IJC Heart & Vasculature 50 (2024) 101336

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

A single-lead ECG based cardiotoxicity detection in patients on polychemotherapy

Dinara F. Mesitskaya [b], Zaki Z.A. Fashafsha [a,*], Maria G. Poltavskaya [b], Denis A. Andreev [b], Anna R. Levshina [b], Elizaveta A. Sultygova [a], Daria Gognieva [a,b], Petr Chomakhidze [a,b], Natalia Kuznetsova [a], Alexander Suvorov [a], Sekacheva Marina I. [a,c], Elena Poddubskaya [b], Alena Novikova [b], Aleksandra Bykova [b], Philipp Kopylov [a,b]

[a] World-Class Research Center "Digital biodesign and personalized healthcare", Sechenov First Moscow State Medical University, Moscow, Russia
[b] Department of Cardiology, Functional and Ultrasound Diagnostics of N.V. Sklifosovsky Institute for Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia
[c] Institute for Personalized Oncology, Center "Digital Biodesign and Personalized Healthcare" I.M. Sechenov First Moscow State Medical University Moscow, Russia Moscow, Russia

ARTICLE INFO

Keywords:
Single-lead electrocardiogram
Chemotherapy
Cardiotoxicity
Left ventricular diastolic dysfunction
Atrial fibrillation
QTc prolongation

ABSTRACT

Background: Anti-cancer treatment can be fraught with cardiovascular complications, which is the most common cause of death among oncological survivors. Without appropriate cardiomonitoring during anti-cancer treatment, it becomes challenging to detect early signs of cardiovascular complications. In order to achieve higher survival rates, it is necessary to monitor oncological patients outpatiently after anti-cancer treatment administration. In this regard, we aim to evaluate the efficacy of single-lead ECG remote monitoring to detect cardiotoxicity in cancer patients with minimal cardiovascular diseases after the first cycle of polychemotherapy.
Materials and methods: The study included patients 162 patients over 18 years old with first diagnosed different types of solid tumors, planed for adjuvant (within 8 weeks after surgery) or neoadjuvant polychemotherapy. All patients were monitored, outpatiently, during 14–21 days (depending on the regimen of polychemotherapy) after polychemotherapy administration using single-lead ECG.
Results: QTc > 500 mc prolongation was detected in 8 patients (6.6 %), first-diagnosed arial fibrillation was detected in 11 patients (9 %) in period after chemotherapy administration. Moreover, left ventricular diastolic dysfunction using single-lead ECG after polychemotherapy was detected in 49 (40.1 %) patients with sensitivity 80 %, specificity 95 %, AUC 0.88 (95 % CI, 0.82–0.93).
Conclusions: The side effects of cancer treatment may cause life-threatening risks. Early identification of cardiotoxicity plays a vital role in the solution of this problem. Using portable devices to detect early cardiotoxicity is a simple, convenient and affordable screening method, that can be used for promptly observation of patients.

1. Introduction

Cardiovascular and oncological diseases are the leading causes of mortality globally, accounting for nearly 10 million deaths in 2020 according to the World Health Organization (WHO) [1,3]. However, cancer survival rates are improving due to highly effective anti-cancer treatment, in particular combination chemotherapy [2]. Unfortunately, anti-cancer treatment can be fraught with cardiovascular

Abbreviations: PCT, polychemotherapy; LVEF, left ventricular ejection fraction; GLS, global myocardial strain; DD, diastolic dysfunction; LVDD, Left ventricular diastolic dysfunction; AUC, the cross-validation area under the curve; ECG, electrocardiogram; AF, atrial fibrillation; AI, artificial intelligence; OR, odds ratio; CI, confidence interval; IHD, Ischemic heart disease.

* Corresponding authors at: st. Bolshaya Pirogovskaya 6, Building 1, 119991 Moscow, Russia.
E-mail addresses: fashafshazaki@gmail.com (Z.Z.A. Fashafsha), m.poltavskaya@yandex.ru (M.G. Poltavskaya), andreev_d_a@staff.sechenov.ru (D.A. Andreev), gognieva_d_g@staff.sechenov.ru (D. Gognieva), chomakhidze_p_sh@staff.sechenov.ru (P. Chomakhidze), kuznetsova_n_o@staff.sechenov.ru (N. Kuznetsova), suvorov_a_yu_1@staff.sechenov.ru (A. Suvorov), sekacheva_m_i@staff.sechenov.ru (S. Marina I.), poddubskaya_e_v@staff.sechenov.ru (E. Poddubskaya), alena.ru89@inbox.ru (A. Novikova), bykova_a_a@staff.sechenov.ru (A. Bykova), kopylov_f_yu@staff.sechenov.ru (P. Kopylov).

https://doi.org/10.1016/j.ijcha.2024.101336
Received 26 September 2023; Received in revised form 4 December 2023; Accepted 4 January 2024
Available online 20 January 2024

complications, which is the most common cause of death among oncological survivors [3]. Cardiac complications developed among oncological patients due to anti-cancer treatment, such as heart failure, arrhythmias, arterial hypertension, used to be called cardiotoxicity. In this regard, numerous studies are now devoted to cardio-oncology, including prevention, diagnosis, and management cancer treatment-induced cardiotoxicity, they highlight the importance of cardiovascular risk assessment and patients' check-up before and after anti-cancer therapy. Moreover, without appropriate cardiomonitoring during anti-cancer treatment, it becomes challenging to detect early signs of cardiovascular complications, potentially causing serious health consequences. Given these issues, European Society of Cardiology (ESC) in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) published Cardio-oncology guidelines in 2022 [4].

In order to achieve higher survival rates, it is necessary to monitor oncological patients at the outpatient stage in the polychemotherapy (PCT) inter-course period, when cardiovascular complications might occur.

