

# Late ECG Changes after Cisplatin-Based Chemotherapy in Testicular Cancer Survivors

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## Abstract

**Background:** Cisplatin-based therapy (CBT) represents currently a standard regimen for the testicular cancer treatment leading to longer survival of patients; as a consequence, the late cardiotoxicity can be manifested. In this study we analyzed the effect of CBT on the standard 12-lead ECG parameters in testicular cancer survivors.

**Material and Methods:** The electrocardiograms (ECG) of 173 patients with the germ cell tumor with a median follow-up duration of 9 years (ranged 5 to 32 years) were retrospectively analyzed. The patients were divided into four groups: Group CT: Orchidectomy plus CBT (n=133); Group AS: Orchidectomy only (n=18); Group RT: Orchidectomy plus adjuvant radiotherapy (n=14); Group CTRT: Orchidectomy plus adjuvant radiotherapy in combination with CBT (n=8). Heart rate (HR), QT and QTc intervals, the maximum spatial QRS vector amplitude, the electrical axis, the QRS complex amplitudes in individual leads and the maximum spatial T vector amplitude were analyzed.

**Results:** The HR and QT/QTc intervals were within normal limits. The most frequent ECG finding was the left anterior fascicular block, with the highest occurrence in the group CTRT (75%). The amplitudes of aVL, V6 and Tmax differed significantly between the AS group and the CT and RT/CTRT groups. The General Linear Model did not show a significant effect of therapy, but a significant effect of age and the waist circumference, respectively.

**Conclusion:** Cisplatin-based therapy did not result in pathological ECG changes. The slight ECG changes were associated with age and obesity, but not the therapy.

**Keywords:** Testicular cancer, Cisplatin-based therapy, Survivors, ECG

## Introduction

Introducing cisplatin-based therapy into testicular cancer treatment represents a substantial progress in therapy leading to a longer survival of patients and less adverse effects; currently it represents the standard therapy [1,2]. However,

both acute and late adverse effects have been documented, introducing related therapeutic, prognostic and public health problems.

The increased number of testicular cancer survivors living from years to decades after treatment [1] provides

opportunity for studying late adverse cardiovascular effects, which are reflected in higher incidence of CV morbidity and mortality. Reported late ECG manifestations of cisplatin-based treatment include severe bradycardia, supraventricular tachycardia, prolonged QT interval, and atrial fibrillation [3], suspected of altered electrical impulse generation and conduction [4]. Survivors of testicular cancer treated cisplatin-based therapy have a higher prevalence of cardiovascular risk factors [5-14] that could further contribute to the increased risk of cardiovascular diseases [5,7,13,15,16].

The acute adverse effects of cisplatin-based therapy include a variety of cardiovascular (CV) events [17-22]. On electrocardiograms (ECG) the transient ECG changes simulating acute myocardial infarction or ischemia [19,23], ST-T changes, atrial fibrillation [24], bradycardia and prolonged QT interval are documented [4]. Animal studies have shown increased serum concentration of cardiac biomarkers of myocardial injury, increased oxidative stress and significant DNA fragmentation, apoptosis after cisplatin [25,26]. These structural and functional changes at the tissue, cellular and subcellular levels can lead to altered electrogenesis. A question arises, to what extent these alterations can be reflected in identifiable ECG changes indicative of late cardiotoxicity.

The aims of this study were: (1) to analyze the effect of cisplatin-based treatment on the ventricular depolarization and repolarization parameters of the standard 12-lead ECG in testicular cancer survivors, (2) and to compare it with ECG findings in testicular cancer survivors with other therapy regimens.

## Material and Methods

The data for this study were obtained from the database of the ongoing translational project (Protocol IZLO-1, principal investigator M.M.) focused on the late toxicity of chemotherapy, radiotherapy or their combination in male patients cured for germ cell tumor (the sub-study principal investigator M. Ch.). The study was approved by the Institutional Review Board (IRB) of the National Institute of Oncology, Bratislava, Slovakia. Patients were enrolled between September 2015 and April 2017 and consented according to the IRB-approved protocol.

