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Prospective examination of Tp-e interval and Tp-e/QT ratio in breast cancer patients receiving radiation therapy

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ABSTRACT

Aims: The aim of this prospective study was to investigate ventricular repolarization using the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in breast cancer patients treated with adjuvant radiotherapy(RT) following systemic chemotherapy.

Methods: The study was designed as a national, single-center prospective study. According to the treatment protocol, electrocardiograms (ECGs) were taken from all patients on their first and last days of RT. Tp-e intervals, Tp-e/QT ratios, and Tp-e/QTc ratios were calculated based on the ECG recordings. The heart doses due to radiation exposure were examined with mean heart dose, V5, V10,V20, and V30 values.

Results: 51 postsurgical patients, who were all treated with AC followed by weekly paclitaxel and had an indication for adjuvant RT, were included in the study. The mean heart dose was observed as median 205 cGy, and the V30 value was 0.01%. When ECG measurements were analyzed, statistically significant increases were observed in Tp-e interval ($p<0.001$), QT interval ($p=0.007$), Tp-e/QT ratio ($p<0.001$), and Tp-e/QTc ratio ($p<0.001$) at the end of RT. Additionally, positive correlations were observed between mean heart dose and post RT Tp-e ($r= 0.770, p<0.01$) and Tp-e/QTc ratio ($r = 0.778, p<0.01$)

Conclusion: When compared to before RT, statistically significant prolongation of Tp-e interval and QT interval and increases in Tp-e/QT ratio and Tp-e/QTc ratio were detected which are thought to be predictive for ventricular repolarization process and ventricular rhythm disorders. In addition, the mean heart dose was positively correlated with Tp-e interval and Tp-e/QTc ratio.

Keywords: Radiotherapy, cardiac toxicity, breast cancer, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio

INTRODUCTION

Breast cancer is one of the most common types of cancer in women. Today, progress has been made in every field of treatment, from local treatments to chemotherapy and hormonal therapies, from targeted agents to immunotherapies. In light of these developments, personalized treatments are used more effectively in breast cancer, and life expectancy has increased. Consequently, patients now face treatment-related toxicities for longer periods of time during follow-up. Therefore, efforts to reduce unnecessary and/or preventable treatment toxicities continue in every field.

RT is one of the most important parts of multidisciplinary breast cancer treatment, due to its contributions to local control and overall survival. However, in patients who survive long-term, radiotherapy-related cardiac toxicity is one of the most remarkable factors affecting life span. One of the leading mechanisms in radiotherapy-induced cardiac pathogenesis is progressively increasing fibrosis and related functional damage in cardiac subunits. This can include atherosclerotic plaque formations in the vascular wall and related circulatory disorder changes due to reactive inflammation in the microenvironment, decreases in cardiac adipose tissue and decreases in myocardial movement and flexibility due to increased fibrosis, valvular degenerations and rhythmic disorders due to damage to the conduction system with increasing fibrosis acute and chronic pericarditis, and restrictive/constrictive cardiomyopathies.[1,2]

Moreover, on the basis of all this pathogenesis, with the influence of high-energy ionizing radiation at the cellular level, RT may have a disruptive role in the functions of cell membranes containing ion gates, mitochondria-like organelles in the cytoplasm, and the nucleus. On the other hand, a process leading to inhibition of the mitotic cycle and cellular apoptosis may occur with the direct effect of ionizing radiation on biomolecules such as DNA, RNA and signaling molecules. As a result of all these effects, ionizing radiation may cause impairment in signal transmission between myocardial cells.[3-5]

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Electrocardiography (ECG) is created by recording electrical data produced by the cardiac neural conduction system. ECG waves are generated by the electrical current produced when myocardial cells contract as a result of depolarization and relax as a result of repolarization. Structural electrocardiographic changes, such as changes in the height and width of these waves and irregularities in the waves, may reflect subclinical cardiac damage. These wave changes can be helpful in detecting conditions such as rhythm changes, conduction disorders, coronary circulation disorders, electrolyte imbalances, ischemia, and infarction.

The QT interval (QT) and the Tpeak-end interval (Tp-e) which represents the interval between the peak of the T wave (Tpeak) and the end of the wave (Tend), corresponds to the process of transmural distribution and myocardial repolarization.

