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The effect of chemotherapy on endothelial function and microcirculation in patients with gastric cancer

Objective To evaluate and study the dynamics of endothelial dysfunction instrumental indicators, vascular wall stiffness and microcirculation state in patients with gastric cancer (adenocarcinoma) before and after chemotherapy; compare it with the results obtained from healthy volunteers and patients with cardio-vascular diseases.

Materials and Methods The study included 65 people: 25 healthy volunteers, 15 patients with known cardio-vascular diseases (CVD) and 25 patients with histologically confirmed gastric cancer (adenocarcinoma) stage 2—4 who underwent surgical treatment followed by chemotherapy according to the FOLFOX, XELOX, and XP regimes. For non-invasive assessment of the vascular wall's state of large vessels and microcirculation, all patients in the main group underwent computer nailfold capillaroscopy and finger photoplethysmography before chemotherapy and within a month after the completion of the last course. For healthy volunteers and patients with CVD, the above studies were performed once during the examination.

Results The data obtained indicate a significant increase in the reflection index of small muscle arteries (RI) and the stiffness index of large conducting arteries (aSI) during chemotherapy. In cancer patients, even before the treatment, endothelial dysfunction was detected, which significantly worsened after treatment (occlusion index (IO) before and after chemotherapy 1.7 (1.38; 1.9) vs. 1.3 (1.2; 1.5), $p<0.0002$, respectively). Significant differences in the compared indices in cancer patients and CVD group were revealed only after chemotherapy. Significant structural and functional disorders of capillaries were noted in the studied groups, which also worsened during chemotherapy in the main group (density of the capillary network at rest 43.23cap/mm2 vs. 42.19cap/mm2, $p<0.01$, respectively; density of the capillary network after the reactive hyperemia test 46.77cap/mm2 vs. 44.11cap/mm2, $p<0,02$, respectively).

Conclusion In this study, for the first time, the dynamics of endothelial dysfunction indicators, vascular wall stiffness and microcirculation state in patients with gastric cancer were studied, and a reliable increasing of these changes was proved during chemotherapy. The results indicate the need for a further search for accurate and effective methods of identifying early signs of close and distant vasculotoxicity, the development of individual prevention programs in order to significantly reduce the risk of cardiovascular events during and after chemotherapy.

Keywords Pulse-wave analysis; computer nailfold capillaroscopy; endothelial dysfunction; microcirculation; gastric cancer; chemotherapy

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Gastric cancer is one of the most prevalent malignant tumors in the world [1]. According to epidemiologic data for 2017, almost 30 thousand people died of gastric cancer in Russia [2]. In recent years, considerable progress had been made in the treatment of various types of cancer, including gastrointestinal tumors. Modern chemo- and radiation therapies combined with surgical interventions increase life expectancy. Thus, the addition of platinum derivatives to fluoropyrimidine-based chemoradiotherapy in patients with gastric cancer increases the time to progression by a mean of 6 months and life expectancy by 12 months [3–5].

However, multiagent regimens contribute in certain groups of patients to development of various severe and often life-threatening conditions, especially cardiovascular disorders, including hypertension, thrombotic complications, chronic heart failure (CHF), cardiomyopathies, and arrhythmias [6]. Cardiovascular

diseases (CVDs) are the leading cause of death in 30% of patients cured of cancer within the following 10 years [7].

In the previous decade, extensive scientific experience has been accumulated in the research of structural and functional changes in the vascular endothelium of various caliber vessels in specific pathological conditions. Several studies demonstrated that both a tumor and subsequent CT had negative effects on endothelial function. Thus, the CANTOS study showed a significant decrease in the incidence of cardiovascular complications (CVCs) during anti-inflammatory therapy [8]. It was proven that endothelial dysfunction (ED) and vascular wall stiffness are independent risk factors and predictors of CVDs in the healthy population, and that these are diagnostic and prognostic markers of CVCs in cardiovascular patients [9, 10]. Long-lasting ED leads to the development of structural changes in the vascular walls of the microvasculature, and these changes participate in the pathogenesis of hypertension, coronary artery disease (CAD), and CHF [11]. Typical changes in the microvasculature are reduction of capillary density (FOS), remodeling, and destruction of capillary loops [12].