### Study population

The study population was selected from patients diagnosed with the germ cell tumor (GCT) treated in the National Institute of Oncology during the period 1983-2012. All survivors who were at least 5 years after the completion of the last treatment for GCT were included. Patients with an unavailable electrocardiogram or the low technical quality of ECG were excluded.

The total number of 173 patients with the median duration of follow-up 9 years (ranged 5 to 32 years) were divided into four groups:

- **Group CT:** Orchidectomy plus consequential cisplatin-based treatment, n=133, aging from 25 to 78 years, (average 41.4 years), median follow up 10 years (ranging from 5 to 32 years). There were no significant differences in ECG parameters between cisplatin cumulative dose  $\leq 400$  mg/m<sup>2</sup> and cisplatin  $> 400$  mg/m<sup>2</sup> patients (data not presented), therefore all patients treated with cisplatin were pooled into one group.
- **Group AS:** active surveillance, the control group; Orchidectomy only, without additional chemo- or radiotherapy; n=18, aging from 27 to 57 years, average age 34.7 years, median follow up 5 years (ranging from 5 to 16 years).
- **Group RT:** Orchidectomy plus consequential adjuvant radiotherapy; n=14, aging 29 to 56 years, average age 43.6 years. median follow up 10 years (ranging from 6 to 16 years).
- **Group CTRT:** Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin-based chemotherapy; n=8, aging 31 to 59 years, average age 46.8 years. median follow up 7 years (ranging from 5 to 15 years).

## Electrocardiography

Standard 12-lead electrocardiograms were recorded at the routine annual follow-up visits during the years 2015 and 2016. The time intervals and amplitudes of the QRS and T waves in individual leads were measured manually; the average of three measurements of consecutive QRS complexes was used for analysis. All R wave and S wave measurements were performed to the nearest 0.1 mV.

The following ECG parameters were analyzed:

Heart rate (HR): Bradycardia was defined as HR  $< 60$  bpm, tachycardia HR  $> 100$  bpm.

Time intervals:

- QRS complex duration (QRSd): the longest QRS duration of all leads;
- QT interval (QT): the longest QT duration of all leads; the corrected QT intervals (QTc) (Bazett correction:  $QTcB = QT / RR^{0.5}$ ; Fridericia correction:  $QTcF = QT / RR^{0.33}$ ) [27,28]. The QTcB values were categorized according [29,30] as follows: normal values  $< 430$  ms, borderline values 430-450 ms, prolonged values  $> 450$  ms.
- The ratio of QT interval and QRS duration: QT/QRSd.

QRS parameters:

- The maximum spatial vector magnitude (QRSmax) calculated as:

$$QRS_{max} = \sqrt{V2^2 + aVF^2 + V5^2}$$

where V2 is the maximum QRS deflection in lead V2; aVF is the maximum QRS deflection in lead aVF; V5 is the maximum QRS deflection in lead V5.

- The electrical QRS axis (EA) in frontal plane calculated as:

$$EA = \arctan\left(\frac{2 * aVF}{I * \sqrt{3}}\right)$$

where aVF is the maximum QRS deflection in lead aVF, I is the maximum QRS deflection in lead I.

- Absolute values of the maximum QRS complex deflections in individual leads

T wave parameter:

- The maximum spatial T vector magnitude (Tmax) calculated as:

$$QRS_{max} = \sqrt{TV2^2 + TaVF^2 + TV5^2}$$

where TV2 is the T amplitude in lead V2; TaVF is the T amplitude in lead aVF; TV5 is the T amplitude in lead V5.

### Clinical and laboratory tests

Clinical and laboratory tests were performed at the time of the follow-up visits, as a part of the routine clinical checkup, data for this study were extracted from the patients' medical records:

- Body mass index (BMI): calculated as a ratio weight/height<sup>2</sup> (kg/ m<sup>2</sup>);

- Blood pressure (BP): measured in supine position in a quiet room after a rest period of 10 minute;

- Complete blood count and basic biochemistry, including serum cholesterol, high-density lipoprotein cholesterol (HDL), very-low-density lipoprotein cholesterol (VLD), triglycerides (TAG), fasting glucose and high-sensitivity troponin T levels.

