Original Article

Chemotherapy-Induced ECG Changes in HCC Patients

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INTRODUCTION

According to Globocan, in 2022, the highest incidence of hepatocellular carcinoma (HCC) was observed in Asia, which accounted for 75% of the global burden of liver cancer [1]. In the Republic of Kazakhstan in 2022, the incidence of liver cancer was 5.1 per 100,000 population, with a mortality rate of 2.9, respectively. For the period 2014-2022, HCC had the lowest five-year survival rate among all malignant neoplasms in Kazakhstan[2,3]. The treatment of HCC across various stages involves a range of clinical strategies[4]. Sorafenib is currently the primary drug in the treatment of HCC [4,5] and doxorubicin is used in transarterial hepatic artery chemoembolization (TACE)[8]. However, their use results in cardiotoxicity leading to cancer therapeutics-related cardiac dysfunction (CTRCD)[9]. CRTCD manifests as cardiovascular disease symptoms in patients with HCC, reflecting irreversible structural changes in the myocardium[10].

Complications developed against the background of chemotherapy, negatively affect the quality of life and overall survival of patients, regardless of the prognosis associated with the underlying disease[11], the actual threat of premature cardiovascular mortality from cardiotoxic complications, according to leading experts of the American College of Cardiology/American Heart Association (ACC/AHA), may be higher, compared with the risk of death from the tumor process.

Unfortunately, many oncology centers in Kazakhstan still lack the equipment needed to detect early signs of heart dysfunction, such as global longitudinal strain. In addition, not all laboratories have the capacity to measure biomarkers like brain natriuretic peptide (BNP) or high-sensitivity troponin. On the other hand, electrocardiography (ECG) is a simple, widely available, and reliable tool that can be used as a standard method for spotting early cardiac problems. In fact, ECG changes are often the first indicators of heart damage caused by cancer treatments[12]. Currently, there is accumulated evidence regarding QTc interval prolongation in patients receiving sorafenib and doxorubicin [(13-18)]. According to the meta-analysis by Porta-Sánchez A. et al. (2017), sorafenib prolongs QTc, initially below 500 ms, in 8.5% of cases [19].

In our study, we analyzed ECG changes in patients with HCC undergoing targeted therapy and targeted therapy combined with TACE. The analysis was conducted at the start of treatment and after three months, both within groups and between groups.

MATERIALS AND METHODS

This study is a multicenter, observational clinical investigation conducted within the framework of a grant from the Ministry of Education and Science of the Republic of Kazakhstan (Individual Registration Number

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AP19176025). The study was carried out from October 2021 to November 2023. The research was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Astana Medical University. All participants provided written informed consent prior to enrollment in the study.

A total of 91 patients with HCC were included in the study. The patients were divided into two groups based on the treatment protocol. The first group consisted of 49 patients who received daily targeted therapy with sorafenib at a dose of 800 mg per day. The second group included 42 patients who, in addition to receiving sorafenib at the same dose, underwent TACE with doxorubicin at a dose of 50 mg.

Exclusion criteria included patients under 18 years of age, those with metastatic liver cancer, cardiovascular diseases, other types of malignancies, any intraventricular conduction abnormalities, ST-segment or T-wave changes, medications affecting the QT interval, and a glomerular filtration rate (GFR) of less than 30 mL/min.

The study was conducted exclusively on the Kazakhstani population; however, the ethnic composition of participants was diverse, with 93% identifying as Asian and 7% as Caucasian.

All patients underwent a resting 12-lead ECG in accordance with AHA/ACC/HRS guidelines [20]. The ECGs were recorded using calibrated equipment (50 mm/s and 10 mm/mV) before the initiation of therapy (4 ± 1 days) and three months after the start of treatment. ECG interpretation was performed manually by two independent experts. The following parameters were assessed based on the electrocardiogram data: heart rate, PQ interval, QRS complex duration, QT interval, QTc (calculated using Fridericia's formula), newly developed intraventricular blocks, amplitude characteristics of the atrioventricular complex, as well as ST-segment and T-wave dynamics. The QRS amplitude was assessed as the sum of the positive and negative deflections. A low-voltage ECG was defined as a QRS amplitude ≤5 mm in standard leads and ≤10 mm in precordial leads. Bundle branch blocks (complete or incomplete) were diagnosed in accordance with AHA/ACC/HRS guidelines [21].