Currently, digital technology and telemonitoring of patients are being actively introduced into medicine, particularly using single-lead electrocardiogram (ECG). Single-lead ECG one of the most simple signal that can be recorded. Rhythm disorders, evaluate left ventricle diastolic and systolic function can be identified by using single-lead ECG monitoring with artificial intelligence (AI), which is available in many devices at the moment [5–7]. Nevertheless, this method can be used for cardiac monitoring of oncological patients for detecting potential cardiotoxicity.

Given the relevance of this issue, we aim to evaluate the efficacy of single-lead ECG remote monitoring to detect the cardiotoxicity in cancer patients with minimal cardiovascular diseases after the first cycle of polychemotherapy.

2. Materials and methods

This prospective, single center, non-randomized, interventional, controlled trial was carried out in the Oncological Department of Antitumor Therapy of the University Clinical Hospital No.1 of the Sechenov University, Moscow, Russia.

It was conducted in accordance with Good Clinical Practice (GCP) and Helsinki Declaration, all patients provided written informed consent. The study was approved by the local ethics committee of the Sechenov University (protocol number 34–20), September 12, 2020). Registration number on ClinicalTrials.gov – NCT05676606).

The study included patients over 18 years on adjuvant (within 8 weeks after surgery) or neoadjuvant polychemotherapy. Patients were not included if they received radiation therapy, was not compliant to chemotherapy, had a morphological abnormality in baseline ECGs, which do not allow to analyze single-lead ECG by machine learning methods (including the pacemaker rhythms, rhythms with resynchronizing intracardiac lesions, full His left bundle branch block, Wolff-Parkinson-White syndrome), severe upper limb motor impairment or hand tremor, life expectancy less than 2 months and were pregnant. Also, patients with intermediate and low LVEF, and permanent form atrial fibrillation were not included.

If during the study a lack of patient adherence to treatment, poor quality of ECG/poor visualization on echocardiography or other noncardiac toxicity revealed the patient was excluded.

All patients underwent clinical examination before, and 14–21 days (depending on the scheme of polychemotherapy) after PCT administration, patients were monitored during this period using single-lead ECG. Mortality rates were also assessed up to 2 months after PCT administration.

Clinical examination included: general examination, 12-lead ECG registration (Using Electrocardiograph MAC 800 (USA) in 12 leads with heart rate, R-wave amplitude, PQ, QRS, QT, QTc intervals, heart rhythm assessment), single-lead ECG registration (a 1-minute ECG record was registered from the patients' right and left fingers using a single-lead electrocardiograph (Fig. 2)), cardiac serum biomarkers detection (n-terminal pro b-type natriuretic peptide (NT-proBNP), highly sensitive troponin I) and transthoracic echocardiography. (Fig. 1).

The echocardiography was performed on the parasternal, 4-chamber, 2-chamber and APLEX views by two independent physicians. The following parameters were evaluated: left ventricular ejection fraction (LVEF) with the BIPLANE Simpson's method, global myocardial strain (GLS), which was assessed using the Speckle-Tracking echocardiography (STE) in 2, 4 and 2 chamber view and left ventricular diastolic dysfunction (LV DD).

The LV DD was assessed according to echocardiography data, based on current recommendations. The main criteria of LV DD reduction were: 1) TDE reduction of mitral annulus movement in $>$ 7 cm/s and $>$ 10 cm/s on the medial and lateral parts, respectively; 2) left atrium (LA) enlargement $>$ 34 ml/m^2; 3) tricuspid regurgitation (TR) with the maximum velocity $>$ 2.8 m/s; 4) Tissue Doppler-derived E/e' ratio $>$ 14. If patients had 3 or 4 out of 4 criteria, LV DD was detected. If only 1 criterion was set, then the diastolic function was considered saved. With only 2 criteria available, we use additional criteria: LA pressure, E/A ratio, and E-wave peak velocity, long first phase of diastole (DT) [8].

* I single- lead ECG records were achieved using portable electrocardiograph "CardioQVARK"-.

CardioQVARK is a cover for a mobile phone with ECG sensor and reflecting sensor MAX30102 for photoplethysmogram (Fig. 2) in pare with original application. Registration as a single-channel portable electrocardiograph in Federal Service for Surveillance in Healthcare of the Russian Federation dated February 15, 2019. №. RZN 2019/8124.

In our study, in order to determine diastolic dysfunction using single-lead electrocardiograph CardioQVARK, we used machine learning algorithms built on the basis of spectral analysis of ECG parameters, where a continuous wavelet transformation was used, and tested by our colleagues Kuznetsova N.O. et al, where the accuracy was 96.5 %. Detailed description of the developed algorithm can be found in their work [20].

*Before patients were discharged from the hospital, we taught them how to register a standard single-lead ECG independently and a portable electrograph was given to each patient for remote ECG recording during 14–21 days while patients were home. Before second cycle of PCT administration, patients underwent the same volume of laboratory and instrumental methods that were mentioned above.

*The results of single-lead ECGs and echocardiography were blinded for operators.

During the outpatiently period 14–21 days, the remote monitoring results were controlled by a team of cardiologists. If there were signs of cardiotoxicity, the patient was invited for a face-to-face consultation to the clinic for further examination and hospitalization, when necessary.