### Statistical analysis

The results are presented as mean ± SD for variables normally distributed, and as median and interquartile range for variables that were not normally distributed. The differences between the groups of normally distributed variables were tested using the analysis of variance (ANOVA) with Tukey HSD post hoc test, the non-normally distributed variables were tested using Kruskal-Wallis test. The frequency data of categorical variables were tested using the  $\chi^2$  test. Univariate regression analysis was performed for selected dependent variables (EA, QRSmax and Tmax) by means of the General Linear Model (GLM), using the therapeutic group, age, BMI and the waist circumference as independent variables. The value p<0.05 was considered statistically significant. Statistical analyses were performed using SPSS-IBM software for windows (version 23, Chicago, Ill, USA).

### Results

The basic characteristics of the study population are presented in Table 1. The patients in AS group were significantly younger and had a shorter time of follow-up compared to the CT, RT and CTRT groups. Except of these parameters, there were no statistically significant differences in basic characteristics between groups.

**Table 1:** Basic characteristics of the study population. Data presented as median (1Q-3Q range), and number (%), respectively.

	AS n = 18	CT n = 133	RT n = 14	CTRT n = 8	p
Age [years] Median (IQR)	33.0 (29.8-38.3)	<b>40.0 (34.0-48.0)**</b>	<b>43.0 (38.0-50.0)**</b>	<b>47.0 (41.3-52.8)**</b>	<b>**&lt;0.01</b>
Time since the treatment [years]	6 (5-7)	<b>10 (7-14)**</b>	<b>10 (7-12) ***</b>	7 (5-9)	<b>**&lt;0.01</b> <b>***&lt;0.001</b>
BMI [kg/ m <sup>2</sup> ]	25.2 (23.6-29.7)	26.3 (24.9-29.9)	26.6 (23.8-29.5)	28.4 (24.7-33.1)	NS
Waist circumference [cm]	95.0 (89.0-105.0)	99.5 (94.0-105.0)	98.0 (91.0-110.0)	100.0 (98.0-113.5)	NS
BPs [mmHg]	136.5 (125.0-145.0)	136.5 (126.0-149.8)	150.0 (137.0-154.0)	125.0 (120.5-151.0)	NS
BPd [mmHg]	82.0 (78.0-92.0)	87.0 (82.0-97.8)	92.0 (83.0-100.0)	90.0 (77.5-100.5)	NS
Cholesterol [mmol/l]	5.2 (4.2-6.0)	5.3 (4.6-5.9)	5.2 (4.1-6.5)	5.2 (4.9-6.2)	NS
HDL [mmol/l]	1.5 (1.3-1.8)	1.3 (1.1-1.6)	1.4 (1.2-1.8)	1.3 (1.0-1.5)	NS
LDL [mmol/l]	2.9 (2.2-3.7)	2.9 (2.4-3.6)	3.3 (2.0-3.4)	3.0 (2.5-3.9)	NS
VLDL [mmol/l]	0.6 (0.4-1.0)	0.8 (0.5-1.0)	0.6 (0.5-0.9)	0.9 (0.8-1.3)	NS
TAG [mmol/l]	1.3 (0.8-2.3)	1.7 (1.1-2.3)	1.8 (1.0-5.5)	2.1 (1.7-2.8)	NS

Glucose [mmol/l]	5.3 (5.1-5.6)	5.4 (5.0-5.8)	5.6 (5.3-6.0)	4.9 (4.8-5.4)	NS
hs Troponin T [ng/L]	1.5 (<3.0-5.5)	3.4 (<3.0-5.4)	3.3 (<3.0-4.4)	4.8 (3.1-6.3)	NS

AS: Active Surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment. RT: Orchidectomy plus consequential adjuvant radiotherapy. CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.

BMI: Body Mass Index; BPs: Systolic Blood Pressure; BPd: Diastolic Blood Pressure; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; TAG: Triglycerides; hs Troponin T: high-sensitivity troponin T; NS: Not Significant;

\*\**p*<0.01; \*\*\**p*<0.001, both compared to AS.

### Heart rate and time intervals

Table 2 presents the heart rate and the time intervals under study. There were no statistically significant differences in the heart rate and the time intervals between the groups. Bradycardia occurred in 28% of CT patients, but the differences between groups were not statistically significant. The occurrence of tachycardia was negligible.