There are currently no data in the literature that show changes in endothelial function, vascular wall stiffness, and the state of the microvasculature in patients with gastric cancer during the course of CT.

Materials and Methods

Before inclusion, all patients signed written, informed consent to participate in the study.

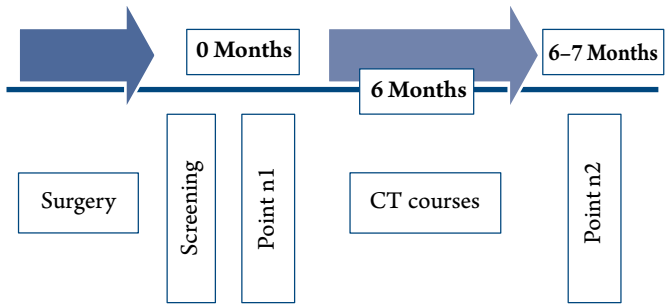
The study included 65 patients in three groups:
1) treatment group (n=25), patients with histologically confirmed stage II–IV gastric cancer (adenocarcinoma) after surgical intervention followed by CT using the FOLFOX, XELOX [CAPOX], XP protocols,
2) control group (n=25), healthy volunteers,
3) a group of patients diagnosed with CVDs (n=15).

The study design is shown in Figure 1.

Subject data are presented in Table 1. The mean age of patients in the treatment group was 63.6±13.4 years old. Two thirds of these patients were male. Concomitant hypertension was identified in 48% of patients (n=12). The group of patients with CVDs was comparable with the treatment group in general characteristics: hypertension 80%, coronary artery disease 53%; mean age 61.4±8.4 years. The mean age of healthy volunteers in the control group was 54.6±10.5 years.

After inclusion, all patients of the treatment group underwent comprehensive laboratory and instrumental examinations, including complete blood count, blood

Figure 1. Study design



CT, chemotherapy.

chemistry to identify lipid and carbohydrate metabolic disorders, electro- and echocardiography, and 24-hour Holter monitoring. Examinations were made of the vascular wall in different parts of the vascular bed and of ED using digital nail fold video capillaroscopy (NVC) (Capillaroscan-1, OOO «New Energy Technologies», Russia) and laser finger photoplethysmography (PPG) (Angioscan-01, OOO «Angioscan», Russia) (Data Point 1). Subsequently, patients repeated CT using approved protocols FOLFOX (5-fluorouracil and oxaliplatin), XELOX (CAPOX) (capecitabine + oxaliplatin), XP (capecitabine + cisplatin). Within one month after the completion of the last course of CT (6–7 months after Data Point 1), the complete, complex examination was repeated (Data Point 2). Patients with CVDs and healthy volunteers underwent all the above tests only once during the study.

According to the literature, 5-fluorouracil (5-FU) and its prodrug capecitabine provoke cardiotoxic effects in 1–68% of cases [13]. Myocardial ischemia is the most common effect, which is associated with damage to endothelial cells, thrombosis, and/or spasms of the coronary arteries [14]. 5-FU also has a direct toxic effect on the endothelium through the inhibition of endothelial NO-synthase and activation of endothelium independent, protein kinase C mediated vasoconstriction [15].

Cardiotoxic effects of oxaliplatin and cisplatin include hypertension, myocardial ischemia, including myocardial infarction, thromboembolism, and cerebrovascular disorders. According to various reports, the prevalence of hypertension ranges from 14% to 53% [16], and its development is associated with activation of endothelial cells, their damage, and subsequent ED [15].