Cardiotoxicity in our study was determined according to the criteria of Cardio-oncology guidelines 2022 [4]:

1. A decrease in LVEF $\geq$ 10 % from baseline;
2. A decrease in global longitude strain (GLS) $>$ 15 % from baseline;
3. QTc $>$ 500 ms and\or QTc $>$ 60 ms deviation from baseline;
4. Atrial fibrillation (AF) development during PCT;
5. Increase of reference values of biochemical blood tests:
   - Troponin I for men, higher than 34.2 pg/ml;
   - Troponin I for women, higher than 15.6 pg/ml.
   - NT-proBNP higher than 125 pg/ml

2.1. Statistical analysis

Statistical analysis utilized R v4.2 programming language. Quantitative indicators such as the normal of the distribution (the Shapiro-Wilk test), mean value, standard deviation, median, interquartile range, 95 %

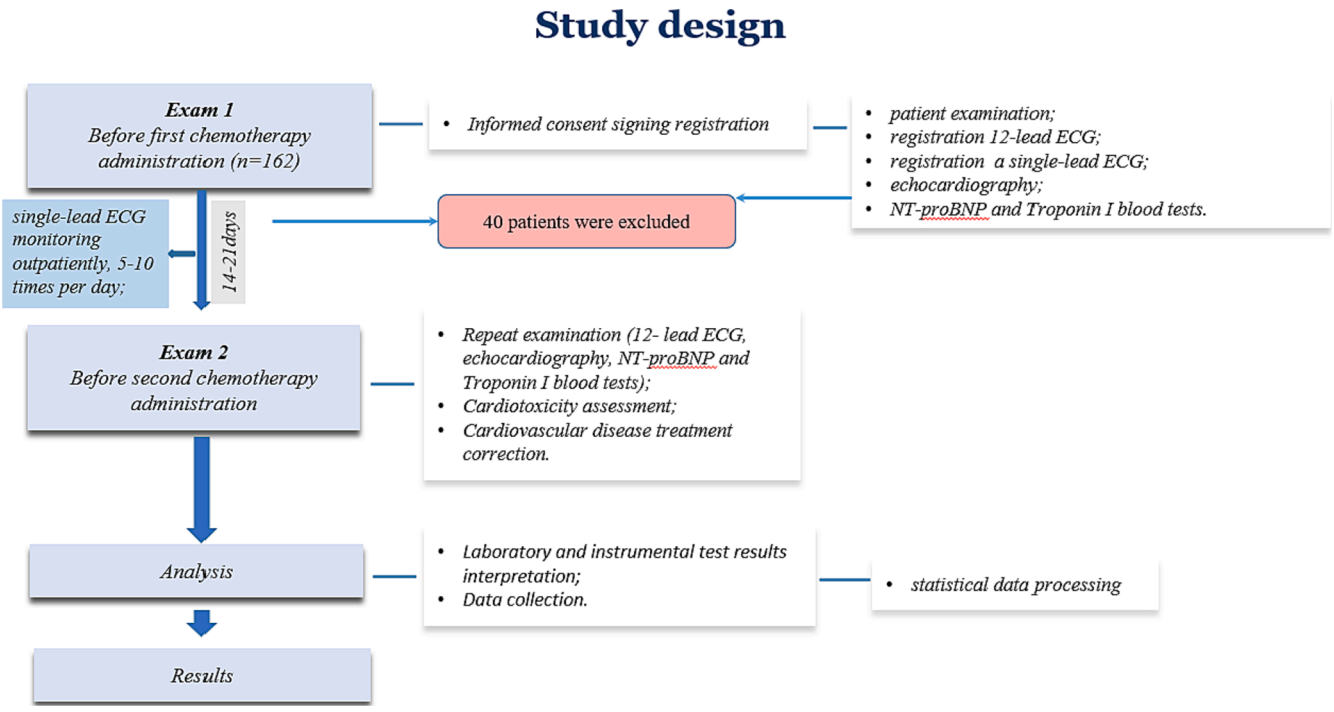

Fig. 1. The study design.

Fig. 2. Single-lead electrocardiograph. It is a cover for a mobile phone with ECG sensor and reflecting sensor MAX30102 for photoplethysmogram.

confidence interval, minimum and limit values were evaluated. Also, the proportion and absolute number of indicators were identified.

In regression analysis, endpoints of interest were estimated included regression with calculation of odds ratios, (OR) and its 95 % CI. Factors found to be significant ($p \leq 0.1$) were included in a single multivariate regression equation to find reliable endpoint predictors using a stepwise selection.

To assess accuracy quantitatively of diagnostic tests, ROC analysis was used. The significant threshold for detection and regression analysis was 0.05.

We used machine learning mathematical algorithms for left ventricular diastolic dysfunction (LVDD) detection with a comprehensive

analysis of the frequency and amplitude ECG parameters, recorded with single-channel ECG monitor created by our colleagues for screening patients with heart failure, where sensitivity and specificity of Lasso logistic regression and Random forest were quite high [5].

3. Results

After enrollment of 162 patients, 40 of them were excluded due to exclusion criteria. Finally, 122 cancer patients' data were analyzed in the trial (Table 1).

The dosage of chemotherapy drugs varied depending on the regimen and cancer type, for each patient the dose was individually administered.

Table 3 demonstrates included patients with various types of cancer, where the predominant cancers were colorectal and breast ones.

Table 4 Demonstrates percentage of different anti-cancer drug medications regimens.Table 5 demonstrates anti-cancer drugs usage frequency, which were used in anti-cancer regimens.

3.1. Detected cardiotoxicity

Different types of cardiovascular events were detected after first cycle of anti-cancer therapy administration (Table 6).

Chemotherapy treatment also had a significant effect on electrocardiography detected with single-lead ECG and echocardiography parameters (Tables 7 and 8).

A decrease in LVEF ≥ 10 % from baseline was detected in 7 (5.7 %) patients, 6 (85.7 %) of them were hospitalized in the cardiology department. Among factors associated with higher risk of decrease in LVEF, detected using the least absolute shrinkage and selection operator (LASSO) regression algorithm, were: presence of LVDD before PCT - odds ratio (OR) 5.64 (95 % CI, 1.16–30.38; P = 0.031), smoking OR 8,37 (95 % CI, 1.37–160.9; P = 0,053) and fasting glucose level before PCT OR 2.8 (95 % CI, 1.15–7.39; P = 0,027).