### Distinct ECG patterns

The occurrence of distinct ECG patterns is presented in Table 3. All patients were on the sinus rhythm, sporadic premature ventricular contractions were observed in one patient in the AS group. No pathological Q waves were observed in any of the groups.

**Table 2:** Heart rate (HR) and the ECG time intervals. Data presented as median (1Q-3Q range), and number (%), respectively.

	AS	CT	RT	CTRT	p
HR [bpm]	60.5 (52.7-69.3)	65.0 (58.0-72.0)	63.0 (57.8-74.0)	67 (53.3-91.0)	NS
Bradycardia < 60 bpm	7 (38.9%)	35 (26.3%)	5 (35.7%)	2 (25%)	NS
Tachycardia	0	0	0	0	NA
QTcB [ms]	383.6 (362.4-413.1)	401.7 (380.3-424.3)	395.2 (379.2-431.0)	405.2(382.1-439.7)	NS
QTcF [ms]	384.0 (371.2-412.1)	396.5 (378.9-414.1)	394.5 (374.7-415.7)	399.7(374.5-414.1)	NS
QT/QRSD	3.7 (3.3-4.1)	3.8 (3.6-4.1)	3.7 (3.6-3.9)	3.5 (3.0-3.8)	NS

AS: Active Surveillance, the control group. CT: Orchidectomy plus consequential cisplatin treatment. RT: Orchidectomy plus consequential adjuvant radiotherapy. CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.

QRSD: QRS complex duration; QTcB: QT interval duration corrected according to Bazett [27]; QTcF: QT interval duration according to Fridericia [28]; NS: Not Significant; NA: Not Applicable due to small numbers.

**Table 3:** The occurrence of distinct ECG patterns.

	AS n = 18	CT n = 133	RT n = 14	CTRT n = 8	p
PVC	1	0	0	0	NA
Q wave	0	0	0	0	NA
LAFB n (%)	1 (5.6)	19 (14.3)	<b>2 (14.3)*</b>	<b>6 (75)***</b>	* <i>p</i> <0.05 *** <i>p</i> <0.001 # <i>p</i> <0.05
LBBB	0	0	1	0	NA
RBBB	0	1	0	0	NA
iRBBB	0	1	0	0	NA

AS: Active Surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment; RT: Orchidectomy plus consequential adjuvant radiotherapy; CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin; PVC: Premature Ventricular Contractions; LAFB: Left Anterior Fascicular Block; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; iRBBB: incomplete Right Bundle Branch Block; ECG-LVH: ECG signs of Left Ventricular Hypertrophy; ECG-RVH: ECG signs of Right Ventricular Hypertrophy. NS: Not Significant; NA: Not Applicable due to small numbers; \**p*<0.05; \*\*\**p*<0.001, both compared to AS as well as to CT; #*p*<0.05, compared to AS.

The left anterior fascicular block (LAFB) was the most frequent finding, it occurred in 19 (14.3%) cisplatin treated patients. The lower proportion was observed in the AS group, and the highest in the CTRT group. The proportion of patients with LAFB was significantly higher in RT and CTRT group compared to CT and AS groups.

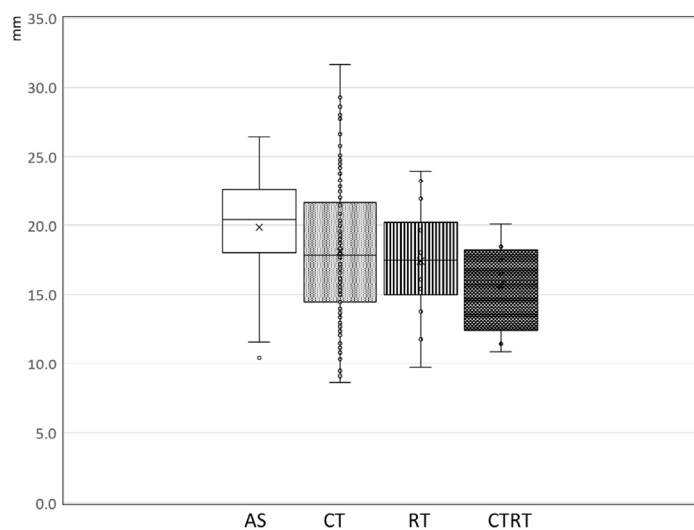
### QRSmax

The values of QRSmax were within normal limits. As shown in the Figure 1, the QRSmax values were the highest in the AS group, slightly lower in the CT group, with the lowest values in the CTRT group; however, these differences were not