Laser finger PPG

The first stage of PPG evaluation was an automated contour analysis of the pulse wave velocity (PWV). Structural changes of the vascular walls of large vessels, specially the brachial artery, and of the microvasculature

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Table 1. Clinical characteristics of subjects included in the study

	1	2	3	
Variable	**Treatment Group (n = 25)**	**CVD Group (n = 15)**	**Control Group (n = 25)**	**p**
Mean age, years	63.6±13.4	61.4±8.44	54.6±10.5	p_{1-2} >0.05 p_{1-3} <0.05
Sex: M/F	17/8 (68 %/32 %)	7/8 (47 %/53 %)	11/14 (44 %/56 %)	p_{1-2} >0.05 p_{1-3} >0.05
BMI before/ after CT, kg/ m^2	25.87 ± 3.52 /22.31 ± 5.86	32.8±4.9	27.71±4.74	p_{1-2} <0.05 p_{1-3} <0.05
Smoking	9 (36 %)	2 (13 %)	7 (28 %)	p_{1-2} >0.05 p_{1-3} >0.05
Hyper-cholestero-laemia	9 (36 %)	9 (60 %)	11 (44 %)	p_{1-2} >0.05 p_{1-3} >0.05
Hypertensive heart disease	12 (48 %)	12 (80 %)	0	p_{1-2} >0.05 p_{1-3} >0.05
CAD	7 (28 %)	8 (53 %)	0	p_{1-2} >0.05 p_{1-3} <0.05
CHF	3 (12 %)	0	0	p_{1-2} <0.05 p_{1-3} <0.05
LVEF before/after CT, %	62 [58; 64.25]/ 59.5 [53; 65]	58 [55; 61]	61 [59; 66]	p_{1-2} >0.05 p_{1-3} >0.05
E/A before/ after CT	0.9 [0.7; 1.11]/ 0.7 [0.6; 0.74]	0.8 [0.65; 1.2]	1.16 [0.77; 1.3]	p_{1-2} >0.05 p_{1-3} <0.05

Data are presented as median [25th percentile; 75th percentile], as absolute and relative (%) value; or as mean ± standard deviation. p values of the intergroup differences were determined by a chi-squared test. CVDs = cardiovascular diseases; BMI = body mass index; CT = chemotherapy; CAD = coronary artery disease; CHF = chronic heart failure; LVEF = left ventricular ejection fraction. p – the statistical significance of intergroup differences was estimated using the χ^2 criterion.

were evaluated by the following variables: pulse rate, stiffness index of large conduit arteries (a8T), reflection index of small muscular arteries (RI), augmentation index (AIx) to estimate the vascular wall stiffness, augmentation normalized for pulse = 75 bpm (AIx75), aging index (AGI), vascular aging (VA), ejection duration in ms (ED) and as % (%ED), and pulse wave duration (PD). A reactive hyperemia test was used to assess endothelial function. Results were evaluated by the increase in the amplitude of pulse waves in the brachial artery (IO) after a 5 min occlusion with a sphygmomanometer, by the delay, or by the «phase shift» parameter (SF).

Computerized video capillaroscopy of the dorsal surface of index finger measured capillary density at rest (CDr), after venous occlusion (CDvo), and after reactive hyperemia (CDrh). The functional state of the capillaries was evaluated from the percentage of capillary recovery (PCR) and the percentage of perfused capillaries (PPC).

The study was performed according to the principles of the Declaration of Helsinki.

The data were analyzed using non-parametric variation statistics, specifically the Wilcoxon test and Mann-Whitney tests, using the GraphPad Prism 8 program. Data are presented as the median [25th percentile; 75th percentile], as the absolute and relative values (%), or as the mean ± standard deviation. The differences were considered significant for $p<0.05$.

Results

Contour analysis of pulse wave velocity

Mean values of aSI, RI, AIx, AIx75 were elevated in all three groups, and no significant differences between the groups were identified. This may indicate that in the treatment group, a history of CVDs contributes more than cancer to the development of structural changes in the vascular bed.

In the treatment group, structural variables were above normal before CT (Table 2). These values reflect the initial high stiffness of the vascular walls. Most of the patients in the treatment group had positive values of AIx and AIx75, which also confirms increased vascular stiffness.