ST-segment depression of ≥0.5 mm or elevation of ≥1 mm in at least two contiguous leads, measured at the J-point, were considered potential ischemic changes. T-wave abnormalities included any morphological deviations, such as inverted T waves, flattened, biphasic, or hyperacute T waves. Changes in the atrial component, including P-wave duration >0.11 seconds, bifid P waves, or P waves with two distinct peaks, were considered possible signs of intra- or interatrial conduction disturbances.

For variables with a non-normal distribution, non-parametric methods were applied: the Mann–Whitney U test (for intergroup comparisons) and the Wilcoxon test (for intragroup comparisons). For variables with a normal distribution, Student's t-test was used. Statistical significance was set at $p < 0.05$. Data are presented as means with standard deviations, and binary variables are presented as frequencies in absolute values and percentages. Statistical analysis was performed using SPSS version 26 (IBM, USA).

ETHICAL CLEARANCE

This study was conducted in accordance with ethical standards. Ethical approval was obtained from the appropriate institutional review board, and informed consent was secured from all participants prior to data collection.

RESULTS

Table 1 summarizes the characteristics of the patients in both groups. In total, 91 patients with primary HCC were analyzed, including 45 women (49.4%). Among them, 12 patients (13.1%) were diagnosed with HCC at the stage of liver cirrhosis, with 8 cases confirmed by histology and 4 diagnosed without histological verification. The average age of the patients was 59.7 ± 10.2 years. Overall, 48 patients (52.7%) underwent surgical treatment during the observation period.

Table 1. Characteristics of Targeted Therapy, Targeted Therapy Groups, and TACE

Indicator	Targeted therapy group (n=49)	Targeted therapy and TACE group (n=42)	p
Female sex, n (%)	28 (57,1)	17 (40,4)	0,467
Age, years	58±10,7	60±8,2	0,782
BMI, kg/m²	25,3±3,7	24,9±4,1	0,637
Hemoglobin, g/L	122,4±20,6	118,3±13,4	0,487

Indicator	Targeted therapy group (n=49)	Targeted therapy and TACE group (n=42)	p
Leukocytes, x10⁹/L	7,7±3,2	6,5±2,9	0,102
Platelets, x10⁹/L	217,8±98,4	198±79,4	0,482
Potassium, µmol/L	4,16±1,1	3,89±0,82	0,140
Glucose, mmol/L	5,4±1,8	5,2±2,4	0,422
Creatinine, µmol/L	76,4±17,4	88,9±13,9	0,067
LVEF (left ventricular ejection fraction), %	61,6±4,4	58,2±3,9	0,299
Surgical treatment, n (%)	11 (23)	37 (88,1)	0,019

In the study, out of 91 patients, 49 (58%) received targeted therapy, while 42 (42%) underwent targeted therapy combined with TACE. The authors compared ECG parameters not only between the two treatment groups but also monitored changes in ECG dynamics within each group over 3 months of therapy.

Table 2. Baseline Electrocardiographic Parameters of Patients in Both Groups

Indicator	Targeted therapy group (n=49)	Targeted therapy and TACE group (n=42)	p
Resting heart rate, bpm	76,9±10,2	70,3±11,3	0,167
PQ interval, ms	160,4±8,6	174,1±9,1	0,098
QRS duration, ms	81,4±2,5	90,6±1,9	0,172
QT interval, ms	388,2±52,8	400,3±32,2	0,516
QTc interval, ms	397,4±33,5	419,8±24,9	0,471
Low voltage electrocardiogram, n (%)	1 (2,04)	0 (0)	0,832

As shown in Table 2, no initial differences in ECG parameters were found between the groups with different treatment protocols. All parameters were within normal ranges, and QTc interval values were close to the upper reference limit. The electrocardiographic characteristics of the targeted therapy group and the targeted therapy combined with TACE group after 3 months of treatment are presented in Table 3.