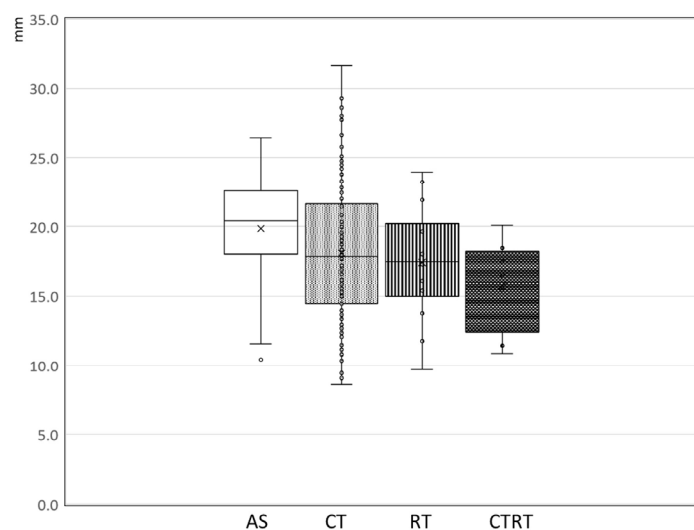
statistically significant. The GLM showed significant effect of age and the waist circumference, but not of the therapeutic group.

### Electrical axis of the QRS complex

The values of electrical axis in the CT group, as well as in the other groups were within normal limits. The electrical axis values were the highest in the AS group, slightly lower in the CT group, with the lowest values in the CTRT group, however, the differences were not statistically significant (Figure 2). The GLM showed significant effect of age and the waist circumference but not of the therapeutic group.



**Figure 1:** Box-whiskers plot: The maximum spatial QRS vector magnitude (QRSmax). AS: active surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment; RT: Orchidectomy plus consequential adjuvant radiotherapy; CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.



**Figure 2:** Box-whiskers plot: The electrical axis of the QRS complex. AS: active surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment; RT: Orchidectomy plus consequential adjuvant radiotherapy; CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.

**QRS complex amplitude in the individual leads of the 12-lead ECG**

Table 4 presents the values of the maximum QRS complex deflections in the individual leads of the electrocardiogram. The QRS amplitude in leads aVL was significantly higher in CT, RT and CTRT groups compared to the AS group (p=0.007). Significantly lower values in CT, RT and CTRT groups were observed in the lead V6 as compared to AS group (p=0.027). In both aVL and V6, the GLM showed significant effect of the waist circumference, but not of the therapeutic group (Table 5).

**The maximum spatial T vector magnitude**

The values of Tmax in the CT group, as well as in the other groups were within normal limits. The Tmax values in CT and CTRT groups were lower compared to the AS group, however, these differences were not statistically significant, the values of Tmax in the RT group were significantly lower compared to the AS group (Figure 3). The GLM showed significant effect of the waist circumference, but not of the therapeutic group (Table 5).

**Table 4:** The maximum QRS complex deflections in the individual leads of the 12-lead standard electrocardiogram in mV. Data are presented as median (1Q-3Q range). NS: Not Significant.