The QT interval (QT) and the Tpeak-end interval (Tp-e) which is from the top of the T wave (Tpeak) to the end (Tend) correspond to the transmural dispersion and myocardial repolarization process. Prolonged QT and QTc are related with prolonged action potential duration at the cellular level. Various studies have shown that prolonged Tpeak-end interval and increased Tpeak-end/QT and Tpeak-end/QTc ratios may be associated with ventricular rhythm disorders.[6-8] From this point of view, the aim of this prospective study is to evaluate the ventricular repolarization effect of breast radiotherapy using electrocardiographic changes.

METHODS

Ethics

This prospective study was approved by the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 26.01.2021, Decision No: 311), and the Turkish Medicines and Medical Devices Agency (Date: 02.03.2021, Decision No: 593/08.12.2015). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population Between January 2020 and February 2022, 51 patients, all treated with postoperative AC followed by weekly paclitaxel and adjuvant RT, were included in the study. All patients were analyzed in terms of age, tumor biology, disease stage, applied local and systemic treatments, ECG findings before and after RT, and heart doses due to RT. The American Cancer Committee (AJCC) TNM staging system (8th edition, 2017) was used for staging. Written consent form was obtained from the patients included in the study.

The Exclusion Criteria

The exclusion criteria were administration of neoadjuvant chemotherapy (CT) , administration of any treatment other than adjuvant doxorubicin/cyclophosphamide (AC) followed by weekly paclitaxel, positivity of human epidermal growth factor receptor 2 (HER2), coronary artery disease, arrhythmia, congenital heart disease, heart valve dysfunction, cardiomyopathy, dyslipidemia, history of myocardial infarction, liver or renal function test abnormality, chronic pulmonary disease, hypocalcemia, hypercalcemia, or other serum electrolyte abnormalities, using a pacemaker or cardioverter defibrillator, heart rate greater than 100 beats per minute, heart rate less than 60 beats per minute, ST-T segment changes, branch block on ECG, and use of any medication that affects the cardiac conduction system, such as antiarrhythmics.

Electrocardiographic Measurements

Electrocardiographic recordings were taken from each patient on the first and last day of radiotherapy. The QT interval was obtained from at least six measurements, of which at least three were from the chest leads. Tp-e/QT ratio was calculated from the manually measured electrocardiographic wave and interval changes. All measurements carried out by a single specialist cardiologist. Bazett's formula was used to calculate the QTc interval and Tp-e/QTc ratios were calculated according to the obtained values.

Treatment Protocol

All patients underwent breast cancer surgery. Total mastectomy was performed in cases that not suitable for the breast-conserving approach. Axillary staging with axillary biopsy, sentinel lymph node biopsy, or lymphatic dissection were performed for each patient as clinically necessary. In order to keep the characteristics of the patient population as homogeneous as possible, only the patients who underwent adjuvant doxorubicin/cyclophosphamide (AC) followed by a weekly paclitaxel regimen were included in the study. In patients for whom hormonotherapy was indicated, it started from the end of RT.

Radiotherapy Planning: Simulation, Volume Definition, and Technique

Adjuvant radiotherapy planning was done within the first four weeks after chemotherapy. Computed tomography (CT) simulations were done with a Philips Brilliance (Amsterdam, Switzerland) scanner, with a slice thickness of 3 mm. Patients were simulated in the supine position and immobilized by a breast board. Target volumes and organs at risk (OAR) were delineated using the Varian Eclipse TPS station (Varian Medical

Systems, Sao Paulo), according to the radiation therapy oncology group (RTOG) breast cancer atlas. The spinal cord, heart, ipsilateral lung, contralateral lung, whole lung, and contralateral breast were defined as OAR. Treatment planning was done with three-dimensional conformal radiotherapy (3DCRT) or forward IMRT (intensity-modulated radiotherapy), using field-in-field (FinF) technique. In case dose tolerance limits could not be met, inverse IMRT or VMAT techniques were used. The heart doses were analyzed with V5 (percent volume of the heart receiving a dose of 5 Gy or more), V10, V20, V30, and mean heart dose values. Patient treatments were applied with a linear accelerator device using 6 MV X-rays.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as median (range). Data distribution was evaluated with the Kolmogorov-Smirnov test and it was observed that the variables were not normally distributed. For this reason, non-parametric Mann-Whitney U test and Chi-square test were used for continuous variables and categorical variables, respectively, in comparisons between groups. Correlations were analyzed using the Spearman correlation test. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago,IL, USA). A probability value of $p<0.05$ was considered significant.