Table 3. Electrocardiographic Parameters of Patients in Both Groups After 3 Months of Treatment

Indicator	Targeted therapy group (n=49)	Targeted therapy and TACE group (n=42)	p
Resting heart rate, bpm	88,4±12,8	74,3±10,8	0,047
PQ interval, ms	165,9±10,5	174,7±8,3	0,058
QRS duration, ms	82,9±3,5	100,4±10,7	0,022
QT interval, ms	398,8±30,9	428,8±32,9	0,199
QTc interval, ms	437,4±27,6	459,8±22,7	0,231
Low voltage electrocardiogram, n (%)	5 (10,2)	11 (26,2)	0,032
T-wave inversion in precordial leads, n (%)	14 (28,6)	17 (40,47)	0,046

The comparison of ECG results between the two groups after 3 months of therapy revealed the following: the QRS complex duration in the targeted therapy and TACE group was significantly longer compared to the targeted therapy group (82.9±3.5 vs. 100.4±10.7 ms, p=0.022), though it remained within the reference range. Incomplete right bundle branch block and left anterior fascicular block were observed in 4 patients. Resting heart rate (HR) was also significantly higher in the targeted therapy group (88.4±12.8 bpm vs. 74.3±10.8 bpm in the targeted therapy and TACE group, p=0.047). Additionally, the percentage of patients with T-wave changes was significantly greater in the targeted therapy combined with the TACE group (40.47% vs. 28.6%, p=0.046). Low-voltage ECG patterns were more frequently observed in the same group (p=0.032).

When comparing baseline ECG parameters to those obtained after 3 months of therapy within each group, notable changes were observed (Tables 4, 5). In the targeted therapy group, a significant increase in HR was noted after 3 months (p=0.02). Moreover, QTc interval prolongation was significant but did not reach values associated with a high risk of arrhythmia (p=0.001). In both groups, the number of patients with reduced QRS complex voltage significantly increased after 3 months (1 vs. 5, p=0.032 in the targeted therapy group and 0 vs. 11, p=0.012 in the targeted therapy and TACE group). Mild pericardial effusion was detected in only two patients in the targeted therapy combined with TACE group, which does not fully explain the cases of ECG voltage reduction due to hydropericardium.After 3 months of therapy, both groups showed a significant increase in the number of cases with T-wave inversion in at least two contiguous leads ($p<0.001$). In the targeted therapy and TACE group, QTc interval duration also increased significantly, reaching pathological values and moderately exceeding the gender- and age-specific norms of the patients (from 419.8±24.9 ms to 459.8±22.7 ms, $p=0.040$).

Table 4. Dynamics of Electrocardiographic Parameters in the Targeted Therapy Group Over 3 Months

Indicator	Baseline electrocardiogram	Three months after the start of therapy	p
Resting heart rate, bpm	76,9±10,2	88,4±12,8	0,002
PQ interval, ms	160,4±8,6	165,9±10,5	0,061
QRS duration, ms	81,4±2,5	82,9±3,5	0,095
QT interval, ms	388,2±52,8	398,8±30,9	0,036
QTc interval, ms	397,4±33,5	437,4±27,6	0,001
Low voltage electrocardiogram, n (%)	1 (2,04)	5 (10,2)	0,032
T-wave inversion in precordial leads, n (%)	0	14 (28,6)	<0,001

Table 5. Electrocardiographic Indicators of Patients in the Targeted Therapy Group Combined with TACE Over 3 Months of Treatment Dynamics

Indicator	Baseline electrocardiogram	Three months after the start of therapy	p
Resting heart rate, bpm	70,3±11,3	74,3±10,8	0,060
PQ interval, ms	174,1±9,1	174,7±8,3	0,077
QRS duration, ms	90,6±1,9	100,4±10,7	0,079
QT interval, ms	400,3±32,2	428,8±32,9	0,085
QTc interval, ms	419,8±24,9	459,8±22,7	0,040
Low voltage electrocardiogram, n (%)	0 (0)	11 (26,1)	0,012
T-wave inversion in precordial leads, n (%)	0	17 (40,5)	<0,001

DISCUSSION

The issue of cardiotoxicity in oncology patients is gaining increasing attention from the medical community. Decades of experience and long-term observations of cancer survivors have revealed a wide range of complications, including myocardial dysfunction, myocardial remodeling, decreased contractility, and potentiation of arrhythmogenesis, which affects all types of cells within the heart's conduction system. The cardiotoxicity of chemotherapy can manifest through a variety of ECG changes, the most common being tachycardia, ST-segment and T-wave abnormalities, ectopic atrial rhythms, intraventricular blocks, prolonged QTc interval, and prolonged PQ interval [22-29].

Our study demonstrated ECG changes in patients with HCC undergoing targeted therapy and TACE. The primary changes were associated with disruptions in myocardial depolarization and repolarization processes.