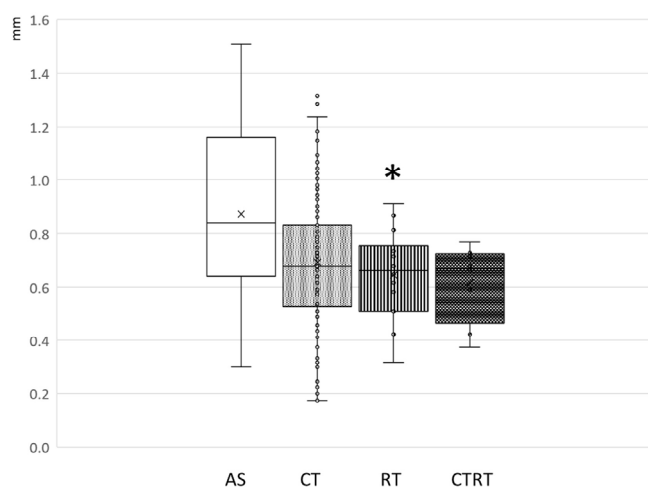
	AS	CT	RT	CTRT	p
<b>I</b>	6.0 (4.0-8.0)	6.0 (4.0-8.0)	6.0 (3.8-8.5)	7.5 (5.5-8.8)	NS
<b>II</b>	7.5 (6.0-9.3)	7.0 (5.0-9.0)	7.0 (5.5-8.3)	4.0 (3.0-8.3)	NS
<b>III</b>	4.0 (2.0-5.3)	5.0 (3.0-7.0)	3.5 (2.4-6.0)	5.5 (4.0-8.0)	NS
<b>aVR</b>	7.0 (5.8-8.3)	7.0 (5.0-8.0)	6.5 (5.8-8.0)	4.5 (4-6.5)	NS
<b>aVL</b>	2.3 (1.8-5.0)	4.0 (3.0-6.0)	4.0 (3.0-5.8)	6.5 (4.5-8.8)	<b>0.007</b>
<b>aVF</b>	5.0 (3.8-6.3)	5.0 (3.0-8.0)	4.5 (3.0-7.5)	3.5 (3.0-5.8)	NS
<b>V1</b>	8.0 (7.0-10.0)	7.0 (5.0-9.5)	6.0 (4.8-9.0)	4.5 (3.3-11.5)	NS
<b>V2</b>	10.0 (7.8-16.0)	10.0 (7.0-12.0)	10.0 (4.8-12.3)	8.0 (3.5-12.5)	NS
<b>V3</b>	10.5 (7.0-14.0)	10.0 (7.0-13.0)	10.0 (9.0-12.5)	13.0 (8.5-14.0)	NS
<b>V4</b>	10.5 (8.0-13.0)	10.0 (8.0-13.5)	10.5 (9.0-12.0)	10.5 (7.5-13.5)	NS
<b>V5</b>	15.0 (10.8-17.3)	12.0 (9.0-15.0)	13.5 (9.8-16.0)	12.5 (9.3-14.5)	NS
<b>V6</b>	15.0 (12.0-18.0)	12.0 (9.0-15.0)	12.5 (10.8-16.8)	10.0 (7.0-14.3)	<b>0.027</b>

AS: Active Surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment; RT: Orchidectomy plus consequential adjuvant radiotherapy; CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.

**Table 5:** Univariate regression analysis performed for selected ECG variables by means of the General Linear Model (GLM): the effect of therapeutic group, age, time from treatment (follow-up), waist circumference. Corr. M.: Correlation Model.

	QRSmax	EA	aVL	V6	Tmax
Corr. M.	<b>0.0001</b>	<b>0.0001</b>	<b>0.0001</b>	<b>0.005</b>	<b>0.0001</b>
intercept	<b>0.0001</b>	<b>0.0001</b>	0.225	<b>0.0001</b>	<b>0.0001</b>
Th group	0.163	0.772	0.106	0.187	0.116
Age	<b>0.042</b>	<b>0.034</b>	0.717	0.488	0.219
Follow-up	0.149	0.211	0.523	0.516	0.982
Waist	<b>0.0001</b>	<b>0.0001</b>	<b>0.0001</b>	<b>0.001</b>	<b>0.0001</b>





**Figure 3:** Box-whiskers plot: the maximum spatial T vector magnitude (Tmax). \* $p > 0.05$  compared to ORCH group; AS: Active Surveillance, the control group; CT: Orchidectomy plus consequential cisplatin treatment; RT: Orchidectomy plus consequential adjuvant radiotherapy; CTRT: Orchidectomy plus consequential adjuvant radiotherapy in combination with cisplatin.