Multivariate regression analysis showed the most significant factor that led to decrease in LVEF was using regimen TPF – OR 14.12 (95 % CI, 1.6–183.19; P = 0.02).

Seventeen patients (19.93 %) had reduced GLS > 15 %. The most significant factors that influenced on GLS reduction were: PCT regimen TPF – OR 3.86 (95 % CI, 1.17–12.1; P = 0.022) and head and neck tumor location – OR 3.56 (95 % CI, 0.99–11.75; P = 0,041).

However, multivariate regression analysis showed that using docetaxel in anti-cancer therapy regimens contributed to decrease GLS > 15 % – OR 6.19 (95 % CI, 1.34–34.40; P = 0.023), moreover, reduced LVEF ≥ 10 % from baseline after therapy directly related with decrease GLS >

Table 1
Patients' baseline characteristics.

Characteristic	Parameter
Age (mean), years	60.4 ± 11.6
Male, n (%)	57 (46.7 %)
Smoking, n (%)	54 (44.3 %)
Body mass index, (kg/m^2), n (%):	
<18	3 (2.5 %)
18–25	35 (28.7 %)
25–30	57 (46.7 %)
30–35	25 (20.5 %)
35–40	2 (1.6 %)
Paroxysmal Atrial fibrillation in anamnesis, n (%)	8(6,6%)
Arterial hypertension in patient's history, n (%)	59 (48.4 %)
Ischemic heart disease in patient's history (IHD) (medical documents), n (%)	31 (25.4 %)
Diabetes mellitus, n (%)	14 (11.5 %)
Fasting glucose level, mmol/l	5.6 ± 0.9
Potassium blood level, mmol/l	4.5 ± 0.4
Creatinine, μmol/l	86.4 ± 31.2
Troponin I, pg/ml	3.0 ± 2.9
NT-proBNP, pg/ml	175.2 ± 236.8

*data presented as M ± SD (M - average value, SD - standard deviation).

62 patients (50.8%) were taking heart disease medications (Table 2). However, after anti-cancer drug therapy cardiovascular treatment were changed in 61 patients (50.0%).

Table 2
Baseline medication and corrected cardiovascular treatment after PCT administration.

Medication	Before PCT administration n = 62n (%)	Corrected treatment after PCT administration n = 61, n (%)
Beta-blockers	45 (36.9 %)	28 (23,0%)
Angiotensin-Converting Enzyme Inhibitors (ACEI)	38 (31.6 %)	32 (26.2 %)
Angiotensin receptor blockers (ARBs)	20 (16.4 %)	11 (9 %)
Acetylsalicylic acid	19 (15.6 %)	18 (14.8 %)
Loop diuretics	24 (19.6 %)	17 (13.9 %)
Aldosterone antagonists	7 (5.7 %)	10 (8,2%)
Calcium channel blockers	11	5
Amlodipine	(9 %)	(4,1%)17
verapamil	-	(13.9 %)
Nitrates	–	22 (18.0 %)
Statins	16 (13.1 %)	11 (9.0 %)
NOAC (Non-Vitamin K antagonist oral anticoagulants)	4 %)10 (8.1 %)	7 (5,74)23 (18.9 %)
rivaroxaban		
apixaban		

Table 3
Cancer location.

Cancer location	Groupn (%)	Cancer location	Groupn (%)
Head and neck	16 (13.12 %)	Bladder	10 (8.2 %)
Esophagus	4 (3.28 %)	Kidney	1 (0.82 %)
Gastric	16 (13.12 %)	Pancreas	7 (5.7 %)
Colorectal	26 (21.32 %)	Breast	23 (18.86 %)
Lung	10 (8.2 %)	Ovary	8 (6.56 %)
Soft tissue sarcoma	1 (0.82 %)		
AC	20 (16.4 %)	AI	4 (3.3 %)
GemCis	4 (3.3 %)		

Table 4
Demonstrates percentage of different anti-cancer drug medications regimens.

Regimen PCT	Group n (%)	Regimen PCT	Group n (%)
Targeted therapy	1 (0.8 %)	FLOT	10 (8.2 %)
FOLFOX	14 (11.2 %)	EP	3 (2.5 %)
XELOX	16 (13,1%)	FOLFIRINOX	7 (5.7 %)
TPF	19 (15.2 %)	GemCarbo	8 (6.6 %)
PC	15 (12.3 %)	FolFiri	1 (0.8 %)

chemotherapy regimens.
FOLFOX – 5-fluorouracil + oxaliplatin
XELOX - capecitabine + oxaliplatin
TPF - docetaxel + cisplatin + 5-fluorouracil.
PC - paclitaxel + carboplatin
AC - doxorubicin + cyclophosphamide.
FLOT – 5-fluorouracil + oxaliplatin + docetaxel.
EP - etoposide + cisplatin
FOLFIRINOX – 5-fluorouracil + irinotecan + oxaliplatin
FOLFIRI – 5-fluorouracil + irinotecan.
AI - doxorubicin + Ifosfamide.
GemCis - gemcitabine + cisplatin
GemCarbo- gemcitabine + carboplatin
Targeted drugs in monotherapy (0.82%), and in combination with chemotherapy (2,46%).

Table 5
Anti-cancer drugs usage frequency.

Medications	Patientsn (%)	Medications	Patientsn (%)
Sunitinib	1 (0.82 %)	Paclitaxel	15 (12.3 %)
Gemcitabine	9 (7.38 %)	Doxorubicin	24 (19.68 %)
Capecitabine	19 (15.58 %)	Cyclophosphamide	20 (16.4 %)
5-fluorouracil	50 (41.0 %)	Ifosfamide	4 (3.28 %)
Oxaliplatin	46 (37.72 %)	Pembrolizumab	2 (1.64 %)
Docetaxel	29 (23.78 %)	Olaparib	1 (0.82 %)
Cisplatin	26 (21.32 %)	Irinotecan	8 (6.2 %)
Etoposide	3 (2.46 %)	Antibiotics	24 (16.6 %)
Carboplatin	23 (18.86 %)		

Table 6
Types of cardiovascular events detected after first cycle of anti-cancer therapy.