Significant advancements in cancer treatment have led to a decrease in patient mortality, positioning cardiovascular diseases as the second leading cause of death among oncology patients [28,30]. In Kazakhstan, over the past two decades, the incidence of newly diagnosed cancer has declined from 195.9 per 100,000 population in 2001 to 94.2 in 2020, with mortality rates decreasing from 134.4 to 75.0, respectively[31]. However, the concurrent presence of oncological and cardiovascular diseases remains a serious concern [32-35]. A study by K.S. Stoltzfus et al. [36] analyzed 7,529,481 cancer patient deaths, revealing that 5.24% were due to heart diseases, with a cardiovascular mortality rate of 10.61 per 10,000 person-years and a standardized mortality ratio of 2.24 (95% CI: 2.23–2.25).

Bellinger A.M. et al. reported that anthracyclines induce cardiomyocyte death, leading to irreversible myocardial damage. The extent of this damage correlates with the cumulative dose of the anticancer drug and results in the development of cardiac rhythm and conduction disorders in 16–36% of oncology patients[37]. Although our study did not identify cardiac rhythm disturbances, a comparison of ECGs between the targeted therapy group and the targeted therapy combined with TACE group after three months of treatment showed differences in resting heart rate, which was significantly higher in the targeted therapy group ($p = 0.047$).

The available literature on QRS complex alterations in oncology patients remains limited; however, several studies report an increase in abnormal fragmented QRS (fQRS) complexes, ranging from 15.8% to 28.9% ($p = 0.041$) in bladder cancer patients and from 26.6% to 53.1% ($p < 0.01$) in breast cancer patients[37]. This condition is linked to myocardial fibrosis induced by antitumor therapy. Notably, Adar et al. observed the presence of fQRS in breast cancer patients not only before clinical manifestations but also prior to echocardiographic changes[38]. In our study, a comparison between the two groups at three months post-therapy initiation revealed that patients in the targeted therapy combined with TACE group exhibited a significantly longer QRS duration, though still within the reference range (82.9 ± 3.5 ms vs. 100.4 ± 10.7 ms, $p = 0.22$). Additionally, fQRS complexes were detected in four patients within this group.

When comparing targeted therapy alone to targeted therapy combined with TACE three months after treatment onset, patterns of low-voltage electrocardiograms (Poor R-wave progression in leads V1–V4) were more frequently observed: five patients in the targeted therapy group versus eleven in the combined therapy group ($p = 0.032$). Within-group analysis over the same period indicated a reduction in QRS voltage amplitude: one versus five patients ($p = 0.032$) in the targeted therapy group, and zero versus eleven patients ($p = 0.012$) in the combined therapy group. According to Felker G.M., patients undergoing taxane and anthracycline chemotherapy exhibited predominantly fibrotic focal changes in myocardial histological samples, potentially resulting from cardiomyocyte apoptosis induced by these chemotherapeutic agents [39].

Prolongation of the QT interval is a significant concern in cardio-oncology, as it can lead to life-threatening ventricular arrhythmias and sudden cardiac death. This prolongation extends the ventricular action potential during repolarization. Certain antitumor agents, such as platinum derivatives, can induce QT interval prolongation by increasing the inward sodium current[40]. In our study, patients receiving combined targeted therapy and TACE exhibited a significant increase in QTc interval over the three months following treatment initiation (from 419.8 ± 24.9 ms to 459.8 ± 22.7 ms, $p = 0.040$), as calculated using Fridericia's formula. Similarly, P. Veronese et al. analyzed QT interval changes in 27 breast cancer patients undergoing anthracycline-based therapy (doxorubicin), cyclophosphamide, and paclitaxel. Doxorubicin administration was associated with a notable QTc prolongation (from 439.7 ± 33.2 ms to 472.5 ± 36.3 ms), calculated using Bazett's formula, with nine patients (30%) experiencing a QTc increase beyond 500 ms. The authors suggest that this QTc prolongation is due to the drug's effect on ion (potassium) channels, leading to an extended action potential [41].

Sorafenib, commonly used as targeted therapy for HCC, is associated with a moderate risk of QTc prolongation, typically not exceeding 10 ms, and carries a low or negligible risk of inducing Torsades de Pointes (TdP)[42,43]. In a small study involving sorafenib, a QTc prolongation of less than 10 ms was observed[44]. Another study with 86 patients receiving sorafenib and sunitinib reported a 9.5% incidence of QTc prolongation of any degree, with no recorded episodes of TdP [45, 46]. In our observation, patients treated with sorafenib for three months exhibited a significant QTc prolongation from 397.4 ± 33.5 ms to 437.4 ± 27.6 ms ($p = 0.001$), as calculated using Fridericia's formula.