The dynamics of the main variables of PWV before and after CT is provided in Table 2. In the treatment group, aSI and RI increased significantly after CT by 15% and 23%, respectively. Post CT values were also greater than those of the healthy volunteer group and the CVD group ($p<0.05$ for both comparisons). Thus, a significant increase was observed during CT in the reflection index of small muscular arteries and the stiffness index of large conduit arteries. When the treatment group was compared with the healthy volunteer group and the CVD group, a significant difference was detected only after CT, which shows that the drugs exhibited a vasculotoxic effect and played a key role in its development rather than cancer.

Assessment of the endothelial function

PPG with the reactive hyperemia test was used to assess the function of vascular endothelium of large and small vessels. The test results were evaluated by the degree of increase in the amplitude of pulse waves, time of delay or the «phase shift» parameter. The signs of ED were observed in all study groups, and there were

Table 2. Results of the contour analysis of PWV before and after CT in the treatment group, in the healthy volunteer group and in the CVD group

Variable	1	2	3	4	
	Control Group (n = 25)	Patients (n = 25)		CVD Group (n = 15)	p
		Before CT	After CT		
aSI, m/s (normal <8 m/s)	8.6 [7.2; 9.6]	8.9 [7.7; 9.76]	10.3 [9.46; 11.18]	9.1 [8.85; 10.15]	p_{1-2} <0.85; p_{1-3} <0.0036 p_{1-4} <0.07; p_{2-4} <0.28 p_{3-4} <0.02; p* <0.0001
RI, % (normal <30%)	31.9 [24.2; 39.3]	32.45 [27.48; 37.68]	40.15 [35.5; 43.58]	35.9 [33.2; 39.4]	p1-2>0.05; p1-3<0.015 p1-4<0.10; p2-4>0.05 p3-4<0.03; p* <0.0014
AIx, %	2.4 [-1.65; 16.05]	2.2 [-9.9; 16.9]	9.7 [1.1; 16.5]	9.7 [7.3; 17.8]	p1-2>0.05; p1-3>0.05 p1-4<0.10; p2-4>0.05 p3-4>0.05; p* >0.05
AIx75, %	5.9 [-2.6; 12.65]	4.2 [-9.9; 11.3]	9 [4; 12.1]	10.9 [5.5; 15.9]	p1-2>0.05; p1-3>0.05 p1-4<0.10; p2-4>0.05 p3-4>0.05; p* >0.05

The data are expressed as the median [25th percentile; 75th percentile]. px-x determined using the Mann-Whitney criterion; p* = p value for intergroup (before CT vs after CT) differences determined using the Wilcoxon test. PWV = pulse wave velocity; CVDs = cardiovascular diseases; CT = chemotherapy.

Table 3. Results of the reactive hyperemia test before and after CT in the treatment group, in the healthy volunteer group, and in the CVD group

Variable	1	2	3	4	
	Control Group (n = 25)	Patients (n = 25)		CVD group (n = 15)	p
		Before CT	After CT		
IO (normal > 1.8)	1.5 [1.2; 1.8]	1.7 [1.4; 1.9]	1.3 [1.2; 1.5]	1.5 [1.3; 1.7]	p_{1-2} <0.31; p_{1-3} <0.07 p_{1-4} <0.4; p_{2-4} <0.39 p_{3-4} <0.03; p* <0.0002
SF, ms (normal > 10 ms)	-4.7 [-8.3; -1.2]	-6.75 [-11.23; -2.15]	-3.7 [-6.33; -2.28]	-3.4 [-8.2; -1.3]	p_{1-2} <0.54; p_{1-3} <0.54 p_{1-4} <0.3; p_{2-4} <0.36 p_{3-4} <0.94; p* <0.18

Data are expressed as the median [25th percentile; 75th percentile]. px-x determined using the Mann–Whitney criterion; p* = p value for intergroup (before CT vs after CT) differences determined using the Wilcoxon test. CVDs = cardiovascular diseases; CT = chemotherapy.

no significant differences in these variables between the treatment group and the CVD group (Table 3). Patients of the treatment group had severe ED before the treatment, which progressed after CT: IO from 1.7 [1.4; 1.9] to 1.3 [1.2; 1.5] (p<0.0002), and SF from –6.75 [–11.23; – 2.15] ms to –3.7 [–6.33; – 2.28] ms. Thus, the reduced amplitude of the pulse waves observed in the treatment group before CT was more likely to be associated with concomitant CVDs rather than cancer. ED worsened significantly during CT.