RESULTS

Patient Characteristics

All patients included in the study were female, and the median age was 62 (range 22-82). 90.2% of cases had invasive ductal carcinoma (IDC) histology. 96.1% of the patients were estrogen receptor-positive. 59% of the patients were 50 years or older, and 62.7% were postmenopausal (Table 1). 39.2% of the patients were in the “normal” body mass index (BMI) range (BMI less than 25). 76.5% of the patients had never smoked. All patients underwent breast cancer surgery and adjuvant AC followed by weekly paclitaxel. The numbers of patients who received right and left breast RT were similar. Adjuvant RT details and heart dose values are given in Table 2.

Electrocardiographic Analyses

The median Tp-e interval values before and after RT were 78 and 84; QT interval values were 362 and 367; QTc interval values were 425 and 422; Tp-e/QT rate values were 0.22 and 0.23; Tp-e/QTc rate values were observed as 0.18 and 0.19, respectively. When ECG measurements obtained at the beginning and end of RT were examined, an increase in Tp-e interval ($p<0.001$), QT interval

Table 1. Patient and tumor characteristics

	Patients (n:51, %)
Age	Median; 62 (range 22-82)
<50 yr	21 (41%)
≥50 yr	30 (59%)
Menopausal status	
Premenopause	19 (37.3%)
Postmenopause	32 (62.7%)
BMI (kg/m2)	Median 25 (range 18.7-32)
18.5-24.9	20 (39.2%)
25-29.9	28 (54.9%)
30-34.9	3 (5.9%)
Smoking	
Former /Current smoker	12 (23.5%)
Nonsmoker	39 (76.5%)
Histology	
IDC	46 (90.2%)
ILC	2 (3.9%)
DCIS	3 (5.9%)
Tumor Laterality	
Left breast	26 (51%)
Right breast	25 (49%)
Quadrant	
Upper outer	25 (49%)
Lower outer	8 (15.7%)
Upper inner	5 (9.8%)
Lower inner	1 (2%)
Central	12 (23.5%)
Tumor grade	
I	4 (7.8%)
II	30 (58.8%)
III	17 (33.3%)
Estrogen-receptor status	
Positive	49 (96.1%)
Negative	2 (3.9%)
Ki 67 Status	
<%14	17 (33.3%)
≥%14	34 (66.7%)
Type of breast Surgery	
Breast Conserving Surgery	38 (74.5%)
Mastectomy	13 (25.5%)
T Stage	
Tis	3 (5.9%)
T1	15 (29.4%)
T2	26 (51%)
T3	6 (11.8%)
T4	1 (2%)
N Stage	
N0	27 (52.9%)
N1	17 (33.3%)
N2	5 (9.8%)
N3	2 (3.9%)

Table 2. Adjuvant radiotherapy details

	Patients (n:51,%)
RT Planning Modality	
Forward-IMRT	34 (66.7%)
Inverse-IMRT	17 (33.3%)
Radiotherapy Dose	Median 50 Gy (range 42.5-52)
Radiotherapy Boost	
Yes	37 (72.5%)
No	14 (27.5%)
Axillary RT	
No	24 (49%)
Yes	27 (51%)
SCN+LEVEL III	16 (32.7%)
SCN +LEVEL I-II-III	5 (10.2%)
SCN +LEVEL I-II-III+IMC	4 (8.2%)
Cardiac dosimetric parameters	Median (range)
Mean dose	205 cGy (83-563)
V5	5.8% (0-40)
V10	2.27% (0-10.2)
V20	0.24% (0-8.3)
V30	0.01% (0-7)

(p=0.007), Tp-e/QT ratio (p<0.001) and Tp-e/QTc ratio (p<0.001) were observed (**Table 3**). Additionally, a positive correlation was observed between mean heart dose and post-RT Tp-e interval (r=0.770, p<0.01, **Figure 1**) and Tp-e/QTc ratio (r=0.778, p<0.01, **Figure 2**). There was no statistically significant relationship between other cardiac dosimetric parameters like as V5, V10, V20, V30 and electrocardiographic measurements.