In addition to QTc interval changes, a comparison of the two groups three months after therapy initiation revealed that patients in the targeted therapy and TACE group were significantly more likely to exhibit T-wave inversion in at least two contiguous leads ($p = 0.046$). Similar changes were also observed within each group over the course of treatment, with a highly significant p-value ($p < 0.001$).

A trend toward differences between the groups was noted in PQ interval duration ($p = 0.058$), although no clinically significant prolongation or development of atrioventricular blocks was observed in either group.

Our study is limited by the small sample size and relatively short observation period. These limitations restrict our ability to assess the long-term cardiovascular changes and extrapolate the findings to patients undergoing extended courses of antitumor therapy.

CONCLUSION

In patients with HCC without pre-existing cardiovascular pathology, a comparison between the targeted therapy group and the targeted therapy combined with TACE group, as well as within-group dynamics over three months after therapy initiation, revealed the following: an increase in resting heart rate, prolongation of QRS duration, a reduction in ECG voltage, QTc interval prolongation, and T-wave inversion. These results highlight the importance of thorough electrocardiographic monitoring during targeted therapy and TACE in patients with HCC, particularly given the potential risk of adverse cardiovascular events.

Overall, our findings contribute to the growing body of evidence on chemotherapy-associated electrocardiographic changes in HCC patients, underscoring the need for comprehensive cardiac monitoring and individualized treatment strategies for this patient population.

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Authors's contribution

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REFERENCES

1. https://gco.iarc.who.int/media/globocan/factsheets/cancers/11-liver-and-intrahepatic-bile-ducts-fact-sheet.pdf
2. Показатели онкологической службы Республики Казахстан за 2022 год. Статистический сборник. Алматы, - 2023г.
3. Malayev, N.; Saparbayev, S.; Kubekova, S.; Donayeva, A.; Zagorulya, N.; Kuanyshbayeva, G. et al. Prevalence of Liver Cancer in Kazakhstan: A Systematic Review. *Bangladesh J Med Sci.* **2024;**23:643-654. https://doi.org/10.3329/bjms.v23i3.75020
4. Xing R, Gao J, Cui Q, Wang Q. Strategies to Improve the Antitumor Effect of Immunotherapy for Hepatocellular Carcinoma. Front Immunol. 2021 Nov 26;12:783236. doi: 10.3389/fimmu.2021.783236. *PMID:* 34899747; PMCID: PMC8660685.
5. G. Fan, X. Wei, X. Xu. Is the era of sorafenib over? A review of the literature. Ther. *Adv. Med. Oncol,* 2020;**12**:
6. Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, Pikarsky E, Zhu AX, Finn RS. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol.* 2022 Mar;**19**(3):151-172. doi: 10.1038/s41571-021-00573-2. Epub 2021 Nov 11. PMID: 34764464.
7. Bernard Escudier, Francis Worden & Masatoshi Kudo () Sorafenib: key lessons from over 10 years of experience, *Expert Review of Anticancer Therapy*, 2019;**19**:2: 177-189, DOI: 10.1080/14737140.2019.1559058
8. Crocetti L, Bargellini I, Cioni R. Loco-regional treatment of HCC: *current status. ClinRadiol.* 2017 Aug;**72**(8):626-635. doi: 10.1016/j.crad.2017.01.013. Epub 2017 Feb 28. *PMID*: 28258743.
9. Cardinale D., Iacopo F., Cipolla C.M. Cardiotoxicity of anthracyclines. *Front CardiovascMed.* 2020; **7**: 26
10. Saleh Y., Abdelkarim O., Herzallah K., Abela G.S. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. *Heart Fail. Rev.* 2020; https://doi.org/10.1007/s10741-020-09968-2
11. Bonow R. O., Bennett S., Casey D. E. et al. ACC/AHA Clinical Performance Measures for Adults with Chronic Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures): endorsed by the Heart Failure Society of America. *Circulation*. 2005; **112** (12): 1853-1887. doi: 10.1161/CIRCULATIONAHA.105.170072.
12. L. Carballo-Folgoso, R. Álvarez-Velasco, R. Lorca, A. Castaño-García, J. Cuevas, M.L. González-Diéguez, et al. Evaluation of cardiovascular events in patients with hepatocellular carcinoma

treated with sorafenib in the clinical practice. The CARDIO-SOR study. *Liver Int*., **41** (9): (2021), pp. 2200-2211