Cardiovascular complications	Patients,n (%)
1 Transient myocardial ischemia	17 (13.6 %)
Stroke	2 (1.6 %)
• Arterial hypertension	9 (7.3 %) 4
Arterial hypotension	(3.3 %)
2Venous thromboembolism	8 (6.5 %)
First detected paroxysms of AF	11 (8.8 %)
Premature ventricular/atrial contractions	28 (23 %)
3Mortality	3 (2.4 %)

1 Transient myocardial ischemia in our study has been evaluated as - a clinical condition characterized by a combination of patient's complaints for signs and/or symptoms (chest pressure or pain, typically on the left side of the chest (angina pectoris), shortness of breath when physically active, etc.) combined with changes on ECG, echocardiography and/or raising the level of cardio-specific enzymes from the base level (troponin I, NT-proBNP).
2 Venous thromboembolism – lower limbs venous thrombosis and/or pulmonary embolism detected by ultrasound or computed tomography).
3Mortality was defined as death during the first two months after inclusion in the study, due to cardiovascular complications or complications leading to cardiovascular mortality.

Table 7
ECG parameters before and after anti-cancer drug therapy (n = 122).

Parameters	Mean-value before therapy	Mean-value after therapy	p-value before therapy	p-value after therapy
Heart rate, beats/min	73.4 ± 9.0	82.3 ± 12.1	0,037	0,009
PQ, ms	147.3 ± 17.8	152.1 ± 18.7	0,08	0,007
QRS, ms	87.0 ± 15.1	89.4 ± 15.5	0,000	0,000
QTc, ms	424.6 ± 22.9	445.3 ± 29.3	0,003	0,02
Diastolic dysfunction, detected by single-lead ECG (n, %)	22 (18.0 %)	49 (40.2 %)	<0.001	<0.001

*data presented as M ± SD (M - average value, SD - standard deviation).

Table 8
Echocardiography parameters before and after anti-cancer treatment (n = 122).

parameter	Mean-value before therapy	Mean-value after therapy	p-value
Left ventricular ejection fraction (%)	62.9 ± 4.0	59.7 ± 4.4	0.04
Global longitudinal strain (%)	20.5 ± 1.9	18.7 ± 2.2	0.01
Diastolic dysfunction, detected by echocardiography (n, %)	26 (21.3 %)	57 (46.7 %)	<0.001

*data presented as M ± SD (M - average value, SD - standard deviation).

15 % – OR 38.3 (95 % CI, 4.45–944.5; P = 0.004), and NT-proBNP level after therapy pointed out decrease GLS > 15 % – OR 1.002 (95 % CI, 1.00–1.004; P = 0.002.

3.2. Diastolic dysfunction

Diastolic dysfunction (DD) by echocardiography was detected in 57 (46.7 %) patients after first course of PCT. Table 9, 10 shows the influence factors.

Moreover, diastolic dysfunction using single-lead ECG after PCT was detected in 49 (40.1 %) patients (Table 7). To assess the quality of the diagnostic method of a single-lead ECG, receiver operating characteristic (ROC) analysis was used with the calculation of sensitivity, specificity, positive and negative predictive value and the area under the curve, compared with echocardiography.

Fig. 3 and Table 10 demonstrates the high accuracy of single-lead ECG in diastolic dysfunction detection in oncological patients compared with echocardiography.

4. Single-lead ECG monitoring

Analysis of the single-lead ECGs was performed in 122 patients between the first and the second chemotherapy courses. On average, 48 electrocardiograms per patient were analyzed.

As a result of the application of single-lead ECG, we detected:

QTc > 500 mc prolongation in 8 patients (6.6 %). Tables 12 demonstrates factors, that had the most influence on QTc prolongation.

However, multivariate regression showed that presence of diastolic dysfunction before chemotherapy might be associated with higher risk of QTc prolongation > 500 mc OR 14.1 (95 % CI, 3.005–101.19; P = 0,001). Moreover, QTc > 60 mc prolongation from baseline was detected in 5 (4.1 %) patients after anti-cancer drug therapy.

Atrial fibrillation after chemotherapy administration was detected in 11 patients (9 %), including 1 patient with diagnosed paroxysmal AF before chemotherapy. Multivariate regression analysis showed that using regimen therapy (FLOT) OR 7.28 (95 % CI, 1.32–34.79; P = 0.014), and esophageal cancer treatment OR 17.00 (95 % CI, 1.79–164.34; P = 0,009) was associated with higher risk of atrial fibrillation development.

Cardiovascular hospitalization among patients in this group was 5 (45.5 %). The total of 9 (81.8 %) patients of the group received cardiovascular drugs after first chemotherapy course including apixaban (81.8 %), calcium channels blockers (27.3 %), beta-blockers (54.5 %), statins (9.1 %), nitrates (18.2 %), loop diuretics (27.3 %), ACE inhibitors or ARBs II (45.5 %), rivaroxaban (18.2 %).

Table 9
Diastolic dysfunction univariate linear regression.