Table 3. Electrocardiographic findings

	Pre –RT (n=51;median)	Post-RT (n=51;median)	p-value
Tp-e interval	78 (56-112)	84 (64-123)	<0.001
QT interval	362 (315-416)	367 (316-451)	0.007
QTc interval	425 (363-487)	422 (364-494)	0.826
Tp-e/QT rate	0.22 (0.15-0.29)	0.23 (0.12-0.50)	<0.001
Tp-e/QTc rate	0.18 (0.13-0.28)	0.19 (0.13-0.49)	<0.001

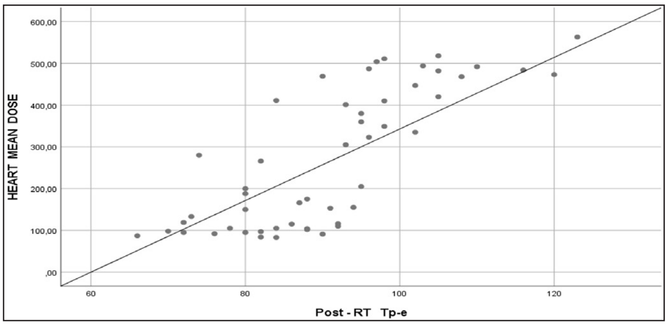

Figure 1. Correlation between post-RT Tp-e and heart mean dose

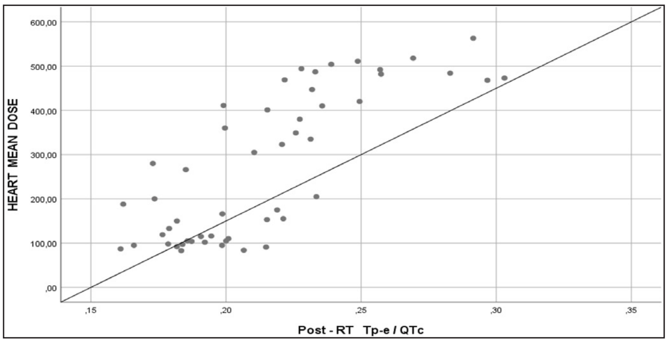

Figure 2. Correlation between post-RT Tp-e /QTc ratio and heart mean dose

DISCUSSION

The present study is one of the rare studies examining the effects of RT on ventricular repolarization in the acute period in patients undergoing RT due to breast cancer.[9] We tried to observe and discuss the acute changes in patient ECGs when the RT was added to the adjuvant therapy following AC plus weekly paclitaxel after breast surgery. Our aim was to observe the acute phase radiation effects on electrical imbalance, intracellular signaling, and action potential duration at the cellular level. In the study, the increases in the Tp-e/QT and Tp-e/QTc ratios and the prolongation of the Tp-e interval and QT interval were statistically significant, which corresponds to the ventricular repolarization process and ventricular rhythm disorders.[1,3,10-14]

We also observed a prolongation of Tp-e interval and an increase in Tp-e/QTc ratio, both of which positively correlated with the mean heart doses.

Many long-term analyses of radiation-associated cardiovascular dysfunction show an increased mortality rate due to ischemic heart disease in the population of patients who received breast RT compared to those who did not.[15-18] Moreover, it has been reported that each Gy increase in the mean heart dose increases the risk of cardiac events by 7.4% in patients undergoing RT for left breast cancer.[16]

RT is indicated in 37% of patients diagnosed with breast cancer; therefore, it is important to examine the pathogenesis of each level of acute change as well as the late effects of this treatment method. In today's complex multimodal treatment of breast cancer, it is difficult to determine the isolated effect of a single modality on the heart. In addition to factors such as the patient's body mass index, dietary habits, family history, smoking, hyperlipidemia, physical activity habits, and comorbidities, the effects of combined treatments converge. Similarly, the acute and chronic effects of each treatment, such as general anesthetic medications, analgesic drugs, combined systemic chemotherapeutic drugs, endocrine treatments, monoclonal antibody treatments, and RT, are observed simultaneously. Although it is a small-scale study, we excluded individuals with coronary artery disease, arrhythmia, congenital heart disease, heart valve dysfunction, cardiomyopathy, dyslipidemia, etc. from the study in order to reduce other comorbidity factors while evaluating acute and subacute electrocardiographic effects.