13. Lamore SD, Kohnken RA, Peters MF, Kolaja KL. Cardiovascular toxicity induced by kinase inhibitors: mechanisms and preclinical approaches. *Chem Res Toxicol*. 2020; **33**: 125-136.
14. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol*. 2020. https://doi.org/10.1038/s41569-020-0347-2.
15. Li M, Ramos LG. Drug-induced QT prolongation and Torsades de pointes. *P & T.* 2017; **42**: 473-477.
16. Anan A. Abu Rmilah, Grace Lin, Kebede H. Begna, Paul A. Friedman, Joerg Herrmann. Risk of QTc prolongation among cancer patients treated with tyrosine kinase inhibitors// *Int.J. of Cancer*. 25 May 2020. https://doi.org/10.1002/ijc.33119
17. Benjanuwattra J, Siri-Angkul N, Chattipakorn SC, Chattipakorn N. Doxorubicin and its proarrhythmic effects: A comprehensive review of the evidence from experimental and clinical studies. *Pharmacol Res.* 2020 Jan;**151**:104542. doi: 10.1016/j.phrs.2019.104542. Epub 2019 Nov 13. PMID: 31730804.
18. Singh M, Kadhim MM, Turki Jalil A, Oudah SK, Aminov Z, Alsaikhan F, Jawhar ZH, Ramírez-Coronel AA, Farhood B. A systematic review of the protective effects of silymarin/silibinin against doxorubicin-induced cardiotoxicity. *Cancer Cell Int.* 2023 May **10**;23(1):88. doi: 10.1186/s12935-023-02936-4. PMID: 37165384; PMCID: PMC10173635.
19. Porta-Sánchez A, Gilbert C, Spears D, et al. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. *J Am Heart Assoc.* 2017; 6:e007724.
20. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ et al. Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part I: The Electrocardiogram and Its Technology. A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. *Circulation*. 2007;115:1306-1324.
21. Rautaharju PM, Borys Surawicz B, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part III: The QRS complex. A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. *Journal of the American College of Cardiology* 2009;**53**(11):
22. Bovelli, D., Plataniotis, G., Roila, F., & ESMO Guidelines Working Group (). Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Annals of oncology : *official journal of the European Society for Medical Oncology*, 2010; **21**(5): v277–v282. https://doi.org/10.1093/annonc/mdq200
23. Chen Z.I., Ai D.I. Cardiotoxicity associated with targeted cancer therapies // *Mol. Clin. Oncol.* – 2016;**4**: p. 675–681.
24. Chang J., Rattner D. W. History of minimally invasive surgical oncology // *Surgical Oncology Clinics of North America.* – 2019;**28**: – p.1–9.
25. Vasyuk YuA, Shupenina EYu, Vyzhigin DA, et al. Atrial Fibrillation in Cancer Patients: Who is at Risk? *Rational Pharmacotherapy in Cardiology*. 2021;**17**(6):900-7.
26. Vasyuk YuA, Shupenina EY, Novosel EO, et al. Heart rhythm and conduction disorders as manifestations of cardiotoxicity of anticancer treatment: myth or reality? *The Siberian Journal of Clinical and Experimental Medicine*. 2020;**35**(1):13-21.
27. Katsume Y., Isawa T., Toi Y., Fukuda R., Kondo Y., Sugawara S. et al. Complete atrioventricular block associated with pembrolizumab-induced acute myocarditis: the need for close cardiac monitoring. *Intern. Med*. 2018;**57**(21):3157–3162. DOI: 10.2169/internalmedicine.0255-17.
28. Yang X., Li X., Yuan M., Tian C., Yang Y., Wang X. et al. Anticancer therapy-induced atrial fibrillation: electrophysiology and related mechanisms. *Front. Pharmacol*. 2018;**9**:1058. DOI: 10.3389/fphar.2018.01058.
29. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R et al; ESC Scientific Document Group. 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). *European Heart Journal.* 2016;21:**37**(36):2768-2801.
30. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA *Cancer J Clin*. 2016;**66**:309–25.
31. Kaidarova D.R., Shatkovskaya, O.V., Ongarbayev, B.T., Seisenbayeva, G.T., Azhmagambetova, A.E., Zhylkaidarova, A.Zh., Lavrentieva, I.K., M., Sagi, S. (2021). INDICATORS OF THE ONCOLOGY SERVICE OF THE REPUBLIC OF KAZAKHSTAN FOR 2020 (statistical and analytical materials). THE MINISTRY OF HEALTHCARE OF THE REPUBLIC OF KAZAKHSTAN: KAZAKH INSTITUTE OF ONCOLOGY AND RADIOLOGY, Almaty, Kazakhstan. Available from: https://onco.kz/kz/news/pokazateli-onkologicheskoj-sluzhby-respubliki-kazahstan-za-2020-god/
32. Zamorano Jl et al. ESC Memorandum on Cancer Treatment and

Cardiovascular Toxicity developed under the auspices of the ESC 2016 Practice Committee by the European Society of Cardiology (ESC) Working Group on Cancer and Cardiovascular Toxicity. *Eur Heart J*. 2016 Sep 21;**37**(36):2768-2801. doi: 10.1093/eurheartj/ehw211.

33. Guidelines for the Diagnosis, Prevention and Management of Cardiovascular Complications of Antitumor Therapy. Part I Collective of authors /Chazova IE, Tyulyandin SA, Vitsenya MV et al. // *Russian Journal of Cardiology*.- 2017;**3** (143):
34. Practical recommendations for correction of cardiovascular toxicity of antitumor drug therapy / M.V. Vitsenya et al. // Malignant tumors: *Practical recommendations RUSSCO* #3s2, 2018;**8**: P. 545-563
35. Gilchrist, S. C. et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association // *Circulation*. 2019; - p.139. - e997-e1012. -.
36. Kelsey C. Stoltzfus, Ying Zhang, Kathleen Sturgeon et al. Fatal heart disease among cancer patients // Nature Communications. - vol. 2011. – 2020;**11**
37. Bellinger A. M., Arteaga, C. L., Force, T., Humphreys, B. D., Demetri, G. D., Druker, B. J., & Moslehi, J. J. (). Cardio-Oncology: How New Targeted Cancer Therapies and Precision Medicine Can Inform Cardiovascular Discovery. *Circulation*, 2015;**132**(23): 2248–2258.
38. Adar A, Canyılmaz E, Kiris A, et al. Radiotherapy induces development of fragmented QRS in patients with breast cancer.. *Breast Care (Basel)* 2015;**10**:277–280. [PMC free article] [PubMed] [Google Scholar
39. Felker, G. M., Thompson, R. E., Hare, J. M., Hruban, R. H., Clemetson, D. E., Howard, D. L., Baughman, K. L., & Kasper, E. K. (2000). Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *The New England journal of medicine*, **342**(15): 1077–1084. https://doi.org/10.1056/NEJM200004133421502
40. Duan J et al. Anticancer drugs-related QTc prolongation, torsade de pointes and sudden death: current evidence and future research perspectives. *Oncotarget* 9, 25738–25749 (2018). [PMC free article] [PubMed] [Google Scholar] [Ref list]
41. Veronese P., Hachul D., Scanavacca M., Hajjar L., Wu T., Sacilotto L. et al. Effects of anthracycline, cyclophosphamide and taxane chemotherapy on QTc measurements in patients with breast cancer. *PLoS One.* 2018;**13**(5):e0196763.
42. Alexander R Lyon et al. 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): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *European Heart Journal*, 2022;**43**(41):4229–4361. https://doi.org/10.1093/eurheartj/ehac244
43. Andreu Porta-Sánchez et al. Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review**.** *J Am Heart Assoc.* 2017;**6**(12): e007724. Published online 2017 Dec 7. doi: 10.1161/JAHA.117.007724
44. Tolcher AW, Appleman LJ, Shapiro GI, Mita AC, Cihon F, Mazzu A, SundaresanPR. A phase I open-label study evaluating the cardiovascular safety of sorafenib in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2011;**67**:751–764. [PMC free article] [PubMed] [Google Scholar]
45. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, Ruhsam M, Hejna M, Schmidinger H. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;**26**:5204–5212. [PubMed] [Google Scholar]
46. Bello CL, Mulay M, Huang X, Patyna S, Dinolfo M, Levine S, Van Vugt A, Toh M, Baum C, Rosen L. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic- pharmacodynamic evaluation of sunitinib. *Clin Cancer Res*. 2009;**15**:7045–7052. [PubMed] [Google Scholar]