## Discussion

In patients with cisplatin-based therapy:

- HR and the time intervals under study were within normal limits and no significant differences between the groups were observed.
- The QRS complex parameters and Tmax values were within normal limits. The GLM did not show a significant effect of therapy, but the significant effect of age and waist circumference;
- The only distinctive pathological ECG finding was LAFB, its significantly highest occurrence was observed in the group CTRT.

The heart rate and the time intervals under study were within normal limits, as well no significant differences were observed between the groups. Changes in HR, both bradycardia and tachycardia, have been reported to be early complications of cisplatin-based therapy: bradycardia can occur as a rare early effect, on the other hand, also tachycardia was reported as an early complication [11,12,31]. In our study however, the occurrence of tachycardia was negligible. Bradycardia occurred in about one third of patients; but there were no differences between groups, therefore we did not assume that bradycardia was related to the treatment. Taking together, no changes in HR were found as a late cisplatin effect in this study.

The QT and QTc values were within normal limits. The QT interval prolongation is used as an indicator of cardiotoxicity [32,33], since it is associated with the risk of ventricular arrhythmias [34]. However, the systematic review showed that the incidence of arrhythmias and sudden cardiac death attributable to QTc prolongation from cancer therapy is extremely rare [33]. Our results are consistent with that

statement.

The QT interval is frequently referred to as a parameter of repolarization; however, it contains both depolarization and repolarization. In order to distinguish the primary and secondary repolarization changes we analyzed the QT/QRSD ratio [35]. This ratio was used in experimental and clinical studies for predicting potential risk of drug-induced ventricular arrhythmias [36,37]. In our study, there were no significant differences in QT/QRSD ratio between the groups.

The QRS complex parameters were within normal limits. They did not differ significantly between the groups and the GLM showed significant effect of age and waist, but not of the therapeutic group. QRSmax represent the summary vector of depolarization. The solid angle theorem postulates that the recorded amplitude depends on the extent of the activation front (i.e. dimensions of the right and left ventricles, the sequence of depolarization) and electrical properties of myocardium (i.e. the transmembrane potential, ratio of electrically active and inactive tissue, conduction characteristics). The data on the heart dimensions were not available in this study; however we do not assume considerable changes in the heart dimensions, since papers focused on cardiotoxicity do not report changes in heart dimensions, as oppose to frequently reported alterations in cardiac functions. On the other hand, both cisplatin-based treatment, as well as radiotherapy cause myocardial changes that might alter the electrical properties of myocardium, and consequently might affect the resultant QRS vector [25,26,38-40]. Also obesity and aging were reported to be associated with the decrease in QRS amplitude [41-46]. Our finding is consistent with results documented the leftward shift of the electrical axis in obese subjects [41,47-49], and its occurrence is increased with age [50,51].

The slight differences in QRSmax in the combination with the differences in the electrical axis were reflected in the changes in the individual leads of 12-lead ECG. Although these differences were within normal limits, they could indicate subtle changes in electrical impulse propagation in ventricles. The combination of the decrease in QRS voltage and the electrical axis leftward shift have been observed in conditions with increased cardiovascular risk, such as aging, obesity, diabetes mellitus, metabolic syndrome and obstructive sleep apnea [41-46,52,53]. In this study, the GLM showed that the ECG changes were not associated with therapy, but with the age and the waist circumference. It could be assumed that these ECG findings are associated with the classical cardiovascular risk factors rather than with the cisplatin therapy *per se*.

In this study we found lower values of T wave amplitude in the CT, RT and CTRT groups as compared to AS group, the difference between AS and RT groups were statistically significant. The decrease in the spatial T vector magnitude was observed also by Wang et al. [54] during the treatment in patients receiving chemotherapy for breast cancer as a possible indicator of electrophysiological abnormalities. However, in this study the GLM did not show a significant effect of the therapeutic group, but of the waist circumference. The low T wave amplitude is a non-specific finding, documented in a variety of cardiac pathologies and associated with CV risk factors. Epidemiological studies have documented that non-specific T wave changes, including the low amplitude T wave, represent a significant independent risk of coronary artery disease and cardiac death [55,56]. Cisplatin has a complex effect on cells through multiple mechanisms [57,58], in combination of age and obesity in patients could affect the repolarization and the subtle Tmax changes might indicate the underlying alterations of electrogenesis [59].