Assessment of the structural and functional state of the capillaries

From assessment of the microvasculature in the finger skin, capillary dysfunction was identified as reduced PCR and CDrh in all study groups (Table 4). In the treatment group, capillary dysfunction was exacerbated significantly in the course of CT. CDrh decreased from 46.77 [38.8; 48.98] cap/mm² to 44.11 [35; 47.5] cap/mm² (p<0.02). Structural changes of the capillary network were detected also in the treatment group. CDr and CDvo were decreased and worsened significantly during the course of CT (Table 4). There were no significant differences in these variables for healthy volunteers and CVD patients.

Discussion

This was the first comprehensive assessment of the effect of CT on the structural and functional state of the vascular endothelium of various caliber vessels, including the microvasculature, using two instrumental techniques (PPG and NVC) in patients with gastric cancer. Since most of these patients had CVDs, we performed a comparative analysis of the data obtained from the treatment group and from CVD patients and healthy volunteers. PPG and NVC were used to assess structural and functional changes in the vascular bed according to the study of Bonetti et al., which showed that the severity of ED of the peripheral vessels in patients with CAD was reliably comparable with that

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Table 4. Parameters of the structural and functional state of the capillaries in all study groups

Variable	1	2	3	4	p
	Control Group (n = 25)	Patients (n = 25)		CVD group (n = 15)	
		Before CT	After CT		
Functional state					
PPC, % (normal 92.5 ± 5.3%)	94.43 [84.88; 98.51]	92.52 [89.52; 96]	97.8 [92; 98.9]	97.2 [95.8; 99.9]	p_{1-2} <0.98; p_{1-3} <0.2 p_{1-4} <0.2; p_{2-4} <0.16 p_{3-4} <0.75; p* <0.09
PCR, % (normal 16.5 ± 7.1 %)	5.77 [4.23; 11.06]	4.1 [1.3; 9.97]	7.37 [3.8; 10.6]	8.95 [8.5; 9.5]	p_{1-2} <0.37; p_{1-3} <0.83 p_{1-4} <0.4; p_{2-4} <0.28 p_{3-4} <0.66; p* <0.82
CDrh, cap/mm² (normal 59 cap/mm²)	45 [38.17; 50.67]	46.77 [38.8; 48.98]	44.11 [35; 47.5]	45.1 [39.4; 49]	p_{1-2} <0.65; p_{1-3} <0.44 p_{1-4} <0.8; p_{2-4} <0.97 p_{3-4} <0.77; p* <0.02
Structural state					
CDr, cap/mm² (normal 53 cap/mm²)	37.08 [36; 47.5]	43.23 [38.42; 46.18]	42.19 [29.8; 45.37]	40.6 [35.8; 44.3]	p_{1-2} <0.8; p_{1-3} <0.85 p_{1-4} <0.8; p_{2-4} <0.8 p_{3-4} <0.88; p* <0.01
CDvo, cap/mm² (normal 87 cap/mm²)	46.67 [41.88; 63.33]	50.73 [47.55; 52.4]	44.67 [39.85; 49.23]	45.1 [40.9; 48.2]	p_{1-2} <0.72; p_{1-3} <0.65 p_{1-4} <0.7; p_{2-4} <0.38 p_{3-4} <0.99; p* <0.01

The results are expressed as the median [25th percentile; 75th percentile]. px-x, determined using the Mann–Whitney criterion; p* = p value for intergroup (before CT vs after CT) differences determined using the Wilcoxon test. PPC = percentage of perfused capillaries; PCR = percentage of capillary recovery; CD = capillary density; CDvo = capillary density after venous occlusion; CDrh = capillary density after reactive hyperemia.

of the coronary arteries, as demonstrated by coronary angiography with acetylcholine stimulation [17]. IO less than 1.35 was shown to have 80% sensitivity and 85% specificity for coronary ED. This non-invasive technique using the EndoPat 2000 device is patented and recommended for the use by the FDA. Angioscan-01 is the Russian alternative for this device.