	OR	CI, 25 %	CI, 95 %	p-value
Age	1,09	1,05	1,14	<0.001
GLS before therapy	1,23	1,01	1,5	0,042
LVEF after therapy	1,1	1,01	1,2	0,029
NT_proBNP before therapy	1,01	1,01	1,02	<0.001
Creatinine before therapy	1,02	1,01	1,04	0,015
Creatinine after therapy	1,03	1,01	1,06	0,006
QTc before therapy, ms	1,02	1	1,04	0,031
QTc after therapy, ms	1,02	1,01	1,04	0,001
IHD before therapy	4,82	2,01	12,62	0,001
QRS before therapy, ms	1,04	1,01	1,07	0,013
QRS after therapy, ms	1,02	1	1,05	0,056
5-fluorouracil	2,5	1,2	5,31	0,015
Diabetes mellitus type 2	3,24	1,02	12,42	0,059
FOLFOX regimen PCT	3,24	1,02	12,42	0,059
Capecitabine	0,35	0,11	0,99	0,06

CI-confidence interval, OR- odds ratio, PCT- polychemotherapy, GLS- global myocardial strain, LVEF- left ventricular ejection fraction, IHD- Ischemic heart disease in patient's history,

Table 10
Diastolic dysfunction multivariate regression.

	OR	CI, 25 %	CI, 95 %	p-value
Age	1.073	1.022	1.13	0.007
LVEF after therapy	1,67	1,28	2,33	<0.001
Creatinine before therapy	1.031	1.007	1.058	<0.01

CI-confidence interval, OR- odds ratio, LVEF- left ventricular ejection fraction

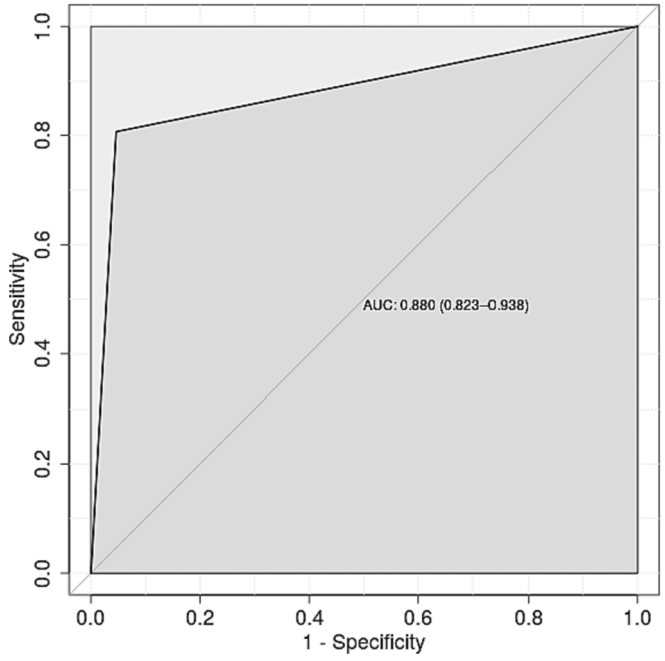

Fig. 3. Receiver operating characteristic (ROC) curve. Diastolic dysfunction detected by echocardiography VS single-lead ECG.

Table 11
Efficiency of single-lead ECG in diastolic dysfunction detection.

	%	CI 2.5 %	CI 97.5 %
Sensitivity	80 %	0.7	0.9
Specificity	95 %	0.89	1
Positive predictive value	94 %	0.87	1
Negative predictive value	85 %	0.78	0.91
AUC*	0.88	0.82	0.93

*the cross-validation area under the curve (AUC), CI-confidence interval.

Table 12
QTc > 500 mc prolongation univariate linear regression.

Parameters	OR	2.5 % CI	97.5 % CI	p-value
QRS before therapy	1,07	1,03	1,12	0,001
Diastolic dysfunction before therapy	14,1	3,01	101,2	0,002
IHD in patient's history	26,25	4,38	503,28	0,003
Age	1,16	1,06	1,3	0,004
Troponin I before therapy	1,3	1,08	1,57	0,005
NT-proBNP before therapy	1	1	1	0,01
Glucose after therapy	2,14	1,2	3,95	0,01
Diabetes mellitus type 2	5,62	1,04	26,31	0,03
Potassium before therapy	6,14	1,11	39,01	0,04
AF in anamnesis	6,1	0,77	33,54	0,051
GemCarbo regimen CT	6,2	0,77	33,54	0,051

CI-confidence interval, OR- odds ratio, PCT- polychemotherapy, GLS- global myocardial strain, LVEF- left ventricular ejection fraction, IHD- Ischemic heart disease in patient's history, CT-chemotherapy.

Due to our observation 21 (17.2 %) patients were hospitalized in the cardiology department as a result of cardiotoxicity, where they received the necessary therapy. Cardiac therapy was corrected in 61 (50 %) patients after PCT administration (Table 2).

5. Discussion

The risk of cardiotoxicity developing is a dynamic variable and the risk changes throughout courses of chemotherapy, and thus early detection of cardiotoxicity is an important cardio-oncology task. According to the recommendations of cardio-oncological association, standard examination methods- ECHCG and ECG are effective to detect cardiotoxicity, but they are not always possible to perform, especially when the patient is being observed outpatiently, in the period between chemotherapy courses.

On the other hand, distance monitoring using artificial intelligence algorithms is a new and quick developed method to detect cardiotoxicity in oncological patients, especially, when this method has shown high accuracy in diagnosis of various disorders in cardiology, such as systolic and diastolic dysfunction, rhythm and conductivity disorders [5].

Also, it is used in oncology, and it showed high effective. A recent study showed that ECG artificial intelligence algorithms, which were trained on 12-lead ECG records obtained on 1,217 adult survivors of childhood, who received anthracycline therapy could predict the development of late cardiomyopathy where AUC was 0.87 (95 % CI, 0.83–0.90) [9].

Moreover, Zhou Y, Hou Y et al in there retrospective study created machine learning algorithms to predict cardiac disorders among cancer patients, involving data of laboratory tests and echocardiography of 4309 cancer patients between 1997 and 2018, models were trained and evaluated for cardiovascular complications, including coronary artery disease AUC 0.821 (95 % CI, 0.815–0.826), atrial fibrillation AUC 0.787 (95 % CI, 0.782–0.792), heart failure AUC 0.882 (95 % CI, 0.878–0.887), stroke AUC 0.660 (95 % CI, 0.650–0.670), myocardial infarction AUC 0.807 (95 % CI, 0.799–0.816)[10].