Regarding distinctive QRS patterns, we found minimum pathological ECG findings in this study. We did not find any ECG signs of MI in our study population, such as angina pectoris, myocardial infarction and ECG changes mimicking MI or ischemia documented as early manifestations of cisplatin toxicity [9,60-62].

In the groups CT, RT and CTRT we observed a higher occurrence of patterns of left anterior fascicular block (LAFB), with the highest occurrence in the CTRT group. The ECG pattern of LAFB is typically attributed to the conduction block in the left anterior fascicle. However, this pattern is not unique just for the block in the left anterior fascicle. LAFB is a common nonspecific abnormality that occurs in a variety of left-sided cardiac pathologies, as well as in persons without overt cardiac disease [63]. We have also shown in our simulation studies that LAFB pattern can result also from diffuse and/or regional alteration in the activation propagation in the myocardium of the left ventricle [64,65]. It is not likely that the radiotherapy would affect selectively only the left anterior fasciculus of the left bundle; therefore we assume that this finding might reflect subtle subclinical conduction alteration of myocardium, more pronounced in the CTRT group.

Several factors could contribute to the alteration of the myocardium, and both cisplatin-based treatment and radiotherapy have been reported to cause structural and functional changes. The effect of cisplatin includes direct damage of myocardium as well as of extracellular matrix, such as oxidative stress and enhanced endoplasmatic reticulum stress, activation of apoptotic processes, nuclear damage and mitochondrial abnormalities, disorganization of cardiomyocytes and widening of intercalated discs, induction of inflammation and fibrosis [25,26,38-40]. Also radiation causes structural and microvascular changes, as was shown in animal as well as in human studies, and late abnormalities can appear months to years later [66-71]. It is also assumed that the combination of chemotherapy and radiotherapy can have a synergetic effect on cardiac function [72].

Additionally, a great proportion on patients in this study were overweight or obese. The structural and functional changes of myocardium in obesity, referred to as "the fatty heart", include altered glucose and lipid metabolism, the lipid accumulation in myocardium and inflammatory infiltrations [73,74]. And finally, an additional factor is the natural aging. Although none of these conditions were explicitly pronounced in any group of patients, they could have additive effect. A combination of these factors can affect electrogenesis, as well as the ratio of electrically active and inactive myocardial tissue, and consequently the sequence of ventricular activation and the morphology of the QRS complex.

### Limitation of the Study

There were several limitations of the study. The project was not originally designed for evaluating ECG, therefore not all pre-treatment ECGs were available, and only standard paper ECG recordings were available for the manual measurement. Neither records nor results of the 24-hour Holter monitoring were available in the patients, therefore the occurrence of arrhythmias could not be better evaluated. As well, no clinical events or complaints related to possible arrhythmias, such as syncope or palpitations were found in patients' medical records.

There were relatively small numbers of patients in the AS, RT and CTRT groups compared to the CT group, since cisplatin is currently the recommended regimen in the treatment of testicular cancer [1,2]. Because of the small sample size the results might not achieve statistical significance. In spite of the small numbers it was documented that the subtle ECG changes were pronounced in RT and CTRT groups, suggesting additive effect of radiotherapy, what is consistent with reported subclinical deterioration of cardiac function [22,38,75]. However, because of these limitation these results needs to be taken with caution.

### Conclusion

It could be concluded that cisplatin treatment did not



show signs of late cardiotoxicity that could be documented by ECG. The ECG findings in patients treated by cisplatin were dominantly within normal limits and the number of pathological ECG findings was negligible. The GLM model did not show a significant effect of cisplatin-based therapy, but the ECG parameters were significantly affected by age and obesity. However, the additive effect of radiotherapy cannot be excluded.

## Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Andreas Thaler, Lucia Petrikova, Beata Mladosevicova, Daniela Svetlovska, Katarina Kalavska, Zora Krivosikova, Jozef Mardiak, Michal Mego, Michal Chovanec and Ljuba Bacharova. The first draft of the manuscript was written by Ljuba Bacharova and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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