The study revealed that cancer patients had vascular disorders before CT, which were characterized by a significant increase in the stiffness of large conduit arteries and in the resistance of small arteries, as well as general endothelial dysfunction. Taking into account that there were no significant differences between the treatment group before CT and the CVD group, it can be suggested that CVDs rather than cancer mainly contribute to the development of the structural and functional changes in the vascular bed at this stage. These vascular disorders deteriorate significantly during CT. This was confirmed by significant increases in the stiffness index from 8.9 m/s to 10.3 m/s (p<0.0001), reflection index from 32.45% to 40.15% (p<0.0014), augmentation index from 2.2% to 9.7%, and significant decreases in the occlusion index and the «shift phase» parameter (p<0.0002). Structural and functional changes were evident in the capillaries, which deteriorated significantly during the course of CT. There were also significant reductions of CDr from 43.23 cap/mm² to 42.19 cap/mm² (p<0.01) and of CDrh from 46.77 cap/mm² to 44.11 cap/mm² (p<0.02).

ED associated with CT toxicity is manifested as inhibition of vasorelaxant effects and as inhibition of anti-inflammatory and vascular recovery functions. This may trigger the onset and further progression of hypertension and atherothrombosis. The microvasculature is also involved in the pathogenesis of hypertension, CAD, and CHF [11]. In addition to the procoagulant effects of malignant tumors, platelet adhesion increases significantly due to the reduced bioavailability of endothelial NO. This is followed by activation of spontaneous lipid peroxidation and reduced antioxidant protection, cytokine imbalance with increased markers of vascular endothelial damage, including von Willebrand factor, circulating endothelial cells, and vascular endothelial growth factor [18–21]. Chronic ED results in structural changes of the vascular wall. Uncontrolled hyperactivation of vasoconstrictor and proaggregatory systems, growth and proliferation factors, and anti-inflammatory cytokines contributes to the exhaustion of endothelial protective functions, and to apoptosis of endothelial, cardiac, and smooth muscle cells. At the tissue level, chronic ED causes hypertrophy and hyperplasia of smooth muscle cells, disorganization of cellular elements, activation of the synthesis of components of the extracellular matrix in the vascular walls, which disturbs the collagen/elastin ratio and thickens the arterial media [22–24]. Cardiotoxicity due to the direct, irreversible damage of the cardiac cell structure, including increased vacuolization, necrosis,

chaotic arrangement of myofibrils, and cellular apoptosis, causes similar phenomena.

In addition to ED, CVDs are associated with structural and functional changes in the microvessels [25]. Thus, in patients with CHF, remodeling of the microcirculatory vessels is manifested as reduced CD, structural rarefaction of capillaries, and changes of capillary loops [26]. Structural changes in the capillary bed have been shown to have prognostic relevance in adverse outcomes of CHF, i.e., ischemic stroke, myocardial infarction, and cardiovascular death [27].

In this study, the changes in endothelial function, vascular wall stiffness, and the state of the microvasculature were evaluated for the first time in patients with gastric cancer during the course of CT. Results showed that the structural and functional state of the vascular wall and that endothelial function at all vascular levels deteriorated significantly in cancer patients during CT.

It is necessary to continue these studies and to carry out larger randomized clinical trials, including more extended follow-up periods, and to develop detailed criteria for the associated cardiac pathologies.

Conclusion

This study may mark the beginning of the development of personalized programs for preventing cardiovascular toxicity and the early onset of cardiovascular diseases in general, as well as for preventing premature «vascular aging» for each cancer patient.

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