In our study, we used machine learning algorithm single-lead ECGs to detect left ventricular diastolic dysfunction, atrial fibrillation and QTc prolongation in oncological patients after first course of anti-tumor drug therapy administration outpatiently, and this model showed high accuracy detecting left ventricular diastolic dysfunction compared with standard transthoracic echocardiography AUC 0.88 (95 % CI, 0.82–0.93), with sensitivity 80 % and specificity 95 %.

In addition, in our study 5-fluorouracil worsened left ventricular diastolic function OR 2.5; 95 % CI, 1.2–5.31, $p = 0.01$, presumably causing coronary vasospasm 14. According to world literature, the frequency of 5-FU-induced cardiotoxicity accounted for 0.7–36 %, the signs depended on the dosage and combination of chemotherapy [11]. Calabrese V et al showed similar results demonstrating developed asymptomatic LVDD in patients with colorectal cancer receiving FOLFOX and XELOX in therapeutic dosage that included 5-FU and capecitabine, respectively [12].

Moreover, distance single-lead ECG monitoring was effective in detecting atrial fibrillation and QTc prolongation. Paroxysmal AF after therapy recorded by a single-lead remote ECG were detected in 11 patients (9 %). Treatment of esophageal cancer (OR 17.0; 95 %CI, 1.79–164.34, $p < 0.01$) and using regimen FLOT chemotherapy (OR 7.28; 95 % CI, 1.32–34.79, $p = 0.014$) more likely contributed to the development of atrial fibrillation. It is worth emphasizing that in patients who were administered chemotherapy consisting of three anticancer drugs, AF was more often diagnosed, especially if the therapy included combination of platinum, taxanes and antimetabolites drugs such as regimes TPF, FLOT. Indeed, in world literature the incidence of AF in oncological patients varies from 4 % to 5 %, depending on the anticancer drug used. When antimetabolites, taxanes and alkylating drugs are administered, AF is diagnosed in 2.6 %, 9.4 %, 15.5 %, respectively [13,14].

Also, using single-lead ECG we detected 8 patients (6.6 %) with QTc > 500 ms prolongation. According to the world literature, currently there are numerous studies using portable devices that can monitor QT interval, but these technologies have not yet been used in oncological patient QTc and AF monitoring [15,16].

However, our results correlate with world literature data with the frequency of QT interval prolongation due to chemotherapy administration, and it varies depending on the drugs and their dose 0–22 %, but it should be noted that QT interval prolongation non-specific during chemotherapy treatment and it occurrence can be caused by metabolic imbalance and depends on other risk factors such as age, CAD in anamnesis, diabetes mellitus, potassium and sodium levels in the blood, gender [17–19]. The results in our study demonstrated that fact (Table11).

6. Conclusion

The progress in cancer treatment continues to improve patient survival. However, the side effects of cancer treatment may cause life-threatening risks or long-term morbidity, and this issue becoming increasingly important. Early identification of cardiotoxicity plays a vital role in the solution of this problem – correction and administration of cardiac therapy on time. Unfortunately, standard diagnostic methods are not always available in the inter-course period to be done frequently in cases of the patient's complaints.

Using portable devices to detect early cardiotoxicity is a simple, convenient and affordable screening method, that can be used for promptly observation of the patient.

Our study demonstrates the effectiveness and the possibility of oncological patients remote monitoring using I single-lead ECG with machine learning algorithms to detect rhythm and conductivity disorders, also demonstrates the high effectiveness of early detection of diastolic dysfunction, and this has enabled timely care and treatment, where 21 (17.2 %) patients were hospitalized in the cardiology department as a result of cardiotoxicity, where they received the necessary therapy, moreover, cardiac therapy was corrected in 61 (50 %) patients after polychemotherapy administration.

6.1. Limitations of study

The registration of singe-lead ECG in our study was mostly depended on mental and physical abilities of the patients, because they recorded ECG remotely, independently, outpatiently.

Application of the technique is limited by the quality of ECG records, particularly by morphological abnormalities of QRS complexes.

The study's sample size and the presence of distinct types of cancer and different regimes did not allow us to evaluate the effectiveness of the described method for each type of cancer and regimen separately.

Our sample did not include patients with intermediate and low LVEF, and permanent form atrial fibrillation, because our main focus was on the effect of combined chemotherapy on oncological patients with minimal cardiovascular diseases before chemotherapy administration, to avoid distort the data.

CRediT authorship contribution statement

Mesitskaya Dinara Feratovna: . **Z.A. Fashafsha Zaki:** . **Maria G. Poltavskaya:** Data curation, Supervision. **Andreev Denis Anatolyevich:** . **R. Levshina Anna:** . **Sultygova Elizaveta Abubakarovna:** . **Gognieva Daria:** . **Chomakhidze Petr:** . **Kuznetsova Natalia:** . **Suvorov Alexander:** . **Marina I. Sekacheva:** Conceptualization, Data curation, Project administration, Validation. **Elena Poddubskaya:** Formal analysis, Writing – review & editing. **Alena Novikova:** Formal analysis, Writing – review & editing. **Aleksandra Bykova:** Data curation, Investigation, Software, Validation. **Kopylov Philipp:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was financed by the Ministry of Science and Higher Education of the Russian Federation within the framework of state support for the creation and development of World-Class Research Centers "Digital biodesign and personalized healthcare" N⁰075-15-2022-304

References

[1] M. Naghavi, A.A. Abajobir, C. Abbafati, et al., Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 390 (10100) (2017) 1151–1210, https://doi.org/10.1016/S0140-6736(17)32152-9.

