діагностованим поширеним раком шийки матки, які пройшли супутню хіміо-променеву терапію. Зразки крові та сечі були зібрані перед лікуванням, у період з грудня 2013 року по квітень 2016 року. Після спостереження, яке в середньому тривало 29 місяців, хворі були розподілені на 3 групи за термінами розвитку рецидиву захворювання. Для оцінки зв'язку між кількісними показниками біомаркерів та розвитком рецидиву було проведено статистичний аналіз. **Результати.** Окремо взяті параметри оксидативного стресу не виявили істотних відмінностей між трьома групами пацієнток у нашому дослідженні. Тим не менш, рівень активності каталази та глутатіон-S-трансферази були найкращими предикторами розвитку рецидиву раку шийки матки. На основі показників активності цих двох окисних ферментів можна було відокремити групу пацієнток без рецидиву впродовж періоду спостереження від пацієнток двох інших груп, в яких розвивався рецидив захворювання. **Висновки.** Параметри оксидативного стресу мають певну предиктивну цінність щодо результатів лікування пацієнток із поширеним раком шийки матки після супутньої хіміо-променевої терапії.

Ключові слова: біомаркери, рак шийки матки, рецидив раку, оксидативний стрес, антиоксидантні ферменти, 8-гідрокси-2-дезоксигуанозин.