Gary et al.[19] investigated the effect of the Tpeak-Tend interval prolongation on arrhythmia and cardiac mortality with a meta-analysis involving 155,856 patients. Their results show prolongation of the Tpeak-Tend interval (mean cut-off: 103.3±17.4 ms) was a statistically significant predictive factor for arrhythmia, cardiovascular death, sudden cardiac death, and overall mortality.

Larsen et al.[20] reported electrocardiographic changes such as QTc prolongation, supraventricular and ventricular rhythm abnormalities in the post-treatment period in 134 patients exposed to anthracycline and/or cardiac irradiation during childhood and adolescence (p<0.001). They recommended ECG monitoring as a part of the follow-up protocol for arrhythmia in this group of patients receiving cardiotoxic therapy.

Herman referred to Larsen's study and emphasized that ventricular arrhythmias can be seen in up to 8% of patients treated for childhood tumors, according to studies on patients receiving thoracic RT and anthracycline therapy. Additionally, he emphasized that RT may cause bradycardia due to its effects on the cardiac conduction system, such as in the atrioventricular (AV) nodal area and in the bundle branches. Furthermore, in order to prevent arrhythmias related to cancer treatment, Herman recommended identifying patients with ECG changes before treatment and eliminating other comorbidities that predispose these patients to arrhythmias.[21]

Chen et al.[22] retrospectively evaluated 168 patients treated for pediatric malignancy in terms of cardiotoxicity. In their analysis of the patients' electrocardiographic findings, which were monitored at regular intervals in the patients' follow-up care, they observed that one of 18 patients (6%) who received thoracic RT developed ventricular systolic dysfunction in the acute period after radiotherapy.

Teng et al.[23] drew attention to cardiac autonomic dysfunction due to RT and chemotherapy and reported that cardiac involvement may be related to multifactorial effects, including direct nerve damage. They also pointed out that cardiac autonomic dysfunction may be a precursor to a more common cardiomyopathy and that early detection and elimination can prevent more serious manifestations.

In a prospective study, Gomez et al.[24] investigated the acute cardiac effects of RT in 25 patients exposed to cardiac irradiation due to thoracic RT and found that approximately half of the patients had changes in T and R waves on their post-RT ECGs.

In the European Society of Cardiology (ESC) guidelines, cardiovascular side effects associated with cancer treatment were examined under nine subtitles. They emphasized that QT prolongation may be associated with ventricular arrhythmia and that this side effect may develop due to both acute and chronic toxicity mechanisms. They pointed out that any type of supraventricular arrhythmia may develop in the acute period during or after RT and that sinus node dysfunction and conduction disorder may occur after RT, and this damage may be permanent. Additionally, the guideline recommendations emphasize the importance of regular cardiac monitoring from the beginning of cancer treatment and evaluating QT interval changes in detail.[25]

Thanks to current technological developments, heart doses are minimized through applications such as respiratory monitoring systems, use of prone treatment positions, and partial breast irradiation in breast cancer RT.[9,26] Widespread usage of these techniques and careful reporting of cardiac doses when planning RT will always remain important. Consequently, we aimed to detect breast cancer patients with possible cardiac risk in the early period, to follow them carefully with cardiac monitoring, and to plan preventive treatment by eliminating underlying factors.

Limitations of the Study

The most important limitation predicted at the beginning of the study is that the patients received systemic chemotherapy before RT. As it is known, some chemotherapeutic agents have side effects such as myocardial infarction and arrhythmia that may affect ventricular repolarization. However, as mentioned above, we attempted to observe ventricular repolarization changes in the acute period at the end of RT in the patients, who all received AC followed by a weekly paclitaxel regimen, which is frequently applied in daily practice in the adjuvant treatment setting before RT. Patients receiving neoadjuvant chemotherapy and patients receiving trastuzumab, whose cardiac effects were the subject of a separate study, were not included. Inability to achieve complete homogenization in terms of other factors such as age, menopause status, BMI that may affect ECG findings can be listed among other limitations.

CONCLUSION

In this study, we aimed to draw attention to the subclinical cardiac effects reflected on ECGs in the acute period with the addition of radiotherapy (RT) in the adjuvant setting. During the RT process, clinicians should consider that the detection of Tp-e interval and QT interval changes, which are thought to be predictive of ventricular arrhythmia, may be beneficial in early identification of patients at risk for cardiac morbidity

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 26.01.2021, Decision No: 311).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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