[2] D. Hashim, P. Boffetta, C. La Vecchia, et al., The global decrease in cancer mortality: trends and disparities, Ann. Oncol. 27 (5) (2016) 926–933, https://doi.org/10.1093/annonc/mdw027.

[3] WHO. Cancer. Published online February 3, 2022. https://www.who.int/news-room/fact-sheets/detail/cancer.

[4] A.R. Lyon, T. López-Fernández, L.S. Couch, et al., 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS), Eur. Heart J. 43 (41) (2022) 4229–4361, https://doi.org/10.1093/eurheartj/ehac244.

[5] N. Kuznetsova A. Gubina Z. Sagirova I. Dhif D. Gognieva A. Melnichuk O. Orlov E. Syrkina V. Sedov P. Chomakhidze H. Saner P. Kopylov Left Ventricular Diastolic Dysfunction Screening by a Smartphone-Case Based on Single Lead ECG Clin Med Insights Cardiol. 23 16 2022 Aug 11795468221120088 10.1177/11795468221120088.

[6] A. Khunte, V. Sangha, E.K. Oikonomou, L.S. Dhingra, A. Aminorroaya, B. J. Mortazavi, A. Coppi, C.A. Brandt, H.M. Krumholz, R. Khera, Detection of left ventricular systolic dysfunction from single-lead electrocardiography adapted for portable and wearable devices, NPJ Digit Med. 6 (1) (2023) 124, https://doi.org/10.1038/s41746-023-00869-w.

[7] G.F. Gensini, C. Alderighi, R. Rasoini, M. Mazzanti, G. Casolo, Value of Telemonitoring and Telemedicine in Heart Failure Management, Card. Fail. Rev. 3 (2) (2017) 116–121, https://doi.org/10.15420/cfr.2017:6:2.

[8] Sherif F. Nagueh, Otto A. Smiseth, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. April 2016.

[9] Fatma Güntürkün, Oguz Akbilgic, Robert L. Davis, et al. Artificial Intelligence Assisted Prediction of Late Onset Cardiomyopathy Among Childhood Cancer Survivors. *The Lancet*. Published online October 13, 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3680602.

[10] Zhou Y, Hou Y, Hussain M, Brown SA, Budd T, Tang WHW, Abraham J, Xu B, Shah C, Moudgil R, Popovic Z, Cho L, Kanj M, Watson C, Griffin B, Chung MK, Kapadia S, Svensson L, Collier P, Cheng F. Machine Learning-Based Risk Assessment for Cancer Therapy-Related Cardiac Dysfunction in 4300 Longitudinal Oncology Patients. J Am Heart Assoc. 2020 Dec;9(23):e019628. doi: 10.1161/JAHA.120.019628. Epub 2020 Nov 26.

[11] T. Ko, A. MsM, A. Haddad, Dose-Dependent 5-Fluorouracil–Associated Coronary Artery Spasm, Am. J .Ther. 29 (1) (2022) e141–e143, https://doi.org/10.1097/MJT.0000000000001428.

[12] J.D. Sara J. Kaur R. Khodadadi et al. 5-fluorouracil and cardiotoxicity: a review Ther Adv Med Oncol. 10 2018 175883591878014 10.1177/1758835918780140.

[13] V. Buza, B. Rajagopalan, A.B. Curtis, Cancer Treatment-Induced Arrhythmias: Focus on Chemotherapy and Targeted Therapies, Circ. Arrhythm. Electrophysiol. 10 (8) (2017) e005443.

[14] X. Yang, X. Li, M. Yuan, et al., Anticancer Therapy-Induced Atrial Fibrillation: Electrophysiology and Related Mechanisms, Front. Pharmacol. 9 (2018) 1058, https://doi.org/10.3389/fphar.2018.01058.

[15] P. Garabelli, S. Stavrakis, M. Albert, E. Koomson, P. Parwani, J. Chohan, et al., Comparison of QT Interval Readings in Normal Sinus Rhythm Between a Smartphone Heart Monitor and a 12-Lead ECG for Healthy Volunteers and Inpatients Receiving Sotalol or Dofetilide, J. Cardiovasc. Electrophysiol. 27 (7) (2016 Jul) 827–832.

[16] M. Azram, N. Ahmed, L. Leese, M. Brigham, R. Bowes, S.B. Wheatcroft, M. Ngantcha, B. Stegemann, G. Crowther, M.H. Tayebjee, Clinical validation and evaluation of a novel six-lead handheld electrocardiogram recorder compared to the 12-lead electrocardiogram in unselected cardiology patients (EVALECG Cardio), Eur Heart J Digit Health. 2 (4) (2021 Sep 28) 643–648, https://doi.org/10.1093/ehjdh/ztab083. PMID: 36713105.

[17] A. Porta-Sánchez, C. Gilbert, D. Spears, J. Chan, K. Nanthakumar, P. Thavendiranathan, Incidence, Diagnosis, and Management of QT Prolongation

Induced by Cancer Therapies: A Systematic Review, J. Am. Heart Assoc. 6 (12) (2017 Dec 7) e007724.

[18] D. Koca, T. Salman, I.T. Unek, et al., Clinical and electrocardiography changes in patients treated with capecitabine, Chemotherapy 57 (5) (2011) 381–387, https://doi.org/10.1159/000331645.

[19] J.L. Zamorano, P. Lancellotti, D. Rodriguez Muñoz, V. Aboyans, R. Asteggiano, et al., 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC), Eur. J. Heart Fail. 19 (1) (2017 Jan) 9–42, https://doi.org/10.1002/ejhf.654. Epub 2016 Aug 27.

[20] Kuznetsova N, Gubina A, Sagirova Z, Dhif I, Gognieva D, et al. Left Ventricular Diastolic Dysfunction Screening by a Smartphone-Case Based on Single Lead ECG. Clin Med Insights Cardiol. 2022;16: 11795468221120088. doi: 10.1177/11795